The effect of high-polyphenol Mediterranean diet (Green-MED) combined with physical activity on age-related brain atrophy: the Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed Study (DIERECT PLUS)
Article Critique

Summary

Researchers Kaplan et al, decided to address the problem of neurodegeneration in adults. In the modern day, the average life expectancy has been steadily increasing, but unfortunately older adults are susceptible to neurodegeneration, or brain atrophy. These researchers wanted to study the possible effects of dietary intervention on age related brain atrophy. A diet high in polyphenols, more specifically the Green MED diet was chosen. The researchers did not include a control group, and instead had three intervention groups in their randomized control trial. Authors hypothesized "The MED diet groups, and specifically the Green-MED diet group, which doubled the polyphenol content provided in the diet, would exhibit attenuated brain atrophy compared with the healthy dietary guidelines (HDG) group."[1]

Study participants were divided into three groups, the healthy diet group (HDG), the MED diet group, and the Green-MED group. All participants were volunteers from a remote worksite in Israel where researchers could control their lunch as well as enact the physical activity interventions that all three groups received. Outside of the worksite, participants filled out verified FFQs to log diet and exercise for the 18 months of the study. The researchers inclusion criteria is discussed in the review; 294 volunteers met the inclusion criteria. Health status prior to intervention and polyphenol consumption (from intervention) were the mediating variables in the study.[1]

Researchers measured brain structure by using MRI's to measure hippocampal occupancy score (HOC) and lateral ventricle volume (LVV) expansion scores as neurodegeneration markers.[1] This served as their dependent variable with polyphenol content in their diet and health status before intervention served as the mediator variables.

Researcher results showed that both MED groups had greater reductions in brain atrophy when compared to the HDG group. Brain atrophy cannot be reversed, and so researchers were looking at which dietary intervention prevented or slowed it's progression the most. The results of the study reflected their hypothesis.

The researchers overall conducted a well-planned and thorough study. By holding exercise constant they removed it as a confounding factor, which allowed the results to reflect the dietary intervention to a greater degree. Their sample was not diverse, but this was to make the study more feasible. Overall, the randomized control trial was able to demonstrate the benefits of polyphenols in decreasing neurodegeneration. The study ends with comparison to previous research as well as the authors recommendations to future researchers.

Introduction

Researchers hypothesized that the MED diet groups, more specifically the Green-MED diet group with doubled the polyphenol content provided in the diet, would exhibit attenuated brain atrophy when compared with the healthy dietary guidelines group. The independent variables were diet and exercise with the dependent variable being brain atrophy. The mediating variables were polyphenol content in diet and health status before intervention. Researchers operationally defined their independent and dependent variables. The authors developed an empirical hypothesis that is tested quantitively.

It is somewhat common knowledge that as we enter old age (above 55), our cognitive functioning begins to due to brain atrophy, or the degeneration of brain tissue. The researchers are looking at ways to slow down neurodegeneration. The researchers provide background information within their introduction. This study utilizes the Green-MED (Mediterranean) diet, which has a focus on decreasing red meat and increasing polyphenols. There have been previous studies on both this diet as well as established research on cognitive decline and brain atrophy, both together and separately. The background information provided by the author is mainly about the benefits of polyphenols in our diet, which are explained to be anti-inflammatory and antioxidant metabolites. The author also discusses the problems of cognitive decline affecting older adults.

The author reviews some literature but does not go into detail about previous research until the discussion section of the paper. Any reference or outside source the author has included are relevant to the problem. Some of the sources used were not for the actual research but were instead to allow the reader(s) to attain background information on the subject being studied. The author has included 55 outside sources with the majority of the sources being primary. There are some reviews included as well. An interesting factor of the sources is that there are only a handful (less than five) studies on nonhuman subjects (mice) with most sources being intervention or observational studies on brain health. Brain health here is a general term used that could include cognition, brain atrophy as screened by MRI, neuroinflammation, and/or changes to white and grey matter to name a few.

The references included were not compared. This is an original study and not a review article, so the author has “sprinkled” in information to help support the reasons for research as

well as to somewhat map out what has been done and what they will do in order to add on to the literature. There is not a “review” section on the article. The author instead uses the previously published literature to support their ideas and provide readers with some baseline knowledge of procedures.

Method

294 volunteers from the Nuclear Research Center Negev in Dimona, Israel met the inclusion criteria. The workers did not leave during the day, and they were provided lunch which was monitored and altered by the researchers into either the Healthy dietary guidelines (HDG), MED diet, or Green-MED diet. The authors were most concerned about the effect of polyphenols and so the HDG group somewhat acted as a control group because they did not receive polyphenols.

The workplace has its own medical department where the majority measurements as well as lifestyle interventions session were performed. The sample was chosen due to researchers’ ease of access. All participants being from the same work location with provided lunches made the intervention study of almost 300 volunteers much more feasible.

To be included in the study, volunteers had to be older than 30, with a waist circumference of > 102 cm for men and > 88 for women or have dyslipidemia with triglycerides >150 mg/dL, HLD $\leq$ 40 mg/dL for men and $\leq$ 50 mg/dL for women. Volunteers were excluded if they could not perform physical activity, had serum creatine $\geq$ 2 mg/dL, serum alanine aminotransferase or aspartate aminotransferase > 3 times above the normal limit, illness worthy of hospitalization, were pregnant or lactating, underwent cancer or chemotherapy treatment within the last 3 years, were on warfarin treatment, had a pacemaker or platinum implant, or had already participated in a different trial.

Every participant took an FFQ that assessed nutritional intake and lifestyle habits. Once participants were randomized into one of the three trial groups, the authors provide details on participants average age, sex, BMI, weight, waist circumference, systolic BP, diastolic BP, blood glucose, homeostasis model assessment for insulin resistance (HOMA-IR), total cholesterol, HDL-C, LDL-c, triglycerides, APOE- ε4 allele, hippocampal occupancy score, lateral ventricle volume, and hippocampus volume. All parameters were measured at baseline then again after the 18-month intervention.

The sample size selection calculation researchers used was based on hippocampal gray matter volume. To detect a difference in hippocampal gray matter volume researchers used a previous 1-year intervention study in which 120 participants were separated into two groups. They noted their detection means to be 0.16 and 0.23 cm3 difference in the left and right hippocampus volume, respectively.

The researchers received ethical approval from the Soroka Medical Center Medical Ethics Board and an IRB. They stated that their participants provided written consent and received no financial compensation.

Instruments

The authors provide a hyperlinked supplemental method. The researchers took blood samples from participants after a 12 hour fast. Within the supplemental methods there is an extensive breakdown of all procedures and equipment used during procedures. Most of the equipment used was for reading the blood samples. The equipment was used “according to manufacturer

protocol" and was up to date. Every instrument used was described, used properly, and was used to measure proper biomarkers. Every marker the researchers mentioned has a measurement displayed that seems appropriate.

Design and Procedure

The researchers separated participants into the Healthy Dietary Guidelines (HDG) group that received standard nutritional counseling and ate a "healthy diet", the MED group that followed a calorie restricted traditional MED pattern low in simple carbohydrates, rich in vegetables, with poultry and fish replacing beef and lamb. This diet included 28 g of walnuts that contained 440 mg of polyphenols, and the Green-MED group that in addition to MED diet restrictions was asked to avoid processed and red meat and consume more plant based food, drank 3-4 cups of green tea per day and ate 100 g of mankai that is rich in polyphonic compounds and protein, adding up to a total 800 mg of polyphenols per day. Every participant was given the same physical activity program and researchers used an electronic self-reported questionnaire that was previously validated.

The researchers were looking for changes in brain size as well as analyzing executive function before and after intervention. In order to scan for brain size, they used an MRI scan to detect Hippocampal occupancy score, lateral ventricle volume, and hippocampus volume. In order to analyze executive function, they used Choice Reaction Time (CRT), a Switching Task, and The Anti-Saccade Task. All participants underwent the executive function analysis.

The CRT had two stages: a low cognitive load phase with three tasks requiring participants to choose between two possibilities, and a high cognitive load phase with three tasks requiring participants to make choices among six options (letters, numerals, and shapes). Prior to the actual trials, each activity had practice trials. Each participant responded with a different finger. The stimuli, which included Hebrew characters, numbers, and shapes, were displayed on a computer screen. Fixations were followed by the target and cue in each trial, and responses were timed.

The Switching Task was administered after finishing the CRT tasks, participants used their knowledge of 2-choice rules and familiar cues to tackle a new task. After showing cues and mappings, the task was presented in a series of trials with a different task (letters, numerals, or shapes) each time. A letter, a digit, and a shape were integrated in each target stimulus, but the presentation and error indication were identical to those of CRT. Two distracting effects were taken into consideration for the 201 trials of the task, which included 6 practice trials.

The Anti-Saccade Task evaluated the participants' capacity to suppress reflexive reactions. A fixation mark appeared on one side of the screen, followed by a cue, and on the other, a target stimulus for each of the 96 trials. Participants were required to disregard the original cue and specify the direction of the arrow. The purpose of the task was to gauge their level of inhibition. These procedures could be duplicated by another researcher as they were more extensively outlined within the article.

The research does not explicitly list any confounding variables that were unaccounted for. The researchers ensured to control for other variables by using proper randomization to ensure an equal distribution of differing characteristics to ensure the groups were as equal as possible.

They also ensured to account for dietary and physical activity compliance by providing all subjects with overseen lunches and physical activity sessions.

Results

The researchers only had one hypothesis that was successfully tested.

The authors do a good job of outlining every statistical test used. They used the Wilcoxon test or paired-sample t tests to analyze changes in blood biomarkers, mri results, and anthropometric measurements. The between group differences were calculated using independent-sample T tests, ANOVA, mann-whitney U tests, Kruskal-wallis test, or chi-square tests. Each test was used appropriately to assess the correct variables. The researchers go into detail to accurately describe values assigned to each of the measures to explain the results presented in the table. The researchers state that all analyses were nonparametric.

The probability level at which researchers tested significance was $P < 0.05$. The researchers predetermined the statistical significance level to assess their findings in a consistent manner. The authors also used the Bonferroni correction and the false discover rate (FDR) which decreased the risk for error via the use of multiple statistical analyses. The researchers did not provide the specific degrees of freedom used. The researchers did, however, provide a detailed outline of the tests they ran. The authors used SPSS software for their statistical analysis, and so we can infer proper degrees of freedom were used in calculations.

Researchers had both a table as well as a written outline of all results recorded. The tables provided were clear and easy to understand with an appropriate description written under each one. Additional tables are provided in the supplemental methods. Every table in both the regular

article and the supplementals provide a description of how tables are meant to be read as well as what the results in each table means. The authors wrote a detailed and easy to read breakdown of each table.

Discussion

Everything included in the discussion relates back to the hypothesis. The authors do a good job of discussing the possible implications of their findings. Hippocampal atrophy and aging were addressed directly in the discussion section with previous evidence presented. The information presented emphasizes how age related atrophy is in neurodegenerative diseases and how the method used, HOC, is more sensitive when compared to other volumetric assessments. The study also discussed the neuroprotective effects of polyphenols, like how they did in the introduction. Authors also made note of the fact that not all previous studies have found beneficial effects of polyphenols. Within the discussion, the researchers also included previous research and whether or not the intervention study's results were in line with current and previous research. Age and brain volume, the APOE- ε4 genotype, physical activity interventions, and white matter integrity were among some topics discussed. Interestingly, the results of the study differed from previous research in the researcher's inability to detect any effect on white-matter integrity from diet intervention. The authors discuss in detail how one of their controlled variables could have had a larger affect on their results than the polyphenols. The Physical activity prescribed to individuals may have had a greater affect on all parameters measured than the diet interventions.

Within the discussion section, authors discuss the theoretical and practical/clinical implications of their study. The authors discuss the main theme of polyphenols in both lights. The clinical interventions align with previous research as well as established health claims. The authors recommend future researchers to explore the exact mechanisms of the specific polyphenol-rich foods on brain anatomy and function. To be specific, the authors mention exercise has previously been shown to have beneficial effects on hippocampal volume, thus possibly effecting the study's outcome more than the dietary interventions. Research suggests future research involving the study of polyphenols including test subjects who do not participate in aerobic exercise. Researchers also bring up the point that their research was not conducted on a diverse population and urge future researchers to have a more diverse sample size.

Instead of only statistical significance, the authors suggestions for future research are based primarily on the practical and clinical significance. The researchers were sure to make distinctions between just the statistical significance and the practical and clinical significance, ensuring to base their recommendations on the latter. The authors make dietary and cardiometabolic recommendations and interventions that they also state should be integrated as soon as possible.

Source:

1. Kaplan A, Zelicha H, Yaskolka Meir A, et al. The effect of a high-polyphenol Mediterranean diet (Green-MED) combined with physical activity on age-related brain atrophy: the Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed Study (DIRECT PLUS). *The American Journal of Clinical Nutrition*. 2022;115(5):1270-1281. doi:https://doi.org/10.1093/ajcn/nqac001