Effect of Astaxanthin for Pain, Function, and Inflammation in Patients with Advanced Osteoarthritis Awaiting Total Knee Replacement Surgery

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1. Background / Justification for Study

Osteoarthritis (OA) is a common degenerative joint disorder that affects a significant portion of the population. Over 30 million Americans are currently affected by the disease, with prevalence expected to increase 40% by 2025 as a result of the aging population and obesity epidemic.[1,2,3] Specifically, symptomatic knee OA is a leading cause of disability, occurring in 10% of men and 13% of women over the age of 60.[1] Patients with symptomatic OA often experience pain, swelling, and stiffness of the knee resulting in a decrease in physical mobility which can have a drastic impact on quality of life.[3,4] In addition to the significant impact on affected individuals, OA is associated with an enormous economic burden estimated at $136.8 billion annually in the US, surpassing costs of tobacco-related health effects, diabetes, and cancer.[5]

Although originally classified as non-inflammatory arthritis, recent studies suggest that a relationship exists between joint inflammation and OA. Specifically, the complex interaction between sites of local tissue damage and immune cells leads to a state of chronic joint inflammation which may play a key role in disease pathogenesis.[2,6,7] The evidence suggesting a role of inflammation in disease progression makes anti-inflammatory agents ideal candidates for symptom management. Astaxanthin is a keto-carotenoid present in many aquatic animals, including salmon, shrimp, and lobster, that has demonstrated heightened antioxidant activity and the ability to suppress inflammation.[2,8,9] Early evidence suggests that astaxanthin may protect against osteoarthritis *in vivo*, illustrating its potential as a therapeutic supplement for patients with OA.[2] However, studies illustrating these effects in humans have yet to be conducted.

This prospective, blinded, randomized, placebo-controlled pilot study will evaluate the effect of astaxanthin in reducing inflammation, controlling pain, and improving physical function in patients with advanced knee osteoarthritis awaiting total joint replacement surgery. Levels of pro- and anti-inflammatory cytokines and chemokines will be measured following the completion of a daily oral regimen of astaxanthin vs. placebo. Additionally, patient-reported outcome measurements assessing physical function and pain interference will be obtained prior to and following completion of treatment allowing for a comparison between treatment groups. Study outcomes will provide evidence to support astaxanthin supplementation as a cost-effective, added strategy for symptom management in patients with advanced osteoarthritis and will lay the foundation to seek additional federal funding to conduct a large-scale clinical trial to further establish the efficacy of this treatment strategy.

2. Objectives / Research Aims

The goals of this study are to:

a. Determine the effect of astaxanthin on pain control and physical function in patients with osteoarthritis who are scheduled to undergo a total knee replacement surgery.
b. Determine the effect of astaxanthin on inflammatory synovial markers in patients with osteoarthritis who are scheduled to undergo a total knee replacement surgery.

3. Setting

This study will take place at Prisma Health Orthopedics clinic facilities and Prisma Health Baptist Hospital.

4. Resources Available

Documentation will be comprised of a thorough history and physical, clinical progress notes, operative reports, anesthesia reports, and post-operative progress notes available on the EPIC EMR as well as patient reported outcome measurements collected via PROMIS surveys and stored on the Prisma Health REDCap server, a secure data collection platform.

Two fellowship trained orthopaedic surgeons will lead the research team.

The research team will be comprised of practicing orthopaedic surgeons, the Chair of the Department of Pathology, Microbiology, and Immunology, resident orthopaedic surgeons in training, medical students, clinical nursing staff, and research assistants.

5. Study Design

This will be a prospective, double-blinded, randomized, placebo-controlled pilot study.

a. Recruitment Methods

Adult patients with advanced osteoarthritis who are scheduled to undergo total knee replacement surgery, meeting all inclusion/exclusion criteria, will be approached by a study team member. The team member will review the study with the patient and, if appropriate, obtain their consent to participate in the study.

b. Inclusion and Exclusion Criteria

Inclusion:

- ≥ 18 years of age
- Radiographic evidence of advanced knee osteoarthritis
- Knee pain
- Scheduled to undergo a total knee replacement

Exclusion:

- < 18 years of age
- Unable to provide written consent
- Known allergy to fish or astaxanthin
- Pregnant and/or breastfeeding
- Received a corticosteroid injection within 3 months of initiating treatment with astaxanthin or placebo
- Currently taking immunosuppressant drugs or drugs which act as a 5-alpha reductase inhibitor

- History of any autoimmune condition
- Known autoimmune etiology for arthritis (e.g. Rheumatoid or Psoriatic arthritis)

c. Number of Subjects

160 total patients included in this study, 80 per treatment arm.

d. Study Procedures

Once patients have been enrolled in the study, they will complete a Patient Reported Outcome Measurement Information System (PROMIS) Physical Function and Pain Interference assessment. This assessment will be administered on an iPad by clinic or research staff and data will be recorded in REDCap.

Participants will be randomized to receive a daily oral regimen of either astaxanthin (12mg) or placebo over a 6-week period prior to surgery. Patients will record compliance with taking the supplement via a log provided to them at the time of consent.

Research staff will call participants biweekly over the 6-week period to assess pain score, supplement compliance and record any side effects from the astaxanthin or placebo.

On the day of surgery, participants will again complete the PROMIS Physical Function and Pain Interference assessment when they arrive at the hospital. This assessment will be administered on an iPad by clinic or research staff and data will be recorded in REDCap.

At the time of surgery, following sedation, an aliquot of synovial fluid will be collected from the affected knee by the orthopedic surgeon performing the surgery. Obtained samples will be analyzed to measure levels of pro- and anti-inflammatory cytokines and chemokines.

e. Study Timelines

Following IRB approval, we will begin prospectively enrolling eligible patients in this study. Currently, Dr. Del Gaizo treats approximately 50 patients in clinic per week, with nearly 50% suffering from knee osteoarthritis. Overall, he performs 2-6 knee replacements for advanced osteoarthritis per week. Given the high volume of patients treated by Dr. Del Gaizo with advanced osteoarthritis who will ultimately undergo total knee replacement surgery, we expect to achieve complete enrollment of 160 participants in a 10-12-month period. Additional orthopedic surgeons may be included to increase enrollment, if necessary.

Following the completion of participant enrollment and data collection, the

obtained results will be reviewed and statistically analyzed over a 2-month period.

f. **Study Endpoints**

Pain interference and physical function between the astaxanthin and placebo control group as measured by PROMIS Physical Function and Pain Interference assessments prior to beginning astaxanthin or placebo treatment regimen and just prior to surgery.

Inflammatory profiles of post-treatment synovial fluid from the astaxanthin and placebo control group as measured by levels of pro- and anti-inflammatory chemokines and cytokines.

g. Medication Treatment protocol

Pre-Operatively:
12mg Astaxanthin or placebo once daily for 6 weeks prior to surgery

h. Data Collection/Banking

All data will be stored on a password-protected, encrypted spreadsheet. Only members of the study team will have access to this information.

Participants will be given a unique study ID and a separate password-protected document will be created linking patients to their study ID.

Data recorded via PROMIS and phone surveys will be stored on the Prisma Health REDCap sever, a secure web application for managing research databases.

Synovial fluid samples will be stored in a -80C freezer in a locked laboratory and will only be accessible to members of the study team. Samples will be labeled with study IDs given to participants.

i. Statistical Analysis

PROMIS assessments will be completed at two time points: prior to beginning the astaxanthin or placebo treatment regimen and just prior to surgery, at the time of completing the treatment regimen. A paired t-test will be performed to detect differences in the before and after measurements per group. These differences will then be compared for patients in the astaxanthin arm vs. placebo arm to determine if participants receiving astaxanthin report a significant difference in pain and physical function ability following completion of the treatment regimen.

Synovial fluid will be collected in heparinized tubes at the time of surgery. A quantitative analysis of immune cell infiltration will be performed from the synovial fluid collected, using a hematology analyzer. This will provide total and

differential WBC counts. Further studies will be done to estimate the cytokine and chemokine levels in synovial fluid. Statistical analysis will be performed and a p value < 0.05 between groups will be considered statistically significant.

j. Data Management

Data will be maintained on a secure password protected server. Only IRB authorized research study members can access this information. The researchers involved in this study commit to handle all information with care and to protect research subjects' identity. The data collected will be kept for at least three years after publication and then destroyed in accordance with the hospital and federal guideline. Participants will be given a unique study ID and a separate password-protected document will be created linking patients to their study ID. No PHI will be disclosed during statistical analysis or subsequent presentations or publications.

k. Confidentiality

All study related data activities will take place on password-protected network supported by the home hospital institution. Study team has been educated and agrees to uphold the hospital and federal confidentiality laws.

l. Provisions to Monitor the Data to Ensure the Safety of Subjects

Data will be maintained on a secure server with password protection. Study data and signed consent documents will be stored in a locked office in Prisma Health Orthopedics. Only authorized research members of this study can access this information. The researchers involved in this study commit to handle all information with care and to protect research subjects' identities.

6. Risks to Subjects

Possible side effects associated with Astaxanthin supplementation are increased bowel movements, red stool color, and stomach pain.

Astaxanthin has been shown to hinder the 5-alpha reductase enzyme in laboratory studies. This may prevent testosterone from changing into the dihydrotestosterone (DHT) hormone. While it is unclear the exact effect that astaxanthin may have due to this interaction, similar medications that affect the 5-alpha reductase enzyme may cause side effects such as lower libido, male breast growth, and erectile dysfunction. Patients who are currently taking medication which acts as a 5-alpha reductase inhibitor will be excluded from this trial.

Astaxanthin has the potential to increase the function of your immune system. Patients who are currently taking immunosuppressant drugs and/or have an autoimmune condition will be excluded from this trial.

As this is a prospective study, there is a slight risk of loss of confidentiality of protected health information (PHI). Members of the study team commit to handle all information with care and protect the identify of research subjects.

7. Potential Benefits to Subject

Patients may potentially benefit by receiving a new regimen of medical care that reduces the inflammation associated with advanced osteoarthritis, subsequently reducing pain improving physical function.

Indirectly, patients may benefit by providing information for medical professionals to better treat patients in the future.

8. Consent Process

During the pre-operative phase, in clinic, eligible patients will be identified. A member of the study team will explain the purpose of the research and what the patient's role will be. The person obtaining consent will adequately review all potential risks and benefits and will not coerce patients to consent. This is outlined on our informed consent document. Written informed consent will be obtained on our informed consent document. These documents will be stored in a locked office Prisma Health Orthopedics Research Department as well as the subject's electronic medical record. Participants will also be provided a signed copy of the informed consent document to keep.

9. Bibliographic References

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

EFFECT OF ASTAXANTHIN FOR PAIN, FUNCTION, AND INFLAMMATION IN PATIENTS WITH ADVANCED OSTEOARTHRITIS AWAITING TOTAL JOINT REPLACEMENT SURGERY

Study to be Conducted at:

Prisma Health Baptist Hospital
Marion Street
Columbia, SC 29220

Prisma Health Baptist Parkridge Hospital
400 Palmetto Health Pkwy
Columbia, SC 29212

Prisma Health Richland Hospital
5 Richland Medical Park Drive
Columbia, SC 29203

Prisma Health Orthopedics Ambulatory Clinics:

14 Richland Medical Park Drive
Suite 200
Columbia, SC 29203

104 Saluda Pointe Drive
Lexington, SC 29072

100 Palmetto Health Pkwy
Suite 320
Columbia, SC 29212

Funding Sources: Prisma Health Grant in Aid Foundation; The Orthopaedic Research and Education Foundation

Principal Investigator: *Daniel Del Gaizo, MD; 803-296-9210*

KEY INFORMATION

You are being asked to participate in a research study. Participation in a research study is voluntary. The information in this consent form is meant to better inform you so you may decide whether or not to participate in this research study. Please ask the study doctor to explain anything you do not understand.

The purpose of this study is to determine the effect of astaxanthin on pain, physical function, and inflammation in patients with knee osteoarthritis who are scheduled to undergo a total knee replacement surgery. Your participation in this study will require you to take the study drug or placebo and complete surveys prior to and

at the time of your total knee replacement. While under anesthesia for your total knee replacement, a small sample of fluid will be removed from your knee for analysis of inflammatory markers. You will be contacted by the study team at routine intervals throughout the study to discuss your pain level, physical capabilities, and any experienced side effects of the study drug.

Your participation in this study will not require any additional office visits outside of the standard visits following a total knee replacement surgery. There is a risk of adverse reactions to these medications such as, increased bowel movements, red stool color, and stomach pain. We cannot promise any benefits to you or others from your taking part in this research. However, taking part in this study may benefit you as the patient directly if you receive astaxanthin by providing decreased pain and improved physical function.

The Institutional Review Board of Prisma Health has reviewed this study for the protection of the rights of human participants in research studies, in accordance with federal and state regulations.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PURPOSE

You are being asked to participate in this study because you have advanced osteoarthritis and are scheduled to undergo a total knee replacement.

Osteoarthritis causes pain, swelling, and stiffness of the knee resulting in a decrease in physical function. A promising treatment option to address swelling associated with this disease includes the use of a naturally occurring compound, astaxanthin, which is commonly used as and is approved by the FDA as a dietary supplement. The goal of this study is to evaluate the use of this dietary supplement in patients with osteoarthritis awaiting total knee replacement surgery. Results from this study may provide an added treatment option to improve the quality of life for those individuals.

We expect about 160 people will be in this research study total. All participants will be treated at Prisma Health Orthopedics. Your participation will last for 6 weeks prior to your total knee replacement.

HOW THE STUDY WORKS

1. If you agree to be in this study, your surgeon and research staff will review your medical history to make sure that you are eligible. Once all of your questions are answered and you are willing to participate, you will be asked to sign and date this consent form.

2. You will complete a survey about your current level of pain and how your pain effects your ability to perform daily activities.

3. You will randomly be assigned to receive astaxanthin or a placebo. A placebo is a substance that has no therapeutic effect and is used as a control when testing new medications in research studies. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor

your doctor will choose what group you will be in or know what group you are assigned to. You will have an equal chance of being placed in any group. Specific members of the research team will know which group you have been assigned to and can provide this information if needed in the event of an emergency.

4. You will be given a 6-week supply of medication (astaxanthin or placebo), to be taken once daily for 6 weeks prior to your total knee replacement surgery. You will record taking your medication on a daily log that will be provided to you at the time of consent. You will bring this document back to your surgeon on the day of your surgery.

5. A member of the study team will call you biweekly at weeks 1, 3, and 5; During these phone calls, you will be asked:
    - To rate your pain level on a scale from 0-10
    - If you have taken any additional medication for pain
    - If you have experienced any side effects such as increased bowel movements, red stool color, or stomach pain.

6. On the day of your surgery, at the hospital, you will be asked to complete a survey about your current level of pain and how your pain effects your ability to perform daily activities.

7. During your surgery, while under anesthesia, your surgeon will obtain a sample of fluid (approximately 1 teaspoon) from your knee to be analyzed for markers of inflammation for the purposes of this research.

8. Following your surgery, you will have completed all activities associated with this study and your participation in the study will end.

RESEARCH USE OF BIOSPECIMENS

This study involves the collection of biospecimens (bodily substances). At the time of your total knee replacement, your surgeon will obtain a sample of fluid from your knee while you are under anesthesia. This fluid will be analyzed to determine levels of common markers of inflammation. No genetic testing will be done in this study. The biospecimens collected for this study will not be used or distributed for future research studies. Findings from this study may be used in publications; however, no identifying information about your specimen will be published.

POSSIBLE RISKS

Any treatment has possible side effects. The treatments and procedures used in this study may cause all, some, or none of the side effects listed. There is always the risk of very uncommon or previously unknown side effects.

You will be receiving the same medical care, and treatment as patients that are not included in this study. The supplement you will be taking has minimal known side effects. There is a risk of adverse reactions to these medications such as increased bowel movements, red stool color, and stomach pain.

Astaxanthin has been shown to hinder the 5-alpha reductase enzyme in laboratory studies. This enzyme is present in high concentrations in male reproductive organs and is important in male reproductive function. Anything that reduces this enzyme may cause side effects such as lower libido, male breast growth, and erectile dysfunction. There are medications that are prescribed to reduce this enzyme to treat conditions such as enlarged prostate or male pattern baldness. Patients who are currently taking such medication that are intended to reduce this enzyme will be excluded from this study. It is very important that you provide your study doctor an accurate list of all medications that you are currently taking so that an appropriate assessment can be done prior to consenting to participate in this study.

Astaxanthin has the potential to increase the function of your immune system (the processes that protect your body from disease.) Patients who are currently taking immunosuppressant drugs (such as prednisone, hydrocortisone and many of the drugs used to treat cancer) and/or have an autoimmune condition (such as Lupus, Rheumatoid Arthritis, Graves' Disease or Inflammatory Bowel Disease) will be excluded from this trial.

As with all medications, side effects may include allergic reactions. Allergic reactions may range from minor itching or rash to major reactions, which can lead to death.

It is possible that receiving the study drug with your regular medications, supplements, or some food (for example, grapefruit juice) may change how the study drug, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study. Tell the study doctor if you are taking any drugs, or non-prescription medications or supplements, including vitamins or herbs, other than those being used in this research study because of the risk of possible and/or serious drug interactions. Tell anyone who gives you medical care that you are participating in a research study.

POSSIBLE BENEFITS

It is not possible to know whether or not you may benefit from participating in this study. The treatment or procedures you receive may even be harmful. The information gained from this study may be useful and may help others.

We cannot promise any benefits to you or others from your taking part in this research. However, taking part in this study may benefit you as the patient directly if you receive astaxanthin by providing decreased pain and improved physical function. Additionally, future patients could benefit from the results of this study if astaxanthin becomes part of the standard of care for osteoarthritis.

ALTERNATIVE (OTHER) TREATMENTS

The decision to participate in this study is entirely up to you. The alternative to participating in this study is simply not to participate. If you decide not to participate in the study, you will not be penalized in any way.

NEW INFORMATION

Your doctor will tell you about new information that may affect your willingness to participate in this research study. Alternatives, or other choices, concerning your care will be discussed at that time. There are no plans to share individual research results with you.

COST TO YOU FOR PARTICIPATING IN THIS STUDY

Subjects will not be responsible for the cost of the study drug or any fees associated with obtaining or analyzing the fluid sample. Study funds will pay for all study-related items and services required by the research.

We will bill you or your health insurer for items and services that are not part of the research and are part of your routine care. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. You will be responsible for the cost of any care not covered by insurance or study funds.

If you have any questions or are unsure about costs from taking part in the research, please speak with the study doctor or staff.

PAYMENT FOR PARTICIPATION

To You:

You will not be paid for participating in this study.

To Investigators:

The investigators will not be paid above their regular salaries for conducting this study.

COMPENSATION FOR INJURY AS A RESULT OF STUDY PARTICIPATION

Prisma Health will provide you the care needed to treat any injury, or illness, that directly results from taking part in this research study.

Injuries sometimes happen in research even when no one is at fault. The study sponsor, Prisma Health, or the investigators as part of this study have no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the 'Contact for Questions' section of this consent.

VOLUNTARY PARTICIPATION

Participation in this research study is voluntary. You may refuse to participate or withdraw from the study at any time. If you refuse to participate or withdraw from the study, you will not be penalized or lose any benefits and your decision will not affect your relationship with your doctor or hospital.

You can withdraw from this study at any time it will not affect your care. If you decide to withdraw from the study, there are no medical risks. If you agree to participate in the study, and then elect to withdraw, the data we have collected up until that point will be maintained for analysis. This data will be handled the same as research data; however, no further data will be collected from you after you withdraw.

However, if you decide to stop study participation, you are encouraged to talk with your doctor regarding safe removal from the study. Further treatment would be discussed at that time.

If your participation in this research study is stopped, your study doctor will discuss any tests or procedures that might be needed for your health and safety, but you may refuse any or all of these tests or procedures. Following this discussion with your study doctor, you still have the right to refuse any or all of these tests or procedures.

AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION

As part of this research study, the study doctor and his/her research team will keep records of your participation in this study. These study records may be kept on a computer and will include all information collected during the research study, and any health information in your medical records that is related to the research study. The study doctor and his/her research team will use and disclose (release) your health information to conduct this study. This study may result in scientific presentations and publications, but steps will be taken to make sure you are not identified.

Some of the organizations/entities that may receive your information are:

- The Institutional Review Board, which is a group of people who review research with the goal of protecting the people who take part in the study
- The Food and Drug Administration (FDA) and the groups it works with to review research.

Under federal privacy laws, your study records cannot be used or released for research purposes unless you agree. If you sign this consent form, you are agreeing to the use and release of your health information. If you do not agree to this use, you will not be able to participate in this study. Once your health information has been released, federal privacy laws may no longer protect it from further release and use.

The right to use your health information for research purposes does not expire unless you withdraw your agreement. You have the right to withdraw your agreement at any time. You can do this by giving written notice to the study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

If you have any questions about the privacy of your health information, please ask the study doctor.

CONTACT FOR QUESTIONS

For more information concerning this study and research-related risks or injuries, or to give comments or express concerns or complaints, you may contact the principal investigator, whose information is included below.

You may also contact a representative of the Prisma Health Office of Human Research Protection for information regarding your rights as a participant involved in a research study or to give comments or express concerns, complaints or offer input. You may obtain the name and number of this person by calling (864) 455-8997.

Principal Investigator Name: Daniel Del Gaizo, MD Telephone Number: 803-296-9210

CONSENT TO PARTICIPATE

The study doctor, _____, has explained the nature and purpose of this study to me. I have been given the time and place to read and review this consent form and I choose to participate in this study. I have been given the opportunity to ask questions about this study and my questions have been answered to my satisfaction. I have been given the opportunity to review my study doctor's Notice of Privacy Practices. I agree that my health information may be used and disclosed (released) as described in this consent form. After I sign this consent form, I will receive a copy of it for my own records. I do not give up any of my legal rights by signing this consent form.

_____
Printed Name of Participant

_____ _____ _____
Signature of Participant Date Time

_____
Printed Name of Investigator

_____ _____ _____
Signature of Investigator Date Time

Principal Investigator	Phone
Daniel Del Gaizo, MD	803-296-9210

Co-Investigators
The following co-investigators may be reached at 803-296-9210:
Corey Hamilton, MD