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Effect of glucomannan supplementation on body weight in overweight and obese children: protocol of a randomised controlled trial

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ABSTRACT

Introduction: Glucomannan (GNN), a water-soluble dietary fibre 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 children who are overweight or obese.

Methods and analysis: Children aged 6–17 years who are overweight or obese (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. Before 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 body mass index-for-age z-score difference between the groups at the end of the intervention.

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

Trial registration number: NCT02280772.

Strengths and limitations of this study

- This randomised, double-blind, placebo-controlled trial will help to resolve the uncertainty regarding the role, if any, of glucomannan (GNN), a water-soluble dietary fibre derived from the plant *Amorphophallus konjac* in the management of children who are overweight or obese, one of the most common problems worldwide.
- This study will be performed at a research centre with experience in conducting independent, investigator-initiated, randomised controlled trials.
- The study is a single-centre study. GNN is not available worldwide. The generalisability 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 counselling 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 fibre 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 randomised 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 any conclusions to be drawn. The overall quality of the trials was moderate, with small study groups and short intervention and follow-up times.[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, randomised, double-blind, placebo-controlled, single-centre 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 randomisation, children eligible for the trial must comply with all of the following inclusion criteria:

- age 6–17 years;
- overweight or obese based on the WHO growth charts/references (>+1 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 programme for treating obesity during the project and/or 3 months before 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/day, 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 is 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 packaging. 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 of the enrolment 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, emphasising 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 versus anticipated capsule 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 dietitian will perform a qualitative and quantitative analysis of the child's food intake, based on a 3-day food record (over 2 week days and 1 weekend day). This will be then reviewed using the computer software DIETA 5.0; http://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 dietitian is planned at the beginning of the study, at week 12, and at week 24.
2. All participants, at each programme 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 h 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 the trial at their request or on the occurrence of serious adverse events.

Table 1 Summary of the trial

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

DXA, dual-energy X-ray absorption.

Outcomes

The primary outcome measure will be the BMI-for-age z-score difference (baseline vs 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 SDs 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 V.1.04. 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 Holtain stadiometer, to the nearest 0.1 cm, barefoot and the head positioned in the Frankfurt horizontal plane. Before all measurements, we will ask the participants to visit a toilet.

The secondary outcome measures will include the following.

- *Body composition. Whole body fat, central body fat, fat-free mass (g).*
- This outcome will be assessed with 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 the 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 dyslipidaemia 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 FPG will be obtained at the baseline visit, at week 12, and at week 24 after 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 (mm Hg) and pulse rates (beats/min) will be taken in the sitting position on the right hand side according to the accepted standards at each study visit using an automatic oscillometer.[14] Briefly, two readings will be taken at intervals of at least 1 min, and the average of those readings will be used for analysis. However, when the difference between the first and second reading is ≥5 mm Hg, additional (one or two) readings will be obtained. The mean change from baseline to week 12 and week 24 will be calculated as an outcome.

- *Energy intake (kJ/day) at baseline and at week 12 and week 24.*
- Assessment will be based on self-written, 3-day food records (reviewed by a dietitian using the computer software DIETA 5.0; http://www.izz.waw.pl (2011, Warsaw, Poland)).
- *Physical activity (h/week) at baseline and at week 12.*
- Physical activity will be assessed using an accelerometer (Actigraph wGT3X-BT). Data will be analysed using Actilife software (V.6; Actigraph).
- *Adverse events.*
- Participants will be encouraged to report all possible adverse outcomes).

Sample size calculation

The primary end point is the difference in BMI-for-age z-scores between groups. Considering data from the literature,[15] we assumed that the mean difference (MD) would be the value 0.17, with an SD 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 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 healthcare 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 enrolment, and a further 3 months for data analysis. No incentives will be provided for study enrolment.

Sequence generation

Participants will be randomly assigned to either GNN or placebo groups with a 1:1 allocation by using a computer-generated randomisation schedule stratified by gender and age (6–11 years, middle childhood; 12–17 years, early adolescence) using permuted blocks of random sizes (the block size will be concealed until the end of the study).[16] The randomisation 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 randomisation list by the hospital pharmacy at the Medical University of Warsaw by independent personnel not involved in the conduct of the trial. The randomisation sequence and codes will be secured until all participants have been recruited into the trial and all data have been analysed.

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 randomised for whom outcomes will be available (including dropouts and withdrawals). Descriptive statistics will be used to summarise 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 χ^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 and 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 MD 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 analysed 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 minimise missing baseline and outcome data. The amount of missing data will be reported for each randomised 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 template consent forms have been reviewed and approved by the Bioethics 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) before the study enrolment. Any modifications to the protocol, which may affect 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 (paediatric, nutrition or gastroenterology). Abstracts will be submitted to relevant national and international conferences. The results of the study will be available to the participants on 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 centre with experience in conducting independent, investigator-initiated RCTs, intends to address a gap in the field and will test the effectiveness of GNN for reducing body weight in overweight and obese children.

Contributors HS conceptualised the study. Both authors contributed to the design of the study and read and approved the manuscript. BMZ 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.

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Competing interests HS has participated as a speaker for Dicopharm, a manufacturer of GNN.

Ethics approval Bioethics Committee of The Medical University of Warsaw.

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