Title: Preoperative dietary fat consumption and baseline inflammatory markers in older patients presenting for major non-cardiac surgery: A pilot study of dietary-related risk factors for perioperative neurocognitive disorders in obese and normal body mass index (BMI) patients

BACKGROUND

Postoperative cognitive impairment (POCI) places a significant burden on patients, caregivers, and healthcare resources. Brief or persistent disruption in cognitive recovery is the most common postoperative complication in older surgical patients, with approximately *1 of every 2 patients potentially experiencing POCI in the highest risk populations* [1]. Postoperative declines in cognitive function are associated with alarming morbidity and mortality rates, including an increased susceptibility to developing Alzheimer's disease [2-5]. Furthermore, a diagnosis of delayed or impaired postoperative cognitive recovery is associated with more than $17,000 additional Medicare charges in the year following surgery [6] and with more than 19 million surgeries a year in patients >65 [7], this is a major public health concern. A multitude of factors contribute to risk of POCI, but the increased incidence and sequalae in older patients is thought to be due to convergent pro-inflammatory responses occurring with aging and perioperative exposure to stress, significant tissue trauma and physiological derangements, and medications with pro-inflammatory characteristics like opiates [8-10].

Diet is not currently emphasized as a significant or modifiable risk factor for postoperative cognitive impairment in older surgical patients. However, it is well known that consumption of diets high in saturated fats leads to increases in proinflammatory cytokines in the circulation and the brain [11-13]. Furthermore, overconsumption of saturated fats is a growing trend across all age groups including older adults, as they account for 55% of their daily calories [14-17]. A proinflammatory milieu has been repeatedly demonstrated through mechanistic and biomarker studies of perioperative cognitive dysfunction in older patients [18-20], but clinical studies on the direct role of diet or obesity status with an aging and cognitive recovery focus are missing from the perioperative literature, yet absolutely warranted based upon our preclinical work [21]. We have recently demonstrated that high-fat diet consumed prior to surgery caused exaggerated neuroinflammation and long-lasting memory impairment after surgery in older rats [21]. Furthermore, these effects were prevented by reducing the neuroinflammatory response either pharmacologically or by supplementing their diet with the omega 3 fatty acid, docosahexaenoic acid (DHA). Thus, we believe the balance of pro-inflammatory and anti-inflammatory effects of diet and nutritional status to be an additional convergent contributor with significant effects on postoperative cognitive recovery.

STUDY QUESTION:

This pilot study will 1) determine the feasibility of the Diet History Questionnaire-III (DHQ-III) for perioperative use and baseline observations of dietary fat consumption levels in geriatric patients; 2) measure levels of perioperative inflammatory markers in blood and cerebral fluid (CSF) in patients with normal body mass index (BMI), obese BMI, and patients with self-reported fat over-consumption 3) measure sample incidence of perioperative neurocognitive disorders in older patients with fat overconsumption including preexisting cognitive impairment, postoperative delirium, and persistent postoperative cognitive impairment, and 4) collect patient-reported considerations for future study of behavioral/dietary interventions in geriatric surgical candidates.

We hypothesize that a correlation will exist between BMI or fat over-consumption and proinflammatory blood and CSF markers in older patients presenting for elective surgery. Likewise, fat over-consumption will increase risk of perioperative neurocognitive disorders.

NULL HYPOTHESIS:
Diet-related information from patients is not easily assessed with the DHQ-III, and no preliminary relationships exist between BMI or fat over-consumption and proinflammatory blood and CSF markers. Likewise, no preliminary relationship exists between fat over-consumption and risk of perioperative neurocognitive disorders.

OBJECTIVES

Primary objective:

- To determine ability to assess important nutritional factors in older surgical patients including dietary levels of fat consumption, waist circumference, BMI, and frailty status prior to surgery for correlation with inflammatory markers in blood and CSF, before and after elective surgery.

Secondary Objectives:

- To estimate incidence of perioperative neurocognitive disorders in the pilot cohort of older surgical patients with obesity or fat-overconsumption.
- To evaluate patient perspectives on the importance of nutrition for recovery after surgery, experiences with dietary changes to improve health prior to any surgery, and willingness to take a supplement (DHA) prior to a future surgery.

EXPERIMENTAL METHODS

Study design:
A single center, prospective pilot study for the examination of dietary levels of fat consumption with correlation of inflammatory markers prior to surgery and incidence of perioperative neurocognitive disorders in older surgical patients.

Study Population:
Obese or normal weight patients over the age of 60 scheduled to undergo a major abdominal or pelvic surgery, or total hip or knee joint arthroplasty at OSUWMC and complete the study.

Sample size:
A total of 60 patients from the Ohio State University Wexner Medical Center (OSUWMC) will be included. In total, 30 subjects with BMI > 30 will be collected for the Obese Group and another 30 subjects for the normal BMI (25-30) group. In total, 15 subjects scheduled to undergo major abdominal or pelvic surgery

and 15 subjects scheduled to undergo total hip or knee joint arthroplasty will be recruited to each BMI group (Normal vs. >30 BMI). Assuming approximately 15% of consented patients either fail screening or do not complete the study after consent, we expect to consent 70 patients.

Table 1. Study population distribution.

N= 60	Obese (BMI >30)	Normal Group (BMI 25-30)
THA-TKA	15	15
Major abdominal or pelvic surgery	15	15

Experimental Methods:

This 60-patient pilot trial will be completed and analyzed over a 12-month period. Because the nutritional status and dietary habits could potentially be very different in patients, we are targeting these separate patient cohorts.

Detailed patient-reported diet information about the month preceding surgery using the "Diet History Questionnaire" **(Appendix C)** will be collected prior to surgery.

Blood draw collection – Up to 32 mL of blood will be collected. A maximum of 16 mL prior to surgery, and 16 mL the morning after surgery.

CSF sample collection - It is routine care at OSUWMC for patients undergoing TKA and knee arthroscopy or, major abdominal or pelvic surgery to receive preoperative neuraxial anesthesia for pain management. In placing the standard local anesthesia spinal block or intrathecal morphine injection, the subarachnoid space is accessed via a spinal needle [22]. Free flow of CSF from the needle is used to confirm that the subarachnoid space has been accessed [22]. In normal situations, this CSF is wasted. Therefore, the selected patient population is an ideal population to study CSF. Up to 1 mL of free flow CSF will be collected, then, the anesthetic/analgesic agent will be injected. CSF will be evaluated for inflammatory markers.

Evaluation of Perioperative Neurocognitive Disorders - A baseline preoperative telephone-Montreal Cognitive Assessment (T-MoCA, **Appendix B)** will be completed prior to surgery to classify participants as 'impaired' or 'not impaired'. We will complete a confusion assessment method assessment (CAM-3D, **Appendix A**) twice daily starting on the day of surgery (postoperative) until discharge day. In addition authorized research personnel will review electronic medical records after surgery to document any clinical delirium diagnostic and classify participants as 'delirium positive' or 'delirium negative'. At 3 months after surgery, the TMoCA will be repeated and compared to preoperative score for an estimate of persistent neurocognitive disorder.

DHQ-III will be administered before surgery. In addition, a patient-centered survey will be administered prior to discharge, we will ask patients about their interest in diet-related factors to support successful recovery after surgery and willingness to consider diet-changes and/or daily use of DHA supplementation for a future surgery, so we can refer them to the appropriate specialist.

Table 2. Scheduled of Procedures

Study Procedure	Screening Day -7 – Day 1	Pre-Op Surgery Day	Post-Op Surgery Day	PO Day 1	Day 2 through Discharge	Day 90 +/- 7 days Phone call Follow-up
Informed Consent & HIPAA	X	X				
Inclusion & Exclusion Criteria	X	X				
Demographics	X	X				
Medical History	X	X				
CSF sample collection		X				
Blood Draw sample collection		X		X		
t-MoCA		X				X
3DCAM Assessment			X (PM)	X (AM+PM)	X (AM+PM)	
DHQ-III		X				
Discharge survey					X (prior to discharge)	
Adverse Events			X	X	X	X

Statistical Method:
Data will be summarized using appropriate descriptive statistics, including means, standard deviations, medians, ranges, and proportions. Continuous data will explore using parametric or non-parametric ttests as appropriate. Categorical data will be presented as frequencies or proportions and explored using a chi-square or Fisher's Exact test. Logistic regression will be employed for patient characteristics, inflammatory markers, diet data, and outcomes to evaluate potential relationships with obesity groups. These analyses will be used to calculate descriptive effect size estimates; however, formal comparisons will be limited due to pilot sample size and study design. All statistical analyses will be performed using SAS/STAT software version 9.4 (SAS Institute Inc., Cary, NC).

Eligibility Criteria:

Inclusion Criteria:

1. ≥ 60 years of age or older
2. Capable and willing to consent
3. English speaking
4. Anticipated ASA physical status I-III
5. Scheduled to undergo major abdominal or pelvic surgery, or total hip or knee joint arthroplasty under general anesthesia with planned spinal anesthetic/analgesic.

Exclusion Criteria:

1. Illiterate
2. ASA physical status V, VI
3. Active Axis I or II psychiatric disorders including bipolar disorder, schizophrenia, dementia, alcohol, or drug abuse.
4. Preoperative benzodiazepine administration (i.e. Midazolam, Diazepam)
5. Past medical history of any inflammatory autoimmune disease processes (rheumatic arthritis (RA), systemic lupus erythematosus (SLE), autoinflamatory syndrome, etc.)

Knowledge Translation / Future Directions:

This pilot study will provide 3 critical pieces of information for future clinical trial design: 1) baseline observations of dietary fat consumption levels, overall nutritional status, and measurement of inflammatory markers in older surgical patients, 2) sample incidence of postoperative delirium and persistent neurocognitive disorder in older patients with fat overconsumption prior to surgery, 3) patient reported considerations for future study of behavioral/dietary interventions in older surgical candidates. It will inform study power and enrollment goals for a future large-scale randomized-controlled trial for further characterization and preoperative nutritional interventions.

Adverse Event Reporting:

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject. An AE can be any unfavorable and unintended sign, symptom, abnormal laboratory finding or a temporally disease associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Planned hospital admissions and/or surgical operations for an illness or disease that existed before the subject was enrolled in a clinical study are not to be considered as AEs.

All adverse events will be evaluated according to their relevance and significance to the study. They will be graded according to severity, expectedness, relation to the study treatment, and whether the event did or did not require additional treatment.

All unanticipated problems that meet the following criteria will be reported to the IRB:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigation Brochure, and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

A Severe Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Results in persistent or significant disability/incapacity.
- Requires in-subject hospitalization or prolongs hospitalization.
- Is a congenital anomaly/birth defect.
- Is another medically-significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Withdrawal Criteria from the study: According with the Declaration of Helsinki, participants have the right to withdraw from the study at any time for any reason. The principal investigator also has the right to remove a subject from the study. Reasons for which a subject may be removed from the study include:

- An adverse event
- The request of the subject, his/her legal representative or caregiver, investigator, whether for administrative or other reasons
- Non - compliance with medication, protocol violation or unreliable, behavior
- Any clinically significant abnormal laboratory values, or other clinically significant abnormalities identified by the principal investigator according to his clinical judgment, will be followed by appropriate tests and/or procedures until these values have returned to normal or to clinically acceptable levels or can be attributed to other causes other than study drug.

The principal Investigator may withdraw an enrolled and treated subject from the study for any of the following reasons:

- Occurrence of a serious or intolerable adverse event.
- Emergence of a clinically significant change in a laboratory parameter(s).
- The subject requests to be discontinued from the study.
- A protocol violation sufficiently serious as to require subject withdrawal. General or specific changes in the subject's condition that render further treatment unreasonable or unsafe within the standards of clinical practice in the judgment of the Principal Investigator or treating physician. Any subject may leave the study at any time. If the subject decides to stop participating in the study, there will be no penalty. The subjects will not lose any benefits to which they are otherwise entitled.

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Appendix A. Confusion Assessment Method (3D-CAM)

3D CAM ASSESSMENT [CAM Copyright 2003, Hospital Elder Life Program, LLC. Not to be reproduced without permission]						
Coding Instructions: Incorrect also includes "I don't know", and No response/non-sensical responses. For any 'Incorrect' or 'Yes' responses, check the box in the final column designating which feature is present.			CAM Feature			
READ: **I have some questions about your thinking and memory....**			1	2	3	4
1. Can you tell me the year we are in right now?	☐ Incorrect	☐ Correct				
2. Can you tell me the day of the week?	☐ Incorrect	☐ Correct				
3. Can you tell me what type of place is this? [hospital]	☐ Incorrect	☐ Correct				
4. **I am going to read some numbers. I want you to repeat them in backwards order from the way I read them to you. For instance, if I say "5 – 2", you would say "2 -5". OK? The first one is "8-2-5" (5-2-8).**	☐ Incorrect	☐ Correct				
5. **The second is "3-1-9-4" (4-9-1-3).**	☐ Incorrect	☐ Correct				
6. **Can you tell me the days of the week backwards, starting with Saturday?** [S,F,T,W,T,M,S] *may prompt with "what is day before ...." for up to 2 prompts.*	☐ Incorrect	☐ Correct				
7. **Can you tell me the months of the year backwards, starting with December?** [D,N,O,S,A,J,J,M,A,M,F,J] *may prompt with "what is month before ...." for up to 2 prompts.*	☐ Incorrect	☐ Correct				
8. **During the past day have you felt confused?**	☐ Yes	☐ No				
9. [IF Q3 is "Incorrect", do not ask and check "Yes", otherwise, ASK:] **During the past day did you think that you were not really in the hospital?**	☐ Yes	☐ No				
10. **During the past day did you see things that were not really there?**	☐ Yes	☐ No				
Observer Ratings: To be completed after asking the patient questions 1-10 above.						
11. Was the patient sleepy, stuporous, or comatose during the interview?	☐ Yes	☐ No				
12. Did the patient show excessive absorption with ordinary objects in the environment (hypervigilant)?	☐ Yes	☐ No				
13. Was the patient's flow of ideas unclear or illogical, for example tell a story unrelated to the interview (tangential)?	☐ Yes	☐ No				
14. Was the patient's conversation rambling, for example did he/she give inappropriately verbose and off target responses?	☐ Yes	☐ No				
15. Was the patient's speech unusually limited or sparse? (e.g. yes/no answers)	☐ Yes	☐ No				
16. Did the patient have trouble keeping track of what was being said during the interview?	☐ Yes	☐ No				
17. Did the patient appear inappropriately distracted by environmental stimuli?	☐ Yes	☐ No				
18. Did the patient's level of consciousness fluctuate during the interview, for example, start to respond appropriately and then drift off?	☐ Yes	☐ No				
19. Did the patient's level of attention fluctuate during the interview, e.g., did the patient's focus on the interview or performance on the attention tasks vary significantly?	☐ Yes	☐ No				
20. Did the patient's speech/thinking fluctuate during the interview, for example, patient spoke slowly, then spoke very fast?	☐ Yes	☐ No				
OPTIONAL QUESTIONS: COMPLETE ONLY IF FEATURE 1 IS NOT CHECKED AND FEATURE 2 IS CHECKED AND EITHER FEATURE 3 OR 4 IS CHECKED						
21. Contact a family member, friend, or health care provider who knows the patient well and ask: "Is there evidence of an acute change in mental status (memory or thinking) from the patient's baseline?"	☐ Yes	☐ No				
22. IF SECOND DAY OF HOSPITALIZATION OR LATER AND PREVIOUS 3D-CAM RATINGS ARE AVAILABLE: Review previous 3D-CAM assessments and determine if there has been an acute change in performance, based on ANY new "positive" items	☐ Yes	☐ No				
CAM Summary: Check if Feature Present in column above			1	2	3	4
DELIRIUM REQUIRES FEATURE 1 AND 2 and EITHER 3 OR 4: _____ Present _____Not Present						

Appendix B. Telephone-Montreal Cognitive Assessment (T-MoCA)

MONTREAL COGNITIVE ASSESSMENT / MoCA-BLIND
Version 7.1 Original Version

Name:
Education:
Sex:
Date of birth:
Date:

MEMORY		FACE	VELVET	CHURCH	DAISY	RED	**POINTS**
Read list of words, subject must repeat them. Do 2 trials even if 1st trial is successful. Do a recall after 5 minutes.	1st trial						No points
	2nd trial						

ATTENTION

Read list of digits (1 digit/sec.) Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/ 2

Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/ 1

Serial 7 subtraction starting at 100

[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/ 3

LANGUAGE

Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/ 2

Fluency / Name maximum number of words in one minute that begin with the letter F.
[ ] _____ (N ≥ 11 words) ___/ 1

ABSTRACTION

Similarity between e.g. banana - orange = fruit
[ ] train - bicycle
[ ] watch - ruler ___/ 2

DELAYED RECALL	Has to recall words **With no cue**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/ 5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/ 6

 www.mocatest.org Normal ≥ 18 / 22

TOTAL ___/ 22
Add 1 point if ≤ 12 yr edu

Administered by:_____

Appendix C. Diet History Questionnaire (file attached)