Yeast-derived beta-glucan supplementation on antibody response following influenza vaccination: A randomized, placebo-controlled study (M-Unity).

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Background

Functional differences in the aging immune system has been studied in animal models and humans (Nikolich-Žugich 2014; Scholz et al. 2013). It has been proposed that these differences are due to immunosenescence, a term used to describe the decline in immune system function with older age. With aging, there is not only an increase in the severity of viral and bacterial infections but also a decrease in vaccine immunological responses, which often leads to a failure to induce long-term protective immunity (Crooke et al. 2019). Hence, there is a need of adjuvant nutritional therapies to improve the immunological response to vaccination. Beta-glucans have been shown to enhance the innate and adaptive immune responses in cell cultures, animal models, and humans (Harnack et al. 2009; Hetland and Sandven 2002; Lehne et al. 2006; Sandvik et al. 2007; Tsukada et al. 2003; Yu et al. 2015). Thus, adults over the age of 50 years receiving the influenza vaccination may benefit in terms of their immunological response from supplementation with beta-glucans.

Study Aims and Outcomes

The primary aim of the study is to determine the effects of beta-glucan, a dietary fiber supplement isolated from baker's yeast, on immune response to the influenza vaccine.

Primary outcome

- Change in immune response to the influenza vaccine after beta-glucan supplementation [Time Frame: 28 days (Baseline (day 1), pre-vaccine visit (~day 1), and study end (~day 28)]; Influenza-specific antibodies (IgM, IgG influenza A and B).

Secondary outcomes

- Inflammatory cytokine profile (TNF-α, IL-1β, IL-6, IL-8, and IFN-γ) [Time Frame: 28 days (Pre-vaccine visit, post-vaccine visit (~day 2-3) and study end)]
- Self-reported incidence of influenza and COVID-19 (Note: Data of subjects reporting incidence of influenza or COVID-19 during the study will be excluded from the final analysis) [Time Frame: 28 days]
- Number of subjects with fever during the study [Time Frame: 28 days] Body temperature (ºC)
- Number of subjects with cold and flu symptoms [Time Frame: 28 days] Modified Jackson Criteria
- Fatigue [Time Frame: 28 days (Days 1 – 28)

Additional information collected

- Demographic data
- Adverse events
- Vaccinations (including COVID-19 booster) received during the month prior to the study start and during the study period
- Compliance

- Reported intake of the supplement.
- Number of unconsumed supplements (returned)

Study Participants

This is a 2-arm placebo, controlled study. A total of 120 volunteers (60 in each arm) will be recruited for the study. Subjects who do not meet the inclusion criteria or who meet any of the exclusion criteria will not be eligible to participate.

Sample Size Calculation

This is a pilot study, and thus sample size is based on similar published studies.

Inclusion criteria

1. Adult volunteers ≥40 years of age.
2. Planning to be vaccinated for influenza
3. Have been immunized for COVID-19 (self-disclosure)
4. Willing and able to provide written informed consent in English.
5. Willing and able to comply with all the study-related procedures, including attending to study visits for blood draw, taking the influenza vaccine, intake of the study supplement, and completing study questionnaires.

Exclusion Criteria

1. Demonstrate an inability to comply with the study-related procedures.
2. Have a history of a severe reaction or hypersensitivity following vaccination with influenza vaccine, vaccination with any other vaccine containing the same substances, or intake of the study product.
3. Be on immune-suppressing treatment (e.g., steroids (last 30 days); cytotoxic drugs, medical surgery, or radiation therapy during the 6 months, previous to enrollment).
4. Be concurrently participating in a clinical trial that, in the judgement of the investigator, would interfere with the evaluation of the study outcomes.

Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

Recruitment

Potential participants will be recruited through flyers and word of mouth at the University of Florida, Oak Hammock Retirement Community, the Village at Gainesville, and the Gainesville Senior Center. We may also distribute the flyer through the Food Science and Human Nutrition (FSHN) department's website and Facebook page and through FSHN department faculty and staff listservs and Oak Hammock listserv. In addition, we will recruit through flyers and word of mouth at Gainesville and area churches, senior centers, senior communities, and local gyms as well as place an ad in the Gainesville Sun newspaper. Individuals interested in participating will be given the option to attend informational meetings in which the study will be explained in more detail.

Pre-screening will occur via an in-person interview or telephone contact script. The study will be described to the potential study participant using the approved script and the inclusion/exclusion criteria will be read. Potential study participants will be directed to listen to the criteria, without directly answering (stating "yes" or "no") after each criterion is read, and then decide whether they would like to continue with study procedures. If the potential participant is still interested in participating and still believes they may qualify, an appointment will be scheduled for consenting.

Investigational Product (IP)

Manufacturing and Storage

The Investigational Products (beta-glucan and placebo) will be manufactured by Biotec Betaglucans (Lallemand inc., Tromsø, Norway) and provided to the study site, FSHN Clinical Lab, Food Science and Human Nutrition Department. The IP will be carefully stored at the study site in a lockable, limited access area, accessible only by study team personnel in compliance with pertinent regulations. Only authorized persons will have access to the IP. The IP should be stored 3–10 °C.

Beta-Glucan

The product under study is beta-glucan at 500 mg/day (2 capsules per day). The group randomized to the beta-glucan intervention will receive sufficient IP to cover the entire length of the intervention period (28 days).

Placebo

The placebo product is cellulose, an inert dietary fiber, 500 mg/day (2 capsules per day). The product has a very similar appearance, texture and taste as the beta-glucan product and will have identical packaging. The group randomized to the placebo intervention will receive sufficient IP to cover the entire length of the intervention period (28 days).

Direction of Use

Participants will be instructed to consume the supplement (500 mg/d) for 28 days following the influenza vaccination.

Study design

This is a 6-week randomized, double-blind, placebo-controlled, 2-arm parallel study designed to evaluate the adjuvant effect of beta-glucan dietary supplementation during influenza vaccination. This study will have a 28-day intervention period.

During the pre-screening by telephone or in-person, the study and inclusion and exclusion criteria will be explained. Any restrictions linked to the study will also be explained. Sufficient time will be allowed for the potential participants to decide whether or not they wish to participate in the clinical study. If the potential participant decides to participate, a screening appointment will be scheduled to sign the informed consent and to perform the first study activities.

During the screening appointment (by Zoom or in person), the inclusion and exclusion criteria will be reviewed without responses to the individual items, and if the participant believes they are qualified, the informed consent will be signed via RedCap or in person. Following informed consent, the inclusion and exclusion criteria will be reviewed again, this time with responses to each item and recorded. Each study participant will receive a unique identifier. Within 24-hr prior to Visit 1, links to the Qualtrics demographic form (age, sex, race, and ethnicity) will be sent to participants for completion. Alternatively, the participant will be given the option of completing the questionnaire in person during Visit 1. At Visit 1, a baseline blood draw will be performed, and the participants will be randomized to either the beta-glucan or placebo group and will be instructed about the daily consumption of the IP for 28 days. Participants will then receive an influenza vaccine. Take-away breakfasts will be offered following blood draws. Participants will be requested to complete an online Qualtrics or paper-based daily questionnaire of compliance, and cold, and flu and fatigue symptoms throughout the 28-day study.

A second blood draw within 24-48 hours following their influenza vaccination (Visit 2) will be taken. A final blood draw will be completed on day 28 (Visit 3 - study end). Adverse events, including any illnesses, will be queried.

Randomization

Participants will be randomized to either the beta-glucan or the placebo group in a 1:1 fashion. Randomization will be used in this study to avoid bias in the assignment of participants to intervention, to increase the likelihood that known and unknown participant attributes (e.g., demographics and baseline characteristics) are balanced across intervention groups, and to ensure the validity of statistical comparisons across intervention groups.

Randomization will be done by a computer-generated code, sealed envelope method and completed by an individual not involved in the study. Each random allocation will be arranged to fit on a single sheet of white paper that indicated the study sequence, and which also had blank spaces for the participant's study number, date, the number of IP provided to the participant, and the number of IP returned by the participant. These sheets will be placed in envelopes and sealed. Each envelope will have an envelope number printed on it. The study staff will unseal the envelopes and assign the participant to a study sequence.

Blinding

Prior to delivery to the study site, the beta-glucan and placebo will be coded by an unblinded personnel at Lallemand inc. who will have no direct contact with participants, and no involvement with study procedures. Blinding to intervention will be used to reduce bias during data collection and evaluation of outcomes.

Unblinding

Unblinding should not occur except in the case of an emergency. In the event that a serious adverse event (SAE) occurs, for which the identity of the study supplement administered is necessary to manage the participant's condition, the randomization code for that participant may be broken and the study supplements identified.

All emergency code breaks must be reported to Lallemand inc. project manager within 24 hours. The time, date, reason and who broke the blind, must be documented in the source documents. Details of participants who are unblinded during the study will be included in the final report.

The probiotic and placebo will be double coded, so in the event of an SAE and unblinding of one code, information about 75% of the subjects will remain blinded.

Compliance

Compliance and adverse events will be monitored in the daily questionnaire throughout the intervention phase. Compliance also will be assessed by counting the number of study supplements returned by the participant at the end of the intervention. Compliance is calculated by determining the number of study supplements consumed from start of study IP (V1) to end of study IP (V3) divided by the number expected to have been taken multiplied by 100 to obtain the percentage consumed. Participants found to have a compliance of <80% will be considered noncompliant.

Data Analysis Plan

Statistical consultation will be utilized for data analyses. Statistical methods will be consistent with the CONSORT 2010 Statement (including statistical methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses).

Data Management Plan

Data about the intervention effects will be collected from the participants electronically and on paper. Data and files will be secured in locked filling cabinets and office space. Paper questionnaires will only include date and research study assigned participant number. Data that is originally captured as hardcopy/paper (e.g., demographics and vital signs) will be transcribed to encrypted electronic files.

Following the completion of the study, identifiers will be removed from data to meet HIPAA de-identification standards (According to the October 2002 Privacy Rule § 164.514.(b).2. the indicated information/will be removed from all study records).

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

Potential Discomforts and Risks

Beta-glucan, a dietary fiber, poses no known risks. Beta-glucan, a fiber, poses no known risks. However, there are some potential discomforts and risks related to the study. Drawing blood from a vein may result in discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure. Some people may feel uncomfortable answering questions about incidence of influenza, cold and flu symptoms, mood and feelings, and fatigue symptoms. Some people may feel uncomfortable or have difficulties swallowing capsules. You can open the capsule and add to a food such as apple sauce if you prefer. There is a risk of possible loss of confidentiality.

Informed consent forms given to all participants specify Dr. Dahl as the contact in the case of issues or questions arising during the study. In the case that a professional intervention is necessary due to an adverse effect on the study subjects, Dr. Dahl will contact the appropriate authority or organization pertinent to the circumstance of the event. Serious adverse events will be reported to the sponsor within 24 h of the PI being notified. In the event of a data safety breach, Dr. Dahl and the appropriate University of Florida personnel will contact participants to inform them of this breach, as well as notify the Institutional Review Board of the University of Florida.

Potential Benefits

It is possible that those participants randomized to the beta-glucan may respond with a greater antibody titer to the influenza vaccine.

Conflict of Interest

The investigator declares no conflict of interest.

Compensation

For participating and completing the study, participants will receive $25 per blood draw and $25 per week for daily questionnaire completion for a total of $175. If a participant drops out during the study, compensation will be prorated at $25 per week and $25 per blood draw. Should a participant not complete the entirety of the study due to a withdrawal, disqualification, or any other reason, compensation will be based upon completing pre-determined benchmarks. In all cases, compensation will be provided at the end of the study.

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