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Muscle Study
HMB & Vitamin D

Date:

Dear Name of Participant,

We are currently inviting healthy women at least 60 years of age to participate in 12- month research study to evaluate the effect of exercise, a nutritional supplement (HMB) and Vitamin D on muscle.

There is a gradual loss of muscle mass and strength with age and this loss increases the risk of falls and fractures in older adults, seriously affects the quality of life and health in older adults. Therefore, this research study is designed to provide effective strength and bone-health recommendations that may help reduce the risk of fractures and falls and thereby, improve the quality of life and health in older adults.

HMB (β -hydroxy- β -methylbutyrate) is the dietary supplement is being tested as part of this study. HMB comes from an amino acid (leucine). Amino acids are the building blocks of protein, which make up muscle HMB is present in foods and is also made in our body after we eat protein (e.g. meat). Some recent research in older adults shows that HMB supplementation tends to increase muscle strength and mass with significant fat loss.

Vitamin D is a fat-soluble vitamin that can be obtained from sun exposure, food or supplements. Vitamin D has widespread effects on metabolism in the body beyond its role in health. Vitamin D has also been associated with muscle strength, and in deficient individuals has been shown to improve muscle strength.

Participation criteria: At least 60 yrs of age; healthy women; willing to exercise 3 days per week for 1 hr/day; willing to consume a nutritional supplement; willing to provide blood and urine samples

If you fit the above criteria, please consider participating in this study. If you would like more information before you decide, please contact Hector Angus at muscle@iastate.edu or 515-294-4852 (local) or 877-578-8848 (toll free). You may also visit (www.nwrc.iastate.edu) for all the details. And if you know others that might be interested, kindly pass on our contact information.

Thank you for your time and consideration.

Yours Sincerely,

Rick L. Sharp, Ph.D.
Professor
Department of Kinesiology
Iowa State University



INFORMED CONSENT DOCUMENT

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

Investigators: Rick L. Sharp, PhD; John Rathmacher, PhD; Hector Angus, MS; Jeanne Stewart, MS; James Lang, PhD (Des Moines site); Kristin Lowry, PhD (Des Moines site)

This form describes a research project. It has information to help you decide whether or not you wish to participate. Research studies include only people who choose to take part—your participation is completely voluntary. Please discuss any questions you have about the study or about this form with the project staff before deciding to participate.

This study is funded by the National Institutes of Health and by Metabolic Technologies, Inc.

Introduction

HMB (B-hydroxy-B-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 supplements HMB plus Vitamin D with and without strength training exercise to prevent and reverse muscle wasting, and improve muscular strength and functionality in older adults during a one-year study period. 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. Bone health in terms of bone mineral content and bone mineral density will also be evaluated as secondary outcomes.

You are being invited to participate because you

- are a female who is at least 60 yrs of age,
- are free from liver and kidney diseases,
- do not have a history of blood clots and/or taking blood thinner medication,
- have no evidence of uncontrolled hypertension,
- have a body mass index (BMI) less than 40,
- are willing to participate 3 times per week for 1 year 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 taking a daily vitamin D supplement at a dose > 1,000 IU/day,

- has or have had any serious acute or chronic medical condition or illness, that would prevent you from participating in an exercise program
- 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 evidence of uncontrolled diabetes mellitus, or Type I diabetes mellitus requiring insulin for glucose control.

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 and 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, calcium, blood fat profiles, liver enzymes, vitamin D status).
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. The signed approval will be sent to Dr. Rick Sharp at fax (515-294-8740). We will contact you as soon as we have heard back from your medical provider regarding your eligibility in the study. You may also contact your doctor and obtain signed approval from them. However, we would need this approval within 5-7 business days after your screening visit or your participation may be terminated. You may send this signed approval to Dr. Rick Sharp at fax (515-294-8740), drop it off with one of the study researchers or mail it to 250 Barbara E. Forker Building, Iowa State University, Ames, IA 50011. We will contact you as soon as we receive this document from you.

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. Dietary placebo plus exercise program,
2. Dietary placebo without exercise program,
3. 2000 IU Vitamin D + HMB, 3.0 g/day without exercise program,
4. 2000 IU Vitamin D + HMB, 3.0 g/day plus exercise program

No matter which treatment group you are assigned to, you will consume the dietary supplement 2 times per day for 12 months. 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 month and you will return the pill bottle each month with the pills you have not consumed (should there be leftovers) when you come to collect the next bottle.

If assigned to one of the exercising groups, you will also participate in a 3-day per week exercise program for 1 year. 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), at 3 months, at 6 months, at 9 months, and after 12 months of participation. Each testing session will last about 90 minutes (details in testing section).

Exercise Training (3-day/week for 1 year)

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 program. We will set-up training sessions at various times of day at both the Nutrition and Wellness Research Center (NWRC) and the Forker Building for participants in the Ames area, and at the Des Moines University Wellness Center for participants living in the Des Moines area.

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.

During the year-long study, there will likely be times when you are travelling or cannot attend the exercise sessions as usual. For these times, we will give you a set of the Therabands and instruct you on how to continue your training while you are away.

Once you have increased muscle strength enough that the Thera-bands no longer are effective in raising your strength further, you will transition to strength training on our Techno-Gym machines where you will use the same lifts and number of repetitions as on the Therabands. The Techno-Gym devices are designed for safe and effective strength training for both younger and older adults. The advantage to switching from Therabands to the machines is that your training loads can be gradually increased beyond what is possible on the rubber bands and as your own adaptation allows. In addition, the TechnoGym devices are networked so that the devices keep track of your training loads and your progress throughout the year-long study. Again, if travelling or other obligations prevent you attending some of the exercise sessions, we will provide a set of Therabands to use in maintaining your improved fitness while away.

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 (5 visits; 90 min each)

These following tests will be conducted on every testing day, except as noted. The testing days will be scheduled at the beginning of the study (month 0), at 3 months, at 6 months, at 9 months and after 12 months of training and supplementation. You will be scheduled between 7 am and 9 am for testing. These testing sessions will be conducted at the Nutrition and Wellness Research Center in Ames. If you need help with transportation to the testing site, please let us know and we will help arrange transportation.

You will maintain a diet record during the week before each testing session 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 at months 3, 6, 9 and 12. (Same as screening).
3. You will provide a urine sample at months 3, 6, 9, and 12. (Same as screening).
4. Your body composition will be measured three different ways:
 - a) Dual-energy X-ray Absorptiometry (DXA): DXA will be used to measure changes in muscle and fat mass. DXA also provides a measure of bone density. You will lie flat on your 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 which will measure your body and bone composition. You will feel nothing during this process. These DXA scans will be conducted at months 0, 6, and 12.

For Females only: All female participants will be asked to complete a pregnancy risk acknowledgement prior to the DXA scan. Women with a child-bearing potential will be administered a urine pregnancy test as a safety measure to ensure that no pregnant female is exposed to X-rays. Female

participants found to be pregnant will be excluded from further participation and will be advised to see their medical care provider.

Also note that all DXA scans will be evaluated by a medical doctor who will determine whether you have osteoporosis and if it is safe for you to participate in this study.

- b) Bioelectrical Impedance Analysis (BIA) (Months 0, 3, 6, 9, and 12): This is used to measure body composition with estimates of muscle mass, total body water, and body fat content. The BIA performs these measurements based on resistance to a very small electrical current flow through the body. You will not feel the current flow during this testing and the device is safe and commonly used in fitness centers for estimating body composition.
 - 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 any one of the researchers.
5. Your leg and elbow strength will be measured using a special machine called a Biodex strength testing apparatus. 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 and the Get-Up test (same as screening). The Up-&-Go and Get-Up tests are widely used functionality tests that involve measuring your ability to rise from a chair and walk a short distance. Specific procedures for each will be explained before testing.
 8. You will also complete questionnaires relating to your health, how you feel, your physical activity level, and how you perceive your health.
 9. During the 12 months of this study, you will be given a "falls calendar" which provides a method for recording every instance of experiencing a fall, if you have any, at any time during the day. Your "fall calendar" will be given to you at the

beginning of each month and you will return the completed form to us at the end of the month.

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

Risks or Discomforts

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

Risks associated with exercise include muscle soreness and joint pain. 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 such as slight discomfort, bruising, swelling, or in rare occasions, bleeding at the site of blood withdrawal. However, these risks will be minimized since blood samples will be collected 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. If you indicate on the medical history questionnaire that you have a history of being diagnosed with kidney stones, we will ask you to complete a 24-hour urine collection at each of the three-month testing sessions. The purpose of this collection is to evaluate the amount of calcium excreted per day which can be used to assess high risk of kidney stone formation. If your calcium excretion is greater than clinical norms, you will be referred to your medical provider for follow-up and to determine if you should continue in the study.

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 through the DXA scan exposures about 4.5 mrem, which 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. In Iowa, the Iowa Department of Public Health (IDPH) enforces the yearly exposure limit of 100 mrem.

Benefits

You will gain valuable information about your health. This includes information regarding diet, physical fitness, body composition, regional 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. As an alternative to participation in this study, many of these same assessments can be obtained through your medical provider. 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 \$150 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 1 year 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 testing sessions completed (for example, completion of 6 months will result in compensation of \$90).

If you are assigned to one of the non-exercise groups and complete the study, you will also be given 10 free sessions in a supervised exercise program led by a professional exercise leader (personal trainer, certified exercise leader, or equivalent) who will lead you through the same or similar exercises to those being used in the exercising groups of this study. The intent of this additional incentive is to provide you the same benefit as the other groups with regard to establishing an exercise program designed to prevent and/or reverse the age-related losses of muscle function. We would hope that this instruction will equip you with an exercise program you can maintain after your study participation has ended. If you discontinue your participation before the end of the study, the number of sessions with supervised exercise program will be prorated based on the number of testing sessions (3-month testing intervals) you completed.

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 meet one of the exclusion criteria during the course of the study your participation will be terminated and you may be referred to your physician for further follow up.

Specifically, if during the DXA scan sessions, we notice abnormalities that may suggest that you have undiagnosed osteoporosis, your participation will be terminated and you will be strongly advised to see your physician immediately for a proper diagnosis, and treatment.

For your own health and safety, you are responsible for informing research personnel if there are any changes to your health, diet, lifestyle, and medications, and/or if you incur any injury, and/or if you begin participation in any other research study. These changes may result in termination of your participation if they fulfill the exclusion criteria, if it is unsafe for you to continue participating or if these changes interfere with the study objectives.

You will not be permitted to participate if we are unable to obtain approval for your participation from your physician.

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.

If significant new findings occur during this study that may influence your decision to continue with the study, we will provide this information to you so that you can make an informed decision about continued participation.

During the course of the study 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. If, during the course of the study, you need to travel out of town, please inform one of the researchers and we will instruct you on how to continue training while you are out of town. We will likely let you take a set of Thera-bands with you during the travel so that you can at least maintain your fitness during the travel.

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

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.

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.

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

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.
- 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

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

For further information about the study contact:

Ames site:	Hector Angus (515) 294-8481	angus@iastate.edu
	Rick Sharp (515) 294-8650	rlsharp@iastate.edu

Des Moines site:	Jim Lang (515) 271-1733	James.Lang@dmu.edu
	Kristin Lowry (515) 271-1488	klowry@dmu.edu

Consent and Authorization Provisions

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)