Feinstein Institutes for Medical Research
Northwell Health

PROTOCOL: INTERVENTION STUDY (CLINICAL TRIALS)

Title: Impact of Vitamin D Therapy on Thyroid Function and Antibody Levels in Pediatric Graves' Disease: A Pilot Feasibility Trial

Protocol Number: 25-0285

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Investigational Product Name(s): ergocalciferol

IND or IDE Number *(if applicable)*: NA

Regulatory Sponsor (*Sponsor-Investigator or IND/IDE holder, if applicable*)**: NA**
Name
Address
Phone number
Email address

Protocol Version and Date: version 1. 6.26.2025

Northwell Health

Campus: Cohen Children's Medical Center, New Hyde Park

Consent for Participation in a Research Study

Title: Impact of Vitamin D therapy on thyroid function and antibody levels in Pediatric Graves' disease: A Pilot Feasibility Trial

Principal Investigator: Dr. Sharon Hyman

Sponsor: Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York

About this research

You are being asked to participate in a research study to investigate whether vitamin D supplementation in addition to methimazole can promote earlier normalization of thyroid function tests and earlier reduction in Graves' antibody levels in newly diagnosed patients with Graves' disease (GD) compared to monotherapy with methimazole alone.

Taking part in this research study is voluntary.
You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled to and will not affect your relationship with Northwell Health.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Important Information

Historically vitamin D has been associated with the regulation of bone metabolism. Recent evidence suggests a strong association with vitamin D and autoimmune regulation in diseases such as Systemic Lupus Erythematosus (SLE), Multiple Sclerosis (MS) and Type 1 Diabetes. Because of the high prevalence of vitamin D insufficiency and deficiency in patients with MS, T1DM, and SLE, vitamin D supplementation has been considered a prospective candidate for the treatment of such autoimmune diseases with some studies showing promising results. Studies in adults and children show a strong association between low vitamin D levels and increased risk of Graves' disease. In adults combined treatment with vitamin D and methimazole may help with

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Graves' disease treatment outcomes however there is very limited information on whether treating low vitamin D levels in children with Graves' disease does the same.

This information gives you an overview of the research. More information about these topics may be found in the pages that follow.

Why am I being asked to provide my consent?	This is a research study, which is different than personal medical care. Scientists do research to answer important questions which might help change or improve the way we do things in the future.
Do I have to join this research study?	No. Taking part in this research study is voluntary. You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled.
Why is this research study being done?	This research study is being done to learn if giving higher-than-normal doses of vitamin D can help children with Graves' disease, a thyroid condition. Children with Graves' disease are usually treated with a medicine called methimazole. We want to find out if adding high doses of vitamin D2 (ergocalciferol), a type of vitamin D already used for other health problems, can make the standard methimazole treatment work even better. In this study, ergocalciferol is considered investigational because we are using it in a way not specifically approved by the Food and Drug Administration (FDA)—as a treatment for Graves' disease in children. This study is a stepping stone. We will use what we learn to design a bigger study that will test how well vitamin D2 actually works for kids with Graves' disease. We hope that, in the future, this research can help other children with Graves' disease.
What will happen to me during the study?	If your qualify for the study, in addition to the initial labs, a vitamin D level will be drawn via a blood test on you. At the initial visit, you will be randomized to one of two arms of the study – Patients in the first arm will receive no additional intervention other than methimazole (standard of care). Your would be allowed to take up to 1000 IU vitamin D2 daily if you choose to do so. Patients in the second intervention arm will be prescribed vitamin D2 50000 IU weekly for 8 weeks followed by 50000 IU every 2 weeks for 4 months in addition to standard of care (methimazole). These vitamin D capsules will be provided at the initial visit or mailed to you. Your endocrinologist will be obtaining thyroid tests on you, initially every 2-4 weeks, as is standard practice for managing Graves' disease. The frequency of these blood draws will be adjusted based on your individual needs and response to treatment as determined by their doctor. At 3 and 6 months we will obtain vitamin D levels from your blood in addition to routine thyroid tests your

	endocrinologist would order. At 6 months your endocrinologist will obtain antibody levels to monitor for changes.
How long will I participate?	Participation will include no additional blood draws than you would normally have. However, we will be obtaining vitamin D levels when your endocrinologist orders your thyroid tests at the time of diagnosis, 3 months and 6 months. Total time of participation in this study is 6 months.
Will taking part expose me to risks?	Depending on which group you are randomly assigned to, your group may receive less effective research procedure(s) or have more side effects than the other group. While short-term use of vitamin D supplements at this dose in vitamin D deficiency is generally considered safe, prolonged use can lead to vitamin D toxicity (hypervitaminosis D), characterized by elevated calcium levels (hypercalcemia). Hypercalcemia can cause a range of symptoms, from mild (nausea, vomiting, constipation) to severe (kidney stones, kidney damage, cardiac arrhythmias). These risks are generally associated with very high vitamin D level > 150 ng/mL. You will be closely monitored with vitamin D levels drawn at the 3 and 6 month mark and if the level is noted to be above 80 ng/mL, we will reduce the dose to 1000 IU daily instead.
Are there any benefits to participation?	Your group might receive more effective research procedure(s) and/or have fewer side effects than the other treatment group(s). Depending on the group you are randomly assigned to, you may or may not receive benefits from this study. Potential benefits may include improvements in your GD symptoms due to either the Vitamin D supplementation or the optimized management of your GD
What are my alternatives to participation?	Standard medical treatment for your Graves' disease, which typically involves medications like methimazole, will continue to be available whether or not you choose to participate in this study. Your endocrinologist can discuss these standard treatment options with you in more detail. This study is exploring *in addition* to the standard treatments.

Please review the rest of this document for details about these topics and additional things you should know before making a decision about whether to participate in this research.

This consent form is written from the point of view of a research participant. If the parent or legal guardian of a minor or a legally authorized representative will be providing consent, the words "you" and "your" should be read as ("your child" or "the research participant").

Introduction

You are being asked whether you want to join a research study. The purpose of a research study is to answer specific questions.
You do not have to be in this study to receive medical care. You should ask questions before you decide if you want to participate. You can also ask questions at any time during the study.

Why is this research study being done?
This research study is being done to learn if giving higher-than-normal doses of vitamin D can help children with Graves' disease, a thyroid condition. Children with Graves' disease are usually treated with a medicine called methimazole. We want to find out if adding high doses of vitamin D2 (ergocalciferol), a type of vitamin D already used for other health problems, can make the standard methimazole treatment work even better. In this study, ergocalciferol is considered investigational because we are using it in a way not specifically approved by the Food and Drug Administration (FDA)—as a treatment for Graves' disease in children. This study is a stepping stone. We will use what we learn to design a bigger study that will test how well vitamin D2 actually works for kids with Graves' disease. We hope that, in the future, this research can help other children with Graves' disease..

Why is this research?
This research study is being done because we want to learn more about whether taking high doses of vitamin D can help children with Graves' disease. Graves' disease is a thyroid problem, and the current way to treat it is with a medicine called methimazole. We want to see if adding high doses of vitamin D2 (also called ergocalciferol), which is already used for other health conditions, can improve how well the standard treatment works in children. Ergocalciferol is considered investigational in this study because it's being used in a way not specifically approved by the Food and Drug Administration (FDA) – to help children with Graves' disease. This study will help us understand if a larger study to test the benefits of vitamin D2 in this situation is feasible. You are being asked to participate because you were recently diagnosed with Graves' disease and you are between 9 and 17 years old.

How many people will take part in this study?
We estimate that about 30-35 children under the age of 18 years will participate here at Northwell Health Pediatric Endocrinology Practice.

What will happen in this research study?
In this study you will be randomized. This means that you will be assigned to a group by chance (like flipping a coin). You will have an equal chance of being in either (or any) group.
Open-Label Study is a study in which all parties, (the person taking part in the study, the doctor and the study coordinator) know the drug and dose being given. In an open-label study, none of the participants are given placebos.

If you qualify for the study, in addition to the initial labs, a vitamin D level will be drawn on your initial bloodwork. At the initial visit, you will be randomized to one of two arms of the study:
Patients in the first arm will receive no additional intervention other than methimazole (standard of care). You would be allowed to take up to 1000 IU vitamin D2 daily if you choose to do so.
Vitamin D refers to a group of fat-soluble vitamins that are important for bone health, immune function, and other bodily processes. Two main forms of vitamin D are important for people: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is the type your body naturally makes when exposed to sunlight and is also commonly found in supplements. Vitamin D2 is produced by plants and is also available as a dietary supplement.
This study uses vitamin D2 (ergocalciferol) supplements. While you would be allowed to take the recommended daily allowance of up to 1000 IU of vitamin D2 even if not enrolled in the study, to ensure the accuracy of our results and avoid potentially confounding effects, we prefer that you do *not* take any vitamin D3 supplements during the study period. Please inform the study team if you are currently taking any vitamin D supplements, including vitamin D3, so we can discuss this further.
Patients in the second intervention arm will be prescribed vitamin D2 50000 IU weekly for 8 weeks followed by 50000 IU every 2 weeks for 4 months in addition to standard of care (methimazole). These vitamin D capsules will be provided at the initial visit or mailed to you.
Your endocrinologist will be obtaining thyroid tests on your labwork initially every 2-4 weeks and then space the lab draws out as your thyroid levels improve from the treatment, which is standard of care. At 3 and 6 months we will obtain vitamin D levels from your blood in addition to routine thyroid tests your endocrinologist would send. At 6 months your endocrinologist will obtain antibody levels to monitor for changes.

We will collect some information from your medical record. We want to understand how your blood sample tests relate to your health information.

What are the risks of the research study? What could go wrong?
Depending on which group you are randomly assigned to, your group may receive less effective research procedure(s) or have more side effects than the other group.

<u>Vitamin D supplementation: Please note that this section only applies to the high dose vitamin D intervention group.</u>
This research study involves giving your child higher-than-normal doses of vitamin D2 (ergocalciferol). While vitamin D is generally safe, taking high doses for a prolonged period can lead to a condition called vitamin D toxicity (hypervitaminosis D). This is marked by elevated calcium levels in the blood (hypercalcemia).
We will monitor you closely for hypercalcemia and hypervitaminosis D throughout the study. This will include regular blood tests to check their vitamin D and calcium levels at the 3- and 6-month marks of the study. If your vitamin D level is above 80 ng/mL, we will reduce your supplement dose to 1000 IU daily. If concerning symptoms or blood test

results suggestive of toxicity emerge, we will interrupt study drug administration and refer to your primary endocrinologist, as per their recommendation.
Potential side effects of high-dose vitamin D can include:

- Mild: Nausea, vomiting, constipation, poor appetite, weight loss, abdominal pain, increased thirst and urination (polyuria), and dehydration.
- Moderate: Hypercalciuria (high calcium in the urine), which can contribute to kidney stones, nephrocalcinosis (calcium deposits in the kidneys).
- Severe (rare but serious): Cardiac arrhythmias (irregular heartbeat), which can range from harmless to life-threatening, and kidney damage, which can be temporary or in rare cases, permanent if very high calcium levels are prolonged. In extreme cases, confusion and coma can occur.

It's important to remember that these side effects are more likely to occur with very high vitamin D levels (typically above 150 ng/mL). The close monitoring in this study, which includes regular blood tests to check vitamin D and calcium levels, is designed to detect and manage any potential problems early. If concerning symptoms or test results emerge, we will discontinue the study drug immediately and refer you to your primary endocrinologist for further management. If you notice any of these symptoms during the study, please contact the study team immediately

Blood Draw

There will be one additional tube of blood drawn in the lab of 0.2 teaspoons of blood (1 milliliter) at the initial visit, then at the 3- and 6-month follow-ups. You will not be expected to go to the lab more times than would be expected for your condition just for the purpose of the study.
There are no major risks of having blood drawn. It can be uncomfortable and can sometimes cause a bruise. In rare cases, it can cause fainting. Only trained staff will draw your blood.

Confidentiality

While we will do everything, we can secure your personal information, there is a chance your personal information could be lost or exposed. This is very unlikely to happen, and we will do everything we can to make sure that your information is protected. We will take necessary precautions to minimize this risk by replacing your name with a study ID that is obtained during the research study.

What are the benefits of this research study?

Your group might receive more effective research procedure(s) and/or have fewer side effects than the other treatment group(s). Depending on the group you are randomly assigned to, you may or may not receive benefits from this study. Potential benefits may include improvements in your GD symptoms (e.g., reduced fatigue, palpitations, anxiety, improved sleep) due to either the Vitamin D supplementation or the optimized

management of your GD.

Will I receive my results?
At the end of the study, we will share a summary of the overall findings with you. This summary will not include any information that can identify you. We will also share your individual vitamin D and calcium levels with you and your primary endocrinologist throughout the study as part of your routine medical care. While we may learn things about your response to vitamin D, the purpose of this study is to assess the feasibility of a larger trial, not to provide individual diagnostic or treatment recommendations. Your doctor will continue to manage your Graves' disease and make any necessary adjustments to your treatment plan based on your overall health, not just the results of this study.

Drug Availability After Completion of Study
At the conclusion of this study, decisions about your ongoing vitamin D supplementation will be made by your treating endocrinologist, not the study team. The study team will share the results of your vitamin D and calcium levels obtained during the study with you and your endocrinologist. However, any decisions about continuing vitamin D supplementation, adjusting dosages, or other aspects of their Graves' disease management will be the responsibility of your regular healthcare provider and will be based on your overall health, not solely on the results of this research study

If you do not want to take part in this research study, what are your other choices?
Standard medical treatment for your Graves' disease, which typically involves antithyroid medications like methimazole will continue to be available whether or not you choose to participate in this study. Radioactive iodine therapy and surgery are also established treatment options for Graves' disease, although less common in children. Your endocrinologist can discuss these standard treatment options with you in more detail. This research study is evaluating high-dose vitamin D *in addition* to standard medical therapies, not as a replacement. Participating in the study does not guarantee you will receive vitamin D; you may be assigned to the control group which receives a standard dose. You are free to decline participation in this study and still pursue any of these other treatment options with your doctor.

Are there any costs for being in this research study?
This research study is funded by the Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York. You will not have any added costs from being in this study.

Will you receive any payments for participating in this research study?
You will not receive any payment for participating in this research study.

What happens if you are injured while participating in this study?

For medical emergencies contact 911 or go to the nearest Emergency Room.
If you think you have been injured as a result of taking part in this research study, tell the principal investigator as soon as possible. The principal investigator's name and phone number are listed in the "Who can answer your questions about this study?" section of this consent form. You will receive medical care and treatment as needed from Northwell Health to treat injuries directly resulting from taking part in this study. However, we may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of those costs. There are no plans for Northwell Health to pay you or give you other compensation for the injury. By signing this form, you do not give up any of your legal rights.

What are your rights as a research participant?
Your participation in this project is voluntary. The quality of your medical care will be the same, whether you join, decline to join, or decide to leave the study.

If you do not join the study, you will not be penalized or lose benefits to which you are entitled. If you join the study, you may withdraw your participation at any time without prejudice to future care at Northwell Health. Follow-up examinations may be needed to assure your well-being.

Could you be taken off the study before it is over?
It is also possible that your participation in this study may end without your consent. This decision may be made by a researcher, study sponsor or the Institutional Review Board (IRB- the committee that oversees research at this institution).

Reasons for withdrawal may include:

- failure to follow instructions,
- failure to show up for study visits,
- it is not in your best interest to continue this study, or
- the study is stopped.

If you withdraw from this study or if you are withdrawn from the study, any data (or samples) already collected will continue to be used. However, no new data will be collected.

What happens if new information is learned?
You will be told of any new findings that may change your decision to continue to participate. Your consent to continue to take part in this study may be obtained again.

What information will be collected and used for this study?

If you agree to be in this study, we will collect health information that identifies you. We may collect the results of tests. We may also collect information from your medical record. We will only collect information that is needed for the research. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. If you do not want to provide authorization, then you cannot participate in this research study.

Who else will see your information?
Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Northwell Health, except as detailed below. Investigators will share information collected from this research study with:
· study sponsor and/or its agents,
· other researchers,
· accrediting agencies,
· data safety monitoring board,
· clinical staff not involved in the study who may be involved in participant's treatment,
· health insurers or payers

The following reviewers may access your study and medical records to make sure that this study is being done properly:
• Representatives from Northwell Health's Human Research Protection Program (the group of people that oversees research at this institution)

We will do our best to protect the privacy of your records, but it is possible that once information is shared with people listed on this form, it may be released to others. If this happens, your information may no longer be protected by the federal law.

In the future, we may publish results of this study in scientific journals and may present it at scientific meetings. If we do, we will not identify you .

If the researchers learn about potential serious harm to you or someone else or other public health concerns, it will be shared with the appropriate authorities.

Will you be able to access your records?
If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, please call the Human Research Protection Program at 516-465-1910.

How long will your health information be kept?
There is no limit on the length of time we will keep your information for this research because it may be analyzed for many years. We will keep it as long as it is useful, unless you decide you no longer want to take part, or we close the study. You are allowing access to this information indefinitely.

Can you change your mind?
If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you will need to send a letter to the researcher at the following address:

Investigator: Dr. Sharon Hyman
Address: 1991 Marcus Avenue, suite M100
New Hyde Park,
NY 11042

Daytime Phone Number: (516) 472-3750

Your letter should say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

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

Will my information be used for research in the future?

Information collected from you may be used for future research studies, or shared with internal or external collaborators. Your data may be retained indefinitely in government-supported or private databases developed to make data available to researchers. Research results and data may be submitted to and shared via these entities. Some databases permit public access to the data for future research. Your data may be combined with data from others, or may be available as individual-level data. Some databases control who has access to the data for use in future data protection policies. In either case, information such as your name or other direct identifier will be removed before any information is shared for future research. Since directly identifying information will be removed, there will not be an additional consent for future research. By consenting to participate in this study you are agreeing to allow your data to be used by future researchers without additional consent.

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Does the investigator of this study receive money if you take part?
The investigators on this study do not receive money for your participation in this study.

Who can answer your questions about this study?
If you have any questions about the study, you may call Dr. Sofya Ilmer at (516) 472-3750. If you have questions about side effects or injury caused by research, you should call Dr. Sharon Hyman at (516) 472-3750. If you need emergency care, dial 911 or go to the nearest Emergency Room. If you have questions about your rights as a research participant, concerns about being in the study, or would like to offer input, you may contact the Office of the Institutional Review Board (the committee that oversees research at this institution) at (516) 465-1910.

A signed copy of this consent form will be given to you.

Summation/Signature
You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. A member of the research team will answer any future questions you may have. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

_____
Printed **Preferred** Name of Participant/Healthcare Agent/Guardian/Next of Kin

_____
Printed **Legal** Name of Participant /Healthcare Agent/Guardian/Next of Kin (***if different from preferred name only***)

_____ _____
Signature of Legal Name of Participant/Healthcare Agent/Guardian/Next of Kin Date

_____ _____ _____
Witness's Printed Name Witness's Signature Date
(Note: A witness can be a member of the research team, but cannot be the same person signing consent as the investigator)

Investigator's Statement
In addition to advising the above participant of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are/or may be associated with this study and to answer any further questions relating to it.

_____	_____	_____
Investigator's Printed Name	Investigator's Signature	Date