INFORMED CONSENT DOCUMENT

Title: Nutritional Intervention for Age-Related Muscular Function and Strength Losses

Investigators: Dr. Rick L. Sharp, Hector Angus

This is a research study. Please take your time in deciding if you would like to participate. Please feel free to ask questions at any time.

INTRODUCTION

HMB (β-hydroxy-β-methylbutyrate) is a dietary supplement that comes from the amino acid leucine. HMB is present in foods and is also made in your body after you eat protein (meat).

Vitamin D is a fat-soluble vitamin that can be obtained from sun exposure, food or supplements. Vitamin D has widespread effects in metabolism in the body beyond its role in calcium absorption and bone health.

Therefore, the primary purpose of this research study will be to test the effect of the dietary supplement HMB with and without Vitamin D to prevent and reverse muscle wasting, and improve muscular strength and functionality in older adults. A secondary aim is to determine if HMB and Vitamin D increase lean mass and improve markers of bone turnover in adults aged 60 plus years.

You are being invited to participate because you

- are male or female who is at least 60 yrs of age,
- are free from liver and kidney diseases,
- have no evidence of uncontrolled hypertension,
- are not morbidly obese,
- are willing to participate 3 times per week in a monitored strength-training program, and
- are willing to consume one of the nutritional supplements for the study period.

You should not participate if you

- are on high-dose Vitamin D Therapies,
- have any serious acute or chronic medical condition or illness,
- have acute or chronic diseases that affect calcium or bone metabolism and health (ex. asthma with chronic use of high dose steroids, inflammatory bowel disease, Crohn's disease, primary hyperparathyroidism, seizure disorder with use of phenobarbital, etc),
- have been diagnosed with osteoporosis,
- are unable to perform exercises or if your physician has restricted exercise
- have had major surgery in the past 6 weeks,
- have had minor surgery in the past 3 weeks, or
- have diabetes controlled with medication.
DESCRIPTION OF PROCEDURES

Informed Consent and Screening (Visit 1, 60 min):

If you agree to participate, you will come in following an overnight fast (12 hr). You are encouraged to drink only water during the fast to prevent dehydration. You will read and sign the informed consent. You will be given the opportunity to ask any questions and are also free to do so at any point during the study.

You are advised to abstain from alcohol consumption for at least 48 hrs prior to the blood draw. Metabolic profile values obtained after consumption of large quantities of alcohol consumption are often erroneous and most likely present abnormal values.

Failure to carry-out the overnight fast will result in your appointment being rescheduled.

1. Your **height**, **weight** will be measured and your **BMI** (Body Mass Index, kg/m²) determined.

2. Your **vital signs** (heart rate and blood pressure) will be measured.

3. Following completion of the measurements, there will be a **blood draw**. About 30 ml (2 tablespoons) of blood will be collected to estimate your baseline biochemical profile (including glucose, blood fat profiles, liver enzymes, Vitamin D status). In addition, your blood will be analyzed for bone specific alkaline phosphatase (BAP), c-terminal telopeptide crosslinks (CTx), 25-OH Vitamin D and PTH analysis. These measurements will give us information about your bone health.

4. You will provide a **urine sample**, which will be the second void of the morning. You may collect this at your home before you come to the laboratory. However, you will have to keep the sample refrigerated until you arrive at the laboratory for testing. You may also provide this sample at the laboratory when you arrive. A urinalysis will be conducted on your urine and will be analyzed for HMB.

5. You will be served a light **breakfast** after the blood draw.

6. You will fill out questionnaires: health, medical history and subject information.

7. Your functional mobility, balance and agility will be assessed using an **Up-&-Go Test**, which is the time it takes for you to rise from a chair, walk around a cone 8 feet in front of the chair and return to the chair.

Signed approval from your primary care provider is necessary before you can begin participation in the study. You will provide the name of your medical provider and we will contact them on your behalf. They will send their signed approval to Dr. Rick Sharp at fax (515/294-8650). We will contact as soon as we have heard back from your medical provider regarding your eligibility in the study.
These preliminary tests will be used to determine your eligibility into the study. There is no compensation for the informed consent and screening visit.

Treatments, Testing and Exercise Training Schedule

If you qualify to participate, you will be randomized to the one of four treatment groups:

1. Control or placebo group,
2. HMB consuming 3.0 g/day,
3. 2000 IU Vitamin D per day,
4. 2000 IU Vitamin D + HMB, 3.0 g/day

No matter which treatment group you are assigned to, you will consume the dietary supplement 2 times per day for 12 weeks. The supplementation will require you take a total of 6 capsules daily, 3 in the morning and 3 in the evening. You may consume the capsules with meals.

The pills will be supplied to you in a bottle every week and you will return the pill bottle each week with the pills you have not consumed (should there be leftovers) when you come to collect the next bottle.

You will also participate in a 3-day per week exercise program for 12 weeks. Each exercise day will require about 60 minutes in the clinical laboratory (details in exercise training section).

You will complete testing at the beginning of the study (week 0), 4 weeks, 8 weeks and end of the study (week 12). Each testing session will last about 90 minutes (details in testing section).

Exercise Training (3-day/week for 12 weeks: 60 min; number of visits will depend on your proficiency with the exercise regimen)

All training will be conducted according to the guidelines of the American College of Sports Medicine (ACSM). Exercise training sessions will be supervised by research personnel who are experienced in administering the exercise tests.

You will participate in a 3-day per week exercise training program consisting of strength training exercises utilizing Theraband® stretch cords and jumping. It is advised that you not eat anything 30 minutes before performing the exercise.

Each time you come to exercise you should either carry with you or wear the appropriate clothing and shoes. Your blood pressure and pulse rate will be measured prior to the start of the training.
You will be instructed on how to perform each exercise and each exercise session will be supervised.

The strength program will incorporate the following exercises: bicep curls, tricep extensions, chair squats, calf raises, ankle dorsiflexion, shoulder front raises and lateral raises, lat pull down, chest press, seated row, knee flexion and extension, and hip flexion.

You will complete each of the 12 exercises or movements for 15 repetitions and repeat this for two sets; a third set will be performed, but you will perform as many repetitions as you can up to 20 repetitions in good form. When you can do the third set 20 times, the resistance will be increased by moving to the next color of the resistance band.

Between each set of exercises, you will perform 5 hops or small jumps. Initially, 5 hops or jumps will be performed following each set of the 12 exercises. The number of hops/jumps will increase by five, every 3 weeks until 25 hops/jumps are achieved. You will remain at 25 hops/jumps between sets for the remainder of the study. The number of hops/jumps will be reduced or omitted if there are any complaints regarding joint pain.

Instruction on how to perform the lifts and hops/jumps will be provided by one of the project workers. Detailed instructions and demonstrations will be performed to help you learn the proper way to perform the lifts focusing on the specific muscle groups of interest. Methods to help with balance and prevent falls during the resistance exercise and the jumps will be demonstrated, but you will be supervised/assisted during the actual jumping so as to prevent falls.

**Testing (4 visits; 90 min each)**

These following tests will be conducted on every testing day. The testing days will be scheduled at the beginning of the study (week 0), 4 weeks, 8 weeks and end of the study (week 12) and you will be scheduled between 7 am and 9 am for testing.

You will maintain a diet record during the weeks 0, 4, 8, and 12 of testing where you will write down everything you eat and drink including water and the provided treatments for 3 days (2 weekdays and 1 weekend day). You will return the diet record to a researcher whenever you come in for testing or arrange for another time when you will be able to drop-off the diet record.

You will come in on all testing days following an overnight fast (12 hr). You are encouraged to drink only water during the fast to prevent dehydration. Failure to carry-out the overnight fast will result in your appointment being rescheduled.

1. Your height, weight, blood pressure, and heart rate will be measured. (Same as screening).

2. You will provide a blood sample during the weeks of 4, 8, and 12. (Same as screening).
3. You will provide a urine sample during the weeks of 4, 8, and 12. (Same as screening).

4. Your body composition will be measured three different ways:

   a) Dual-emission X-ray Absorptiometry (DXA): DXA will be used to measure changes in muscle and fat mass at only at weeks 0, 8, and 12 weeks, not week 4. DXA also provides a measure of bone density. You will lie flat on you back and the machine will slowly scan your body. You will hear the machine noise as the arm moves the length of the table. The machine will expose you to a very small amount of x-ray radiation (see comparison below) which will measure your body and bone composition. You will feel nothing during this process.

   b) Bioelectrical Impedance Analysis (BIA) (same as screening)

   c) The BODPOD is a computerized closed-chamber in which the participant's body composition is estimated by air displacement. While the chamber is relatively small, there is a large glass window in the front and you will be in constant communication with the technician. You will be required to wear snug fitting clothing such as spandex or swimming suits while sitting inside the closed-chamber. The measurement lasts about 5-8 minutes. Hence, you will have to bring/wear under your clothes a snugly fitting swim-suit. The swim-suit should not have any wires or loose fabric since that affects the accuracy of the measurement. We have a male and female BODPOD operator. If you feel uncomfortable and would prefer a person of the same gender operating the BODPOD, do not hesitate to mention it to the any one of the researchers.

5. Your leg and elbow strength will be measured using a special machine called a isokinetic dynamometer. The machine measures the strength you are able to apply as the machine arm travels away from you (extension) and towards you (flexion).

6. Your handgrip strength will be measured using a handgrip dynamometer, which is a small device similar to a nutcracker which you will squeeze with your hand while the instrument records your strength.

7. Your functional mobility, balance and agility will be assessed using an Up-&-Go Test (same as screening).

8. You will also complete questionnaires relating to your health, how you feel, and how you perceive your health.

9. During the week 12 visit, you will complete a final questionnaire about your thoughts on the treatment you were in.
RISKS

While participating in this study you may experience the following risks:

Risks associated with exercise include muscle soreness. Severe risks include strains and sprains and possibly stress fractures. There is a potential for muscle strains to occur during strength training sessions. However, the exercise sessions will be supervised and you will be instructed and trained on the correct way to perform each exercise to minimize the chance of experiencing muscle soreness, a strain or sprain. To minimize risks all participants will perform a warm-up and cool down.

Additionally, there is the risk of falling during participation in the exercises. All reasonable care will be taken to protect against this such as using a chair or bar to stabilize yourself if necessary and having a trained technician act as a spotter to help you maintain balance.

It is also possible that you may experience some lightheadedness or the feeling of fainting when exercising. If you experience symptoms of being lightheaded sit down and inform the exercise technician immediately.

There are possible, but minimal risks during blood draws which include slight discomfort, bruising, swelling or in rare occasions, bleeding at the site of blood withdrawal. However, these risks will be minimized with blood samples been taken under strict aseptic conditions by an experienced phlebotomist.

With vitamin D supplementation there is some risk of developing vitamin D toxicity when vitamin D status becomes extremely high. Developing symptoms of toxicity are unlikely at daily intakes below 10,000 IU/day. The dose of 4000 IU per day has been set by the Institute of Medicine as the Tolerable Upper Limit (UL). We will assess vitamin D status throughout the study and assess your blood calcium to minimize risks.

Radiation risk from x-rays associated with the bone measurements (DXA) is minimal. Every person is exposed on a daily basis to a certain amount of background radiation originating from soil, rocks, outer space, and within the body itself. The total amount of radiation received by participating in this study is less than what a person would receive during a transcontinental round-trip air flight (approximately 5.0 mrem) and well below the 500 mrem annual public exposure limit for infrequent exposures and the 100 mrem annual public exposure limit for frequent or continuous exposures recommended by the National Council for Radiation Protection.

BENEFITS

You will gain valuable information about your health. This includes information regarding diet, physical fitness, body composition, and bone health status. These assessments are costly in a clinical setting and will be free to you for participating in the study. This research will provide benefits to others; once we better understand the effect of the supplementation and exercise in
older adults, we will be able to provide additional effective strength and bone-health interventions for this “at risk” population.

COSTS AND COMPENSATION

You will not have any costs from participating in this study other than your time and cost of transportation to and from the testing and training site. You will be compensated $100 for participating in this study. There is no compensation for the screening visit. Your compensation will be paid to you at the conclusion of your participation (at the end of the 12 week intervention). If for any reason you are unable to continue in the study and/or choose to discontinue participation part way through the study, your compensation will be pro-rated depending on the number of weeks completed (for example, completion of 6 weeks will result in compensation of $50).

You will need to complete a form to receive payment. Please know that payments may be subject to tax withholding requirements, which vary depending upon whether you are a legal resident of the U.S. or another country. If required, taxes will be withheld from the payment you receive.

You will need to provide your social security number (SSN) and address on the form in order for us to pay you. This information allows the University to fulfill government reporting requirements. Confidentiality measures are in place to keep this information secure. You may forego receipt of payment(s) and continue in the research study if you do not wish to provide your social security number and address. Information regarding documentation required for participant compensation may be obtained from the Controller’s Department; 294-2555 or http://www.controller.iastate.edu.

PARTICIPANT RIGHTS

Your participation in this study is completely voluntary and you may refuse to participate or leave the study at any time. If you decide to not participate in the study or leave the study early, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

In filling out surveys, you can skip any questions that you do not wish to answer.

You are entitled to review, and to a copy of all data collected from you at the completion of the study.

If you fail to meet all the inclusion criteria or do meet one of the exclusion criteria during the course of the study your participation will be terminated and you may be referred to your own physician for further follow up.

Specifically, if during the Week 0 DXA, we notice abnormalities that may suggest that you have undiagnosed osteoporosis, you participation will be terminated and you will be advised to see your physician immediately for a proper diagnosis.
For your own health and safety, you are responsible for informing research personnel if there are any changes to your health, diet, lifestyle, medications, injury, or if you begin participation in any other research study. This may result in termination of participation if the changes are such that you now meet one of the exclusion criteria, it is no longer safe for you to continue participating or if the changes interfere with the study objectives.

You will not be permitted to participate if you are unable to provide approval from your Primary Care Physician, allowing your participation.

Also, if during the course of the study you develop a medical condition or injury that would not automatically exclude you from participating, you may be required to provide approval from your Primary Care Physician, confirming that it is still safe for you to continue participating in this study.

During the course of the study if Vitamin D or calcium levels in your blood will be monitored and if Vitamin D values appear to be above normal values, your participation will be terminated immediately and you will be advised to see your physician.

If compliance is deemed insufficient (e.g. supplement not being consumed, diet records incomplete, inadequate performance during exercise training) to the principal investigator your participation may be terminated.

Failure to show up to 3 consecutive appointments may result in termination of participation.

Failure to carry-out an overnight fast on 3 consecutive occasions may result in termination of participation.

RESEARCH INJURY

Emergency treatment of any injuries that may occur as a direct result of participation in this research is available at the Iowa State University Thomas B. Thielen Student Health Center, and/or referred to Mary Greeley Medical Center or another physician or medical facility at the location of the research activity. Compensation for any injuries will be paid if it is determined under the Iowa Tort Claims Act, Chapter 669 Iowa Code. Claims for compensation should be submitted on approved forms to the State Appeals Board and are available from the Iowa State University Office of Risk Management and Insurance.

CONFIDENTIALITY

Records identifying participants will be kept confidential to the extent permitted by applicable laws and regulations and will not be made publicly available. However, federal government regulatory agencies, Food and Drug Administration, National Institutes of Health, National Institute of Aging, Office of Human Research Protection, auditing departments of Iowa State University, and the Institutional Review Board (a committee that reviews and approves human subject research studies) may inspect and/or copy your records for quality assurance and data analysis. These records may contain private information. This study is also being conducted
under an Investigational New Drug application and as such the Food and Drug Administration may inspect or copy records.

To ensure confidentiality to the extent permitted by law, the following measures will be taken:

- The data collected from the study will be regarded as privileged and confidential.

- You will be assigned a unique identifier code and all the information you provide will be listed under your code.

- There will be only one hard copy with your name/identity and all information (e.g. questionnaires, diet record, clinical measures) will be stored in a secure filing cabinet. This cabinet can only be accessed by the PI and co-investigators.

- There will only be one file maintained on a password protected server, one back-up file on a CD/USB and one hard-copy connecting your name with this unique identifier code. This file can only be accessed by the PI and co-investigators.

- The de-identified data will be kept indefinitely and if the results are published or presented, your identity will remain confidential.

- Your data will be shared with researchers in South Dakota State University, but researchers there will not have access to your identity, which will remain confidential.

- Should it become necessary or desirable to release identifiable health information, a disclosure authorization will be obtained from you prior to release of the information. A record of all disclosures and authorizations will be kept with your information. All records and information will be stored for a minimum of 3 years past the last subject finishing study protocols.

- The sponsoring company (Metabolic Technologies, Inc, Ames, IA) will receive the data files from the trials, but will not have access to your identity, which will remain confidential.

QUESTIONS OR PROBLEMS

You are encouraged to ask questions at any time during this study.

- For further information about the study contact Dr. Rick Sharp (515) 294-8650 or Hector Angus (515) 294-8481.

- If you have any questions about the rights of research subjects or research-related injury, please contact the IRB Administrator, (515) 294-4566, IRB@iastate.edu, or Director, (515) 294-3115, Office for Responsible Research, Iowa State University, Ames, Iowa 50011.
PARTICIPANT SIGNATURE

Your signature indicates that you voluntarily agree to participate in this study, that the study has been explained to you, that you have been given the time to read the document, and that your questions have been satisfactorily answered. You will receive a copy of the written informed consent prior to your participation in the study.

Participant’s Name (printed) _____________________________________________

(Participant’s Signature) _____________________________________________ (Date) ______________________

(Researcher Signature) ________________________________________________ (Date) ______________________