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Effect of NMN Supplementation on Metabolic and Muscle Function in Prediabetes

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CONTRACTING ORGANIZATION: Washington University School of Medicine

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13. SUPPLEMENTARY NOTES

We have experienced delays in VASTLHCS IRB/RDC approval processes, due to issues related to the Covid-19 response.

14. ABSTRACT

The overall goal of the study is to expand our pilot clinical study and further evaluate the translation of our preclinical findings of NMN supplementation on metabolic health in rodents to clinical therapy in people. To this end, we will conduct a randomized placebo-controlled trial in men and women with prediabetes to assess the effect of NMN supplementation on key metabolic, mitochondrial and inflammation outcomes in collaboration with VA St. Louis Health Care System (VASTLHCS). We coordinated the implementation of the research protocol with Washington University (WU) and VASTLHCS; finalized the study protocol and informed consent form to be used at WU and VASTLHCS; obtained WU IRB approval (December 5, 2019), VASTLHCS IRB (March 17, 2020), and VASTLHCS RDC (April 24, 2020); had obtain obtained a WOC appointment at VASTLHCS for three WU study team members; and obtained DoD HRPO approval (September 19, 2020). The study is registered at ClinicalTrials.gov. We are actively recruiting study participants.

15. SUBJECT TERMS

Prediabetes, insulin sensitivity, and NMN supplementation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Contents

1. INTRODUCTION

Prediabetes has become a major public health problem in the U.S. and among US Military Veterans because of its high and increasing prevalence, causal relationship with serious medical complications and increased risk of developing type 2 diabetes (T2D). Prediabetes is associated with a constellation of metabolic abnormalities, including insulin resistance, β-cell dysfunction, mitochondrial dysfunction, inflammation, atherogenic dyslipidemia (high triglycerides and low HDL-cholesterol), and nonalcoholic fatty liver disease (NAFLD), and about 5-10% of people with prediabetes convert to T2D every year. Accordingly, therapies that can improve metabolic function in people with prediabetes have important implications for improving metabolic health and preventing the development of T2D. Although weight loss is the cornerstone of therapy for patients with prediabetes lifestyle intervention programs designed to promote weight loss within the VA population have not demonstrated long-term clinical efficacy for weight or metabolic outcomes. Therefore, additional safe and effective treatments for prediabetes are needed. Inadequate NAD^+ biosynthesis is associated with metabolic abnormalities in rodent models. We have found administration of NAD^+ precursor (e.g., Nicotinamide mononucleotide, NMN) increases NAD^+ concentrations in key metabolic organs and improves age-induced or diet-induced metabolic dysfunction in rodent models. The overall goal of this proposal is to assess whether beneficial effect of NMN supplementation on metabolic health and inflammation in rodents translate to people. To this end, we will conduct a randomized placebo-controlled trial in men and women with prediabetes to assess the effect of NMN supplementation on key metabolic, mitochondrial and inflammation outcomes. Due to issues related to the Covid-19 response, we have experienced delays in VASTLHCS IRB/RDC approval processes, that affected timing of DoD HRPO initial submission. After obtaining DoD HRPO approval in September 2020, we are now actively recruiting participants for this study.

2. KEYWORDS

Prediabetes, insulin resistance, NMN supplementation, and metabolic dysfunction

3. ACCOMPLISHMENTS

a. What were the major goals of the project?

		Research Sites	
	Timeline	**WU**	**VA**
Major Task 1: Initiate study	Months		
Coordinate research plan and implementation between WU and VA sites	1	Completed	Completed
Finalize consent form & human subjects protocol	1-2	Completed	Completed
Coordinate with Sites for IRB protocol submission	1-2	Completed	Completed
Submit amendments, adverse events and protocol deviations as needed	As needed	As needed	As needed
Coordinate with Sites for annual IRB report for continuing review	Annually	Oct 2020	March 2021
Milestone Achieved: Local IRB and HRPO approval at WU and VA	3	Dec 2019	April 2020
Major Task 2: Conduct Randomized Controlled Trial	Months		
Begin subject recruitment	4-40	Sept 2020	
Continue enrollment, baseline testing, randomization, treatment intervention and follow-up testing	4-42		
Milestone Achieved: final participant consented, screened, and enrolled in study	36-39		
Milestone Achieved: final participant completes study	39-42		

We have achieved the major goals stated in the approved SOW of the project. We recently started subject recruitment and will continue recruitment, enrollment, randomization, treatment, and follow-up testing to achieve milestones under Major Task 2 within the proposed time frame.

b. What was accomplished under these goals?

1) Major activities. The following has been accomplished: i) coordinated the implementation of the research protocol with Washington University (WU) and VASTLHCS; ii) finalized the study protocol and informed

consent form to be used at WU and VASTLHCS; iii) obtained WU IRB approval (December 5, 2019), VASTLHCS IRB (March 17, 2020), and VASTLHCS RDC (April 24, 2020); iv) obtained a WOC appointment at VASTLHCS for three WU study team members; v) obtained DoD HRPO approval (September 19, 2020; and vi) initiated study subject recruitment. We made several amendments that were submitted to the IRB at both research sites, including VA PI change, which was approved by the DoD HRPO.

2) Specific objectives: We have achieved Major Task 1, "Initiate study". We recently initiated subject participant recruitment needed to achieve milestones listed in Major Task 2, "Conduct Randomized Controlled Trial". In addition, three WU study team members obtained WOC status at VASTLHCS to enhance research coordination between WU and VASTLHCS.
3) Significant results or key outcomes, including major findings, developments, or conclusions: Not applicable.
4) Other achievements: Major tasks stated in the approved SOW were mostly met, with the exception that we were not able to start study subject recruitment until recently. The delay was caused by delays in local IRB review processes due to issues related to the Covid-19 response occurred in the early spring of 2020. Recruitment at has not yet started, but will begin after data use agreement between WU and the VASTLHCS obtains approval. We believe we can achieve Major Task 2, within the time frame proposed in the approved SOW.

c. What opportunities for training and professional development has the project provided?
Nothing to report

d. How were the results disseminated to communities of interest?
Nothing to report during this reporting period

e. What do you plan to do during the next reporting period to accomplish the goals?
We will continue recruitment, enrollment, randomization, treatment, and follow-up testing to achieve milestones proposed in the approved SOW within the time frame.

4. IMPACT

a. What was the impact on the development of the principal discipline(s) of the project?
Nothing significant to report during this reporting period

b. What was the impact on other disciplines?
Nothing significant to report during this reporting period

c. What was the impact on technology transfer?
Nothing significant to report during this reporting period

d. What was the impact on society beyond science and technology?
Nothing significant to report during this reporting period

5. CHANGES/PROBLEMS

We have reported and obtained prior written approval from the awarding agency when we had significant changes in the project.

a. Changes in approach and reasons for change
Nothing to report

b. Actual or anticipated problems or delays and actions or plans to resolve them
We have experienced delays in VASTLHCS IRB/RDC approval processes, due to issues related to the Covid-19 pandemic. The continuing spread of Covid-19 remains a public health problem. We will follow Covid-19 guidelines and recommendations in conducting our studies.

c. Changes that had a significant impact on expenditures
Nothing to report

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

6. PRODUCTS

a. Publications, conference papers, and presentations
Nothing to report

b. Website(s) or other Internet site(s)
Nothing to report

c. Technologies or techniques
Nothing to report

d. Inventions, patent applications, and/or licenses
Nothing to report

e. Other Products
Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: Samuel Klein, M.D.
Project Role: Principal Investigator
Research Identifier: 0000-0001-7127-1156
Nearest person month Worked: 1.8
Contribution to Project: Dr. Klein developed the study protocol and the collaborative relationship between WU and VA STLHCS. He provides supervision for all aspect of the study, including medical supervision.
Funding support: Nothing to report

Name: Mihoko Yoshino, M.D., Ph.D.
Project Role: Co-Investigator
Research Identifier: 0000-0003-4123-7699
Nearest person month Worked: 6.0
Contribution to Project: Dr. Yoshino has worked with local and DoD HRPO officers and will conduct studies.
Funding support: Nothing to report

Name: Jun Yoshino, M.D., Ph.D.
Project Role: Co-Investigator
Research Identifier: 0000-0001-9833-4356
Nearest person month Worked: 1.8
Contribution to Project: Dr. Yoshino has worked on research method development for the study.
Funding support: Nothing to report

Name: Shin-Ichiro Imai, M.D., Ph.D.
Project Role: Co-Investigator
Research Identifier: 0000-0003-3742-5777
Nearest person month Worked: 1.2
Contribution to Project: Dr. Imai has worked on research method development for the study**.**
Funding support: Nothing to report

Name: Mauricio Lisker-Melman, M.D.
Project Role: VA Principal Investigator

Research Identifier: 0000-0001-7929-6841
Nearest person month Worked: 0.5
Contribution to Project: Dr. Lisker-Melman is a VA PI who has organized set up at VA STLHCS. He will supervise study team and provide medical supervision at VASTLHCS.
Funding support: Nothing to report

Name: Sally Torbitzky, RN
Project Role: Study coordinator
Nearest person month Worked: 1.2
Contribution to Project: She will develop recruitment strategies for the study and coordinate study visits.
Funding support: Nothing to report

Name: Janet Winkelmann
Project Role: Study coordinator
Nearest person month Worked: 1.2
Contribution to Project: She will develop recruitment strategies for the study and coordinate study visits.
Funding support: Nothing to report

Name: Bruce Patterson, Ph.D.
Project Role: Co-investigator
Research Identifier: 0000-0001-9261-0233
Nearest person month Worked: 0.2
Contribution to Project: Dr. Patterson will supervise lab technicians and analyze tracer kinetics for the study.
Funding support: Nothing to report

Name: Ken Schechtman, Ph.D.
Project Role: Study statistician
Nearest person month Worked:0.1
Contribution to Project: Dr. Schechtman will supervise statistical analyses for the study.
Funding support: Nothing to report

Name: Jessica Britt, N.P.
Project Role: Study nurse practitioner
Nearest person month Worked: 2.0
Contribution to Project: She will perform medical procedures and provide medical supervision for the study subjects.
Funding support: Nothing to report

Name: Miranda Giuffrida, N.P.
Project Role: Study nurse practitioner
Nearest person month Worked: 2.0
Contribution to Project: She will perform medical procedures and provide medical supervision for the study subjects.
Funding support: Nothing to report

Name: Freida Custodio
Project Role: Lab technician
Nearest person month Worked: 1.8
Contribution to Project: She will perform laboratory assays necessary for the study.
Funding support: Nothing to report

Name: Michael Franczyk
Project Role: Lab technician
Nearest person month Worked: 6.0
Contribution to Project: He will perform laboratory assays necessary for the study.
Funding support: Nothing to report

Name: Kathryn Mills
Project Role: Lab technician
Nearest person month Worked: 0.2
Contribution to Project: She has worked to optimize laboratory techniques necessary for the study.
Funding support: Nothing to report

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Samuel Klein, MD
NIH R01 DK101578 *"Weight Loss-Independent Metabolic Effects of RYGB in Diabetes"* ended 07/31/2020
NIH R44 DK108308 sub award *"Assessment of Multiple Dose Administration of Glucagon Receptor Blocker REMD477 in Type 1 Diabetes"* support ended 6/30/2020
NIH P01 DK078669 "*Metagenomic Studies of the Gut Microbiomes of Obese and Lean Twins"* support ended 06/30/2020

c. What other organizations were involved as partners?
Organization Name: Department of Veterans Affairs St. Louis Health Care System
Location of Organization: 915N Grand Blvd, St. Louis, MO 63106
Partner's contribution to the project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

Nothing to report