Cognitive Improvements in Patients with Mild Cognitive Impairment and Alzheimer's Disease though a Personalized Mito Food Plan Diet and Cell Repair Therapy

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Abstract

Currently, over 50 million people worldwide are diagnosed with Alzheimer's Disease (AD) and more than 16 million Americans suffer from Mild Cognitive Impairment (MCI). Despite unremitting scientific and clinical efforts, there has yet to be therapy that has abated disease progression. Currently there are no FDA approved medications for MCI and it has been over 15 years since a new therapy has been commercially available for AD. In the last two decades, clinical trials have focused on beta amyloid (Aβ), which has been known to play a key role in the pathogenesis of AD; however, drug therapies in AD research have had a 99.6% failure rate. With continuous and recent clinical trial failures, designing a clinical trial to examine different etiologies and studying underlying causes is warranted. In this study, 3 MCI and 2 AD patients who met eligibility criteria underwent cognitive and physiological testing, as well as cellular health assessments to test degrees of cognitive impairment, chronic inflammation, oxidative stress, metabolic issues, and cellular health. All study patients were then provided with a personalized Mito Food Plan, and four of the five subjects adjunctively underwent Cellular Repair Therapy. Results demonstrated significant improvements in cognitive testing scores, Quality of Life and reduction of chronic inflammation.

Introduction

Mild cognitive impairment (MCI) causes a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills. People affected by MCI have a four-fold increased risk of developing dementia or Alzheimer's disease (AD) compared to cognitively healthy individuals (1). Although it is unknown if AD is the leading cause of MCI, recent evidence has shown that MCI often occurs due to the same type of brain damage found in

Alzheimer's disease and other forms of dementia (2). There are currently no accepted treatments for MCI, nor are there any treatments that have demonstrated prevention of progression to AD, which is the leading cause of dementia worldwide. AD is considered the most prevalent neurodegenerative disorder, progressing from inconsiderable memory loss to eventually death, and has become the most expensive disease in America (3). At the microscopic and imaging level, the core hallmarks of AD are characterized by hyperphosphorylated and misfolded tau proteins and accumulated beta amyloid (Aβ). For the last two decades, beta amyloid has been the primary paradigm of AD research; however, since 2003, over 250 compounds in more than 400 clinical trials (Phases 1-3) of potential new AD treatments have been studied, with only one (memantine) leading to FDA approval (4). This 99.6% clinical trial failure rate is the highest of all diseases including cancer (81% failure rate) (5), suggesting that beta amyloid may not be the cause of the disease, and specific etiologies that have been suggested to be prominent in the pathogenesis of AD need to be more thoroughly studied. Chronic inflammation, for example, initiated by infection, virus, toxins or autoimmunity, has been known to contribute to the weakening of the blood brain barrier, causing neurodegeneration and neuroinflammation. This eventually leads to a weakened immune system, contributing to several diseases including Alzheimer's Disease (6). Metabolic dysfunction, such as uncontrolled progressive weight gain and abnormal glucose tolerance, have also been linked to the incidence and progression of neurodegeneration, negatively impacting overall prognosis of AD (7). In addition, oxidative stress, which can occur as a result of increased free radicals, and damaging of mitochondria, has also been deemed to be a prominent early event in the pathogenesis of AD (8). To date, failure to treat MCI and AD effectively may be due to poor understanding of the mechanisms that cause the disease, or that existing diagnostic criteria exclude factors of etiologic importance such as tackling inflammation, metabolic dysfunction, and oxidative stress collectively. In addition, other than failed anti-inflammatory medications, there has been a lack of treatments including non-drug therapies and diets that have been utilized in previous studies. Although diet has been suggestive in being a component in cognition and disease progression, there has yet to be a specific diet that has been universally studied in both MCI and AD. Although macronutrient and micronutrient intake has been examined in relation to the risk of developing dementia or MCI, such as carbohydrate intake being linked to a higher cognitive risk and higher percentage of protein and fat intake linked to a relatively lower risk (9), a specific diet

plan tailored exclusively to each individuals' physiological body results has yet to be studied in the AD population.

The Mito-AD-01 study (clinical trial NCT03630419) was conducted in hopes of determining that oxidative stress and inflammation could be measured and ameliorated through specific, individualized treatment; therefore, improving all around cognition and mental clarity in patients with MCI and AD. Since diet has been thought to play a role in decreasing cognitive decline, a specific Mito Food plan geared to decrease inflammation and work on mitochondria was created for each subject based on individual physiological and metabolic results. Cellular Repair therapy was also implemented as an adjunctive therapy to incorporate an all-encompassing non-drug, quickly implemented treatment that could slow disease progression and even improve cognition in those with MCI and AD.

Methods/Materials

Subjects

Eligible patients, 50-90 years of age who met criteria for mild to moderate probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria, were enrolled. Eligible MCI patients had to be clinically diagnosed with amnestic MCI as defined and documented by their neurologist. All patients were required to have a Mini Mental State Examination (MMSE) score greater than 24 and score greater than a 10 on the Montreal Orientation Cognitive Assessment (MoCA) at screening to meet study eligibility. Additional inclusion criteria included scoring a 4 or greater on the Constructional Praxis exam portion of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) test. Study participants were also required to provide informed consent and (a caregiver/significant other) keep track of their daily food intake (Mito Food Plan Diary). In addition to meeting eligibility criteria, study subjects had to avoid high-intensity activity 24 hours prior to day of comprehensive body assessment and had to avoid all physical exercise for at least three hours prior. Treatment with approved or off label use of AD medications or anti-inflammatory supplements were permitted as long as they were on a stable dose for at least 3 months prior to screening. All study procedures were approved by the Western Institutional Review Board (WIRB) and were conducted with the understanding and consent of all subjects. Informed consents were obtained from all individuals in accordance with

institutional review board requirements prior to the start of any study-related procedures at screening.

Study Procedures

Prior to enrollment, potential subjects were evaluated, screened, and consented. Medical history was captured, and a physical and neurological exam was performed at screening. A Mini-Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment in Cognition (ADAS-Cog) constructional praxis, and Quality of Life in AD (QOL-AD) questionnaires were completed for eligibility purposes and for baseline measures. All subjects who met study eligibility underwent Cellular and Physiological Comprehensive Body Assessments at Cerulean Advanced Wellness and Fitness. These comprehensive assessments included a series of non-invasive Physiological and Cellular Health tests that were able to measure body fat, lean muscle, total body water, cellular health index, inflammation, and body hydration through Bioelectrical Impedance Analysis (BIA), manufactured by the BodyStat QuadScan 4000. An electrocardiograph (ECG) and hemodynamic diagnostics such as heart rate (HR), blood pressure (BP) and arterial oxygen saturation (SpO2) were also recorded for safety measures. Once these assessments were completed and analyzed, each study subject was given a specific Mito Food Plan. The Mito Food Plan was created based on individual subject assessments and results. Caloric intake was based on Resting Metabolic Rate (RMR), Respiratory Quotient (RQ), and Metabolic Efficiency (ME) as measured through RMR testing. Daily recommended servings of specific macronutrients varied for each subject. Since the macronutrient recommendations yielded from the RMR and BodyStat results, the Mito Food Plan was individualized to each subject's physiological body results. All subjects were required to fill out a daily diet dairy which was reviewed at each visit. Four of the five subjects opted to undergo adjunctive Cellular Repair Therapy for 30 minutes 3 times a week for a total of 12 weeks.

Bioelectrical Impedance Analysis (BIA)

Bioelectrical Impedance Analysis (BIA) is a non-invasive and objective tool that measures reactance and resistance at difference frequencies against the various tissues in the body. Given its simplicity and reliability, BIA has become a widespread technique, both in clinical and non-clinical settings, to verify body composition and detect the percentage of Fat Mass (FM) and Free-Fat Mass (FFM). (10)

This assessment also determines chronic inflammation by how well nutrients can infiltrate and nourish cells by measuring the ratio of intracellular versus extracellular water. Cellular Health was also measured through BIA by determining Phase Angle and Prediction Markers. Phase Angle measures the integrity of the cell membranes and how well they function, which degrades with age, poor diet, and various medical conditions. Prediction Marker is a powerful diagnostic tool that can predict the risk of chronic and degenerative medical conditions. BIA was utilized for body composition since it is more accurate than BMI. While BMI only takes height and weight into account, the BIA is a test that considers a person's height, weight, body type, gender, age, and fitness level. Furthermore, BMI does not give an accurate result as it is limited to few factors. BIA, on the other hand has only 3% to 4% margin error. However, there are other factors that can have an impact on the reading such as dehydration, eating, or exercising prior to testing. Therefore, all subjects were required not to exercise 24 hours prior and not to eat 3-5 hours prior to testing. The BIA measures body composition by sending a very small electrical signal at 50kHz through two outer pairs of electrodes placed on the right wrist and right ankle. Two inner pairs of electrodes detect resistance to the introduced signal as a function of body conductance, measuring resistance and reactance. The resistance reflects extracellular space, and the reactance indicates cellular activity (11). These currents are conducted almost completely through the fluid compartment of the fat-free mass, which is an equivalent of total body water (TBW). It measures the flow of current through the body (impedance) and is dependent on the frequency applied. Fat contains less water than the rest of the body; hence it takes longer for the electrical signal to pass through it. By measuring the time, it takes for the signal to pass through the body, and taking into account the person's height, weight, body type, gender, age, and fitness level, it calculates the percentage of body fat, fat-free mass, hydration level, and other body composition values.
It measures the impedance and by applying predictive equations, it estimates both ECW and TBW (Total Body Water) respectively and by deduction, ICW. ECW can be related to Extra-Cellular Mass and ICW to Body Cell Mass. This calculation was able to determine cellular health along with inflammation in all subjects at Baseline, Week 8 and Week 12.

Metabolic Function Testing

Resting Metabolic Rate (RMR) was tested for an objective measurement of metabolism through Ultima™ CardiO2® gas exchange analysis system. This machine measures resting energy metabolism through the measurement of oxygen (O2) consumption and carbon dioxide (CO2)

production. Each subject was required to wear a flow sensor mask for 20 minutes. From the measurement of VO2 and VCO2, the resting energy expenditure (REE) was calculated to assess energy fuel utilization and energy expenditure. In the body, the calories from food are burned in the presence of oxygen, and because the process of oxidation in the body is well understood, the amount of total heat or energy produced by the body at rest (RMR) can be measured. Energy produced by the body at rest is measured from the measured amounts of oxygen consumed and the carbon dioxide produced (exhaled). Resting metabolism occurs in a continual process 24 hours a day and remains relatively constant over time. Resting metabolism is the largest component (typically 60 to 70 percent) of "calories out" in the energy equation. Performing an RMR assessment allowed for an individualized predictable approach to how many calories and macros each subject should consume during the course of the study. In order to determine the exact amount of caloric intake a subject was allotted, the level of physical activity, otherwise known as the activity coefficient was also factored in; however, all six of the study subjects had little to no physical activity. Once each subject's RMR and body composition values were calculated, a Mito Food Plan was designed and reviewed with each subject and was implemented immediately following Baseline.

Treatments

The Mito Food Plan

Diet has been suggestive in playing a large role in cognition and disease progression, and a variety of natural antioxidants that exist in foods have been known to reduce oxidative stress levels in the brain, as well as have anti-inflammatory effects. (12, 13). The Mito Food Plan is described as an anti-inflammatory, low-glycemic, gluten-free, low-grain, high-quality fat approach to eating. Developed by physicians and nutritionist from The Institute for Functional Medicine, this food plan focuses on supporting healthy mitochondria through the use of therapeutic foods that improve energy production. This specific food plan was utilized for this study since it has been known to improve brain function, decrease inflammation and inflammation cytokines from infection (14). It also provides key vitamins, antioxidants, and dietary fiber for detoxification, in hopes of repairing and grow cell energy (mitochondria) found in every cell. The plan focuses on providing 60% of calories from healthy fats, 20% from protein, and 20% from complex carbohydrates. It is similar to the Mediterranean and Paleo diet; however, the Mito food plan avoids all grains, is gluten-free and more importantly, focuses on

healthy fats and anti-inflammatory therapeutic foods. The vegetables the diet plan focuses on requires a rainbow of colors in a day to provide key vitamins and antioxidants. During this study, subjects were required to eat all organic, all natural, non- Genetically modified organisms (GMO), free-range, grass-fed, organically grown animal and plant and wild-caught protein. Through establishing each individual's metabolism, and the minimum number of calories determined to support physiological function, a specific Mito Plan diet was created for each subject, through breakdown of proteins, fats, and non-starch carbohydrates.

Cellular Repair Therapy (NanoVi ™)

Oxygen metabolism is involved in cell metabolism and is essential for energy production (ATP); however, it generates oxidative stress by producing free radicals. To minimize cellular damage caused by free radicals, the body relies on two phases of oxidative response. Oxidative response is the body's natural defense against damage caused by free radicals which are also called reactive oxygen species (ROS). The first phase is to avoid damage by neutralizing reactive oxygen species (ROS), the second phase of oxidative response is to repair unavoidable damage (15). Repair is initiated through biological signaling from certain ROS. Unfortunately, with age, mitochondria degrades and becomes dysfunctional, damaged and has become a primary cause of age-related decline (15). A myriad of recent scientific reports has linked defective and deficient mitochondria to virtually all degenerative diseases including Alzheimer's, type 2 diabetes, heart failure, and cancer (16). Prior to Eng3's NanoVi™ Cellular repair therapy, the only natural ways to stimulate mitochondrial biogenesis was from calorie restriction or extensive physical activity.

In this study, treatment with the NanoVi™, a cellular repair therapy device manufactured by Eng3, was utilized on four of the five patients. The NanoVi™ is a class one FDA approved device that assists with the second phase of oxidative response caused by oxidative stress. It was utilized in this study because it is the only technology to precisely produce ROS-specific signal without generating any damaging ROS. The NanoVi™ technology mimics a biological process that has been known for many decades, as a physical repair process, not a chemical interaction, that repairs damaged proteins in cells by helping proteins refold back into their correct shape, which allows proteins to function correctly. Previous studies with the NanoVi™ confirm the positive impact on cellular activity by essentially being bio-identical. The bio-identical signal is transferred from the NanoVi™ device to the patient by humidity in an airstream. This signal

connects through the mucus membrane and cascades throughout the body. The use of near infra-red light, without the use of any drug or pharmaceutical, mimics a naturally occurring signal that cells produce and use. This patented technology utilizes an airstream with increased humidity to deliver the signal through the mucous membranes of the body. The device contains distilled water in the humidifier which is changed daily. The NanoVi™ device delivers humidified air through the flex-air. A nasal cannula is attached to the flex-air. Each subject had their own nasal cannula for sanitary purposes. A technician at Cerulean Advanced Fitness and Wellness ensured that each subject correctly inserted the nasal cannula and started the therapy. A self-test ran for 10 seconds prior to each session to make sure the cannula was properly placed. In this study four out of the five patients underwent Cellular Repair therapy. Subject #001 was not able to participate due to conflicts with his work schedule. All subjects who participated came to Cerulean Advanced Fitness and Wellness, three times a week for 12 weeks. Therapy was administered to each subject for 30 minutes each visit, in a relaxing, private room.
The objective of utilizing this cell repair therapy was to support the body's own processes to repair protein structures and maintain the health of the DNA, both of which have been damaged by internal and external factors. By doing so, it is surmised that protein functions are restored, DNA is repaired, cellular activity improves, and health can be maintained; possibly improving inflammation and cognition.

Results

Subject Recruitment

A total of 5 subjects were enrolled during a 6-month period between January 2018 and June 2018. Eleven patients were initially recruited; however, only 5 patients met criteria and were interested in participation. Three of the five subjects were medically diagnosed with Mild Cognitive Impairment and two were medically diagnosed with Alzheimer’s Disease based on criteria from the Alzheimer's Association and the National Institute on Aging (NIA), an agency of the U.S. National Institutes of Health (NIH). All five patients followed an individualized Mito Food Plan, and on average were 81% compliant with their diet. Four of the five patients received adjunctive Cellular Repair Therapy (NanoVi™). All patients completed the full 12 weeks of therapy and study procedures. All study procedures were completed at each visit for each subject. Four out of the five subjects experienced an adverse event; however, all AEs that were possibly or probably related to therapy were considered mild in severity.

Subject Baseline and Disease Characteristics

The mean age of the study subjects was 71.6 years old (SD 6.07). The ratio of males to females was 4:1. Both study subjects diagnosed with AD, had immediate family members pass away from AD. All subjects had a family history of coronary heart disease and cancer. Eighty percent of study subjects have coronary heart disease (CAD) and are currently under medical treatment. Sixty percent of the subjects were currently taking hypertension medication, and all 5 subjects were taking a statin for their hypercholesterolemia during the course of the study. All patients who were being treated with a statin suffered from lower extremity pain. Sixty percent of the patients were being treated with Metformin for their diabetes, of which, one patient complained of blurred vision, neuropathy and foot ulcers caused by history of hyperglycemia. Three subjects had anxiety, and two subjects suffered from mild depression. Both patients with AD were recently diagnosed, (2015 and 2017 respectively); however, have been symptomatic for an average of 6.5 years. All subjects diagnosed with MCI have had symptoms for an average of 2.7 years but have only been recently diagnosed (2015 and 2016 respectively). None of the subjects were currently being medically treated for their MCI during the duration of the study; however, both subjects with AD were under medical management for their AD.

Effects of Therapy on Disease Progression

MMSE and MOCA testing was administered at Screening, Week 8 and Week 12 for all subjects. As illustrated in Figures 1 and 2, scores for both MoCA and MMSE improved from Screening to Week 8 for all patients over the course of treatment and statistically improved in 80% of the subjects from Screening to Week 12 ($p=.008$, $p=.007$). Subject #05 was the only subject whose scores decreased from Week 8 to Week 12. This was attributed to the subject's lack of diet compliance for three weeks (53%) prior to Week 12 due to being on vacation. The subject also consumed a diet rich in simple carbohydrates and no lean protein or healthy fat the night before. Interestingly, he also had an increase in his A1c over the course of the study and missed three weeks of cellular repair therapy between his Week 8 and Week 12 visit.

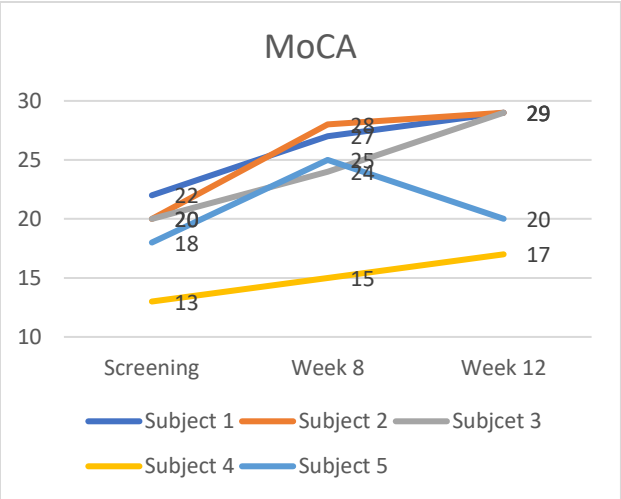

Figure 1: MoCA Scores for all Subjects from Screening to Week 12

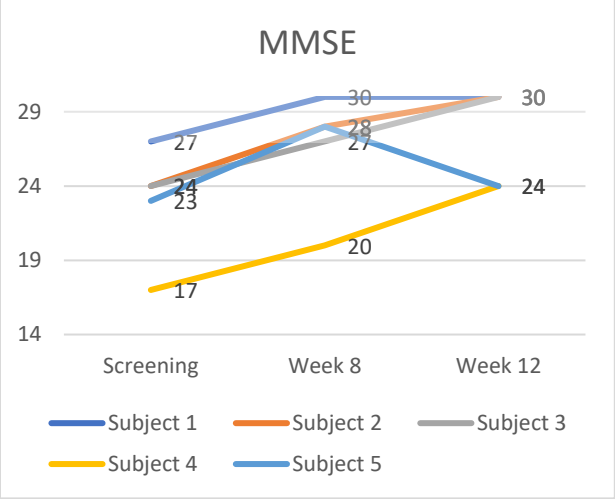

Figure 2: MMSE Scores for all Subjects from Screening to Week 12

Quality of Life of AD (QOL-AD) was also administered at Screening, Week 8 and Week 12 (Figure 3). Subjects #01, #02, #04, and #05 all improved from screening to Week 8. Scores further improved from Week 8 to Week 12. Changes from Screening to Week 12 were statistically significant (p=.004). Scores for #03 decreased slightly from screening (26) to Week 8 (25), which was attributed to symptoms of depression, headaches and insomnia that occurred after the subject incurred a concussion three weeks into therapy.

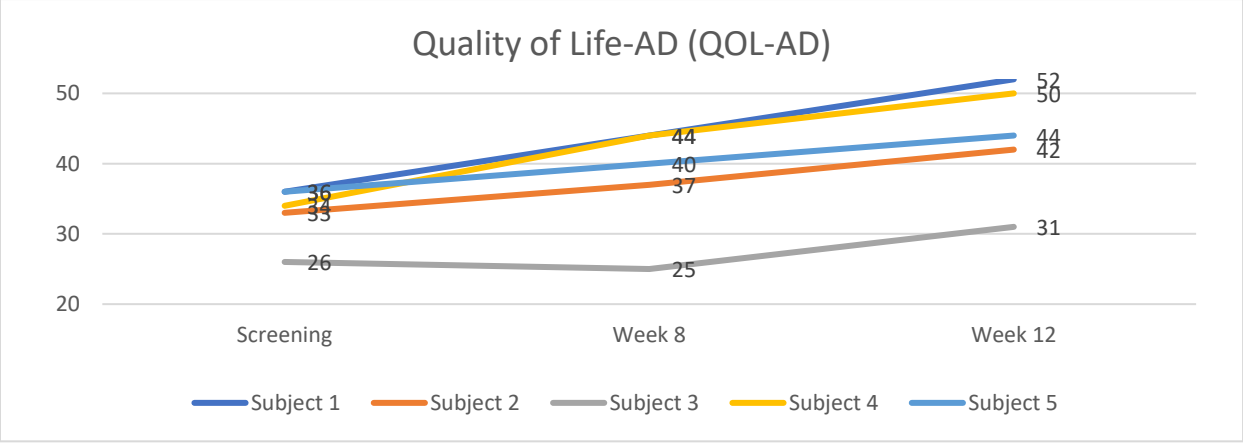

Figure 3: QOL-AD Scores for all Subjects from Screening to Week 12

Inflammation

As aforementioned, The Bodystat QuadScan 4000 was the device that was utilized to determine total body composition throughout the course of the study. All subjects were required to fast for

3-5 hours and restrict all physical activity 24 hours prior to testing at Baseline, Week 8 and Week 12. Inflammation was measured through the formula of extracellular water (ECW) in liters divided by total body water in liters (TBW) minus overhydration in liters (OHY) multiplied by 100 (for percent) and then subtracted by 40. The ratio of ECW/TBW in a healthy adult is 40%, therefore it is the number that is subtracted for diseased individuals, with equal $\leq$ 3% being the standard normal percentage of inflammation.

Inflammation= [ECW (L)/ (TBW (L) - OHY (L) x 100] - 40

Inflammation was elevated in 4 out of the 5 subjects at Baseline. Subject #01 was the only subject whose inflammation was within normal limits at Baseline and remained normal over the course of treatment. On average, the subjects' percentage of inflammation significantly decreased from Baseline to Week 8 and remained consistent at Week 12. With the exception of Subject #02, the percentage of inflammation dropped within normal limits by Week 12 for all subjects. While percentage of inflammation was above normal for Subject #02 (8.5%) at Week12, the change from Baseline to Week 12 was statistically significant (p=.04).

Percentage of inflammation was compared to non-MCI/AD controls ranging from 57-76 years of age (Mean=66.7). The average percentage of inflammation in controls in this group was 3.8% compared to 8.2% in the MCI/AD study population, demonstrating that this population has a higher percentage of inflammation than a similar aged, non-cognitively impaired group of controls. Based on the study's results, inflammation is incontestably elevated in patients with both MCI and AD. One of the objectives of this study was to not only to determine if inflammation was elevated, but if it could be significantly decreased in non-drug therapies such as diet and cellular repair therapy. Data provided in Table 1 illustrates the average changes of inflammation over the course of treatment. The average among all subjects' percentage of inflammation decreased significantly from 8.3% at Baseline to 3.9% at Week 12 (p=.017)

Body Composition

Body Composition as depicted by percentage of water, excess fat, dry lean mass and goal fat were also measured for all subjects at Baseline, Week 8 and Week 12. Table 1 demonstrates average change of body percentage among all subjects over the course of the study. Although data wasn't statistically significant, body fat decreased for all subjects from Baseline to Week 12.

Data was calculated by the BodyStat QuadScan 4000 which takes into account the sum of body fat mass and lean body mass.

Cellular Health

Cellular health in this study was measured and analyzed through the BodyStat QuadScan 4000. Through this device, Phase Angle was determined, which is a direct measurement of a cell membrane. Reactance and Resistance are the two elements in Phase Angle, that essentially measure healthy and unhealthy cells. A low phase angle is consistent with an inability of cells to store energy and an indication of breakdown in the selective permeability of cellular membranes. A high phase angle is consistent with large quantities of intact cell membranes and body cell mass. The reactance element reflects the body cell mass and the resistance reflects the water or fluid in the body. A higher Phase Angle could be indicative of increased muscle mass (body cell mass), loss of fat, or a decrease in fluid; either from recovery from infection or injury, or a decrease in fluid from dehydration. A lower Phase Angle could mean a loss of muscle mass, increase of fat, increase of fluid, sign of inflammation, or infection. In this study, it was predicted that cellular health would improve (increase) from Baseline to Week 12 for all subjects who went through cellular repair therapy. Unfortunately, results were not statistically significant (p=.385) as illustrated in Table 1. Although there wasn't a significant change in cell health for all subjects, cell health did improve from Baseline to Week 12 for all subjects with the exception of Subject #01, who was the only subject who did not undergo adjunctive cell repair therapy. Changes; however, were too minimal to conclude cellular repair therapy improved all around cellular health.

Table 1: Average Test Results for all Subjects from Baseline to Week 12

Test Results	Baseline	Week 12
Inflammation	8.3%	3.9%
Body Fat %	33.7%	30%
Cell Health	4.4%	4.9%

Laboratory Results

A ChemBasic Panel was collected on all subjects at Screening, this included, but was not limited to: cholesterol, triglycerides, lactate dehydrogenase, sodium and calcium levels. A1c was also collected at screening to determine glucose and inflammation levels. Labs were mainly drawn for safety levels; however, noticeable changes in cholesterol were observed over the course of treatment. Cholesterol levels for all patients demonstrated a statistical significance from Screening to Week 12 ($p=.04$). All subjects' cholesterol levels decreased during therapy with the exception of subject #05, who had an insignificant increase of 2mg/L. A1c levels also decreased during the course of the treatment in 80% of the patients ($p=.02$). Subjects #01 and #02 had their A1c levels tested with their primary care physicians twice over the course of the study. Due to significant changes in daily glucose and A1c, Metformin was lowered by half in both subjects by their physicians. Results at Week 12 reflect changes in A1c for these patients despite lowering their diabetic medication, illustrating that diet, and decreasing of inflammation can improve overall glucose levels.

Compliance and Safety

Food diaries were reviewed over the course of the study to determine study compliance. All subjects were required to submit daily food diaries weekly for review and were re-reviewed at each study visit. The amount of daily caloric intake and ounces of specific food groups varied for each subject based on individual RMR results. The average compliance among each subject for each day was calculated by the average of compliance per food group (i.e., proteins, fats, fruits, etc.), and then averaged for each month. The average compliance for all subjects was 81%. All subjects tolerated the diet and cellular repair therapy. There were no subjects who dropped out due to adverse events (AE) or intolerability. Subjects who underwent cellular repair therapy were 89% compliant with their treatments. The overall rate of AEs was higher in MCI than AD patients. All adverse events that were possibly or probably related to therapy were considered Grade 1 in severity. The only Grade 2 (concussion), was unrelated to therapy. No SAEs occurred or were reported over the course of the study. All AEs were transient and resolved prior to the end of the study.

Summary

This proof of concept study using an individualized diet plan treated adjunctively with cellular repair therapy, had significant effects on cognition and chronic inflammation in patients with MCI and AD. Chronic inflammation has been an area of interest in Alzheimer's disease and other neurodegenerative diseases. However, there has been lack of data or study medications that have demonstrated efficacy when specifically targeting inflammation. This study was designed to not only tackle inflammation, but oxidative stress and any other metabolic issues that cause inflammation or specific risk factors associated with AD. In this study, several objectives that were originally created in the Mito-AD-01 protocol, were met. For example, elevated inflammation as measured through BIA testing, were observed and measured in both MCI and AD patients. It was possible that inflammation could be elevated in patients over a certain age; however, when compared to similar aged controls without cognitive impairment, inflammation, on average, was not elevated. Inflammation in the control population averaged 3.8% while the affected population had an elevated value of 8.3%.

It was also suggested that through a proper specialized diet, inflammation would decrease over the course of treatment. A variety of natural antioxidants that exist in foods have been thought to reduce oxidative stress levels and inflammation. Having been previously demonstrated, the Mito Food Plan was utilized as a form of therapy for this study. While other diets have been suggestive in AD prevention, studies are limited, and data is lacking. Although the Mito Food Plan is not a novel diet; creating a specific Mito Food Plan based on physiological and comprehensive body composition and resting metabolic rate is a novel concept in this disease population. Eating all natural, non-GMO, grass fed, organic food high in fat and protein, may seem rudimentary; however, eating the exact amount of macronutrients needed for each individuals makeup, and avoiding foods with added chemicals and sugar is what cells need to stay healthy and prevent chronic inflammation. The Mito Food Plan was created to improve mitochondria production and decrease inflammation. In this study, data illustrated that the Mito Plan not only decreased inflammation in 80% of the subjects, but is also partially responsible for cognitive improvement in 100% of the subjects enrolled in the study.

Due to four of the five subjects adjunctively participating in cell repair therapy, it is indefinite if inflammation and cellular health were improved through diet alone. Subject #05 was the only

subject whose cognitive scores did not increase from Week 8 to Week 12. This result could be attributed to lack of therapy compliance prior to his Week 12 visit, which could also suggest combination treatment as tested in this study is effective when followed properly and consistently. Subject #01 was the only subject whose inflammation percentage did not decrease over the course of treatment and was the only subject who did not undergo adjunctive cellular repair therapy. This could mean that either diet alone isn't fully responsible for decreasing inflammation, or because his inflammation was low at baseline (1.2%), there was not considerable room for improvement. Interestingly, even though his inflammation percentage did not decrease, his cognitive scores on all scales improved consistently from Baseline to Week 8 to Week 12. While the correlation between decreased inflammation and improved scores in MoCA, QOL-AD and MMSE were all statistically significant, improvements in A1c, Cholesterol and body fat also improved. Since subjects, #01, #02 and #03, are diabetic, insulin and hyperglycemia could truly affect cognition. By decreasing A1c and glucose, the brain could actually function more clearly; therefore, improving cognition. Oxidative stress was also an area of interest as well as an objective in the study protocol. Increasing evidence has shown that oxidative stress causes excessive formation of free radicals and reactive oxygen species (ROS) which damages cell function, ROS has also been involved in age-related disorders including AD, determining if specific treatments could ameliorate this dysfunction, could assist with slowing disease progression or even prevent MCI from advancing to AD. In this study, the NanoVi™ (cell repair therapy) was utilized to repair protein structures and maintain the health of the DNA, both of which have been damaged by internal and external factors. By doing so, it is surmised that protein functions are restored, DNA is repaired, cellular activity improves, and health can be maintained. Although cellular health scores did not significantly improve over the course of the study, scores did improve. It is; however, unknown if the cell repair therapy was responsible for the improvement in free radical damage, or if it was attributed to the adjunctive cell repair and diet treatment.

Not only did this study demonstrate decreased inflammation and improved cellular health for the majority of MCI and both AD subjects, but cognitive scores improved in 100% of the participating subjects. These improvements were demonstrated in all neurological assessments. Changes in MMSE had a statistical significance of p=.007, MoCA had statistical significance of p=.008, and the largest statistical significance was seen in QOL-AD (p=.004). Results from the

QOL-AD alone demonstrates that all subjects feel considerably better. This data was not only surprising, but extremely hopeful and exciting for all subjects. After administering each scale at subsequent visits, every subject commented on their "mental clarity" and ease of the test from the previous visit.

Conclusion

Currently there are no approved treatments available for MCI, and no way of detecting who will go on to develop AD. AD has become the most expensive disease in the United States and affects over 50 million worldwide with exponential growth. Alzheimer's Disease drug studies have the highest failure rate of any disease at 99.6%, yet clinicians and researchers continue to proceed with new concepts and compounds in hopes of slowing disease progression. Despite a myriad of research studies concerning AD pathophysiology, the initial events that initiate Aβ plaque formation are uncertain; to date, no effective treatments are available that can stop or reverse the AD-related neurodegeneration.

Even though the sample size of this study was small, it was determined that chronic inflammation and other risk factors for MCI and AD can be ameliorated; therefore, improving cognitive function, and preventing disease progression through effective, non-drug therapies. Since this was proven, providing specific therapies that can be quickly implemented into the life of a person with cognitive impairment, not only decrease the prevalence and slow disease progression of AD, but could also cut annual health care spending costs. Developing a larger, randomized study for MCI and AD patients is warranted; however, through this data alone, Cerulean Advanced Wellness and Fitness has the capability of not only providing patients with MCI and AD testing that can assess and monitor specific etiologies of the diseases, but may also be an all in one inclusive center for treating various medical conditions.

References

1. De Bruijn RF, Akoudad S, Cremers LG, Hofman A, Niessen WJ, van der Lugt A, Koudstaal PJ, Vernooij MW, Ikram MA (2014). Determinants, MRI correlates, and prognosis of mild cognitive impairment: the Rotterdam Study.J Alzheimers Dis.42 Suppl 3:S239-49
2. Mitchell AJ et al. (2009). Rate of progression of mild cognitive impairment to dementia – meta-analyssis of 41 robust inception cohort studies. Acta Psychiatr Scand, 119:252-265.
3. Apostolova, L. G. (2016). Alzheimer Disease. Continuum : Lifelong Learning in Neurology, 22(2 Dementia), 419–434.

4. Cummings, J., Lee, G., Mortsdorf, T., Ritter, A., & Zhong, K. (2017). Alzheimer's disease drug development pipeline: 2017. Alzheimer's & Dementia : Translational Research & Clinical Interventions, 3(3), 367–384.
5. Zhong K and Cummings J. (2016). Healthybrains.org: From registry to randomization. J Prev Alz Dis, 3(3):123-126.
6. Van J., Eldika M. C., Carrillo, E. Cole, Domini, Feuerbach, Greenberge J. et al. (2016). Interventions The roles of inflammation and immune mechanisms in Alzheimer's disease, Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2(2), 99-109.
7. Cai, H., Cong, W., Ji, S., Rothman, S., Maudsley, S., & Martin, B. (2012). Metabolic Dysfunction in Alzheimer's Disease and Related Neurodegenerative Disorders. Current Alzheimer Research, 9(1), 5–17.
8. Guo, C., Sun, L., Chen, X., & Zhang, D. (2013). Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regeneration Research, 8(21), 2003–2014.
9. Roberts RO, Roberts LA, Geda YE, Cha RH, Pankratz VS, O'Connor HM, et al (2012). Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. Journal of Alzheimer's Disease: JAD
10. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff (2017). ESPEN guidelines on definitions and terminology of clinical nutrition. ClinNutr. 36: 49-64.
11. Rinninella E, Cintoni M, Addolorato G, Triarico S, Ruggiero A, et al (2018). Phase angle and impedance ratio: Two specular ways to analyze body composition. Ann Clin Nutr. 1: 1003.
12. Crichton GE, Bryan J, Murphy KJ (2013). Dietary antioxidants, cognitive function and dementia—a systematic review. Plant Foods for Human Nutrition Dordrecht, Netherlands ;68(3):279-92.
13. Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Reviews, 4(8), 118–126.
14. The Mito Food Comprehensive Guide (2016). Institutional of Functional Medicine.
15. Davalli, P., Mitic, T., Caporali, A., Lauriola, A., & D'Arca, D. (2016). ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related Diseases. Oxidative Medicine and Cellular Longevity, 7 (10): 12-14.
16. Wei YH, Ma YS, Lee HC, Lee CF, Lu C (2001)Y. Mitochondrial theory of aging matures—roles of mtDNA mutation and oxidative stress in human aging.64(5):259-70.