PERSPECTIVES

NEWSLETTER OF THE NORTHERN CALIFORNIA THALASSEMIA CENTER

UCSF Benioff Children's Hospital Oakland

Winter 2017

THE BENEFITS OF EXERCISE

By Elijah Goldberg, Ellen Fung, PhD RD, Shannon Gaine, FNP

What is Exercise?

Exercise encompasses a variety of activities, many of which we engage in every day.

Activities can be categorized as weight bearing or aerobic, and by level of intensity: light, moderate, and vigorous. Light intensity exercises include gardening or slow walking, while moderate intensity exercises include brisk walking or water aerobics. Vigorous activities may include running, aerobic dance, or any other activity that increases your heart rate and causes you to sweat.

Both light and moderate intensity exercise should be engaged in often, and sedentary, or non-active, behaviors should be minimized. These include watching TV, playing video games, or sitting at a computer for long hours. In the U.S. and around the world people are increasingly sedentary, paired with reduced physical activity.

Why is Exercise Important?

Exercise is a cornerstone to both physical and mental well-being. In individuals without chronic illness, exercise has been shown to provide a wide variety of benefits including: improved sleep, reduced stress, increased energy and stamina, body fat reduction, improved cardiovascular fitness, and reduced heart disease. These rewards lead to an increase in personal productivity, life span, and enable individuals to live more fulfilling, active lives.

Studies in young children have demonstrated that exercise improves school performance, and reduces mental illness in adults.

For those with chronic illnesses, the benefits of exercise may also increase feelings of normalcy, improve quality of life, and significantly increase academic success. The overall advantages of physical activity stretch across the entirety of one's life, and it can't be stressed enough how important it is to get out there and exercise.

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THE BENEFITS OF EXERCISE

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Why is exercise important for patients with Thalassemia?

For patients with thalassemia, exercise could be viewed as an uphill battle. Studies have shown that patients with thalassemia engage in significantly less physical activity and spend more time on sedentary activities than healthy individuals. A busy lifestyle along with frequent hospital visits can reduce time to exercise. Some patients may also experience pain which is a physical barrier to exercise. Additionally, significant cardiac iron overload may further decrease exercise capacity. Finally, many patients experience fatigue, often close to the time of transfusion, which can affect the motivation to exercise.

Individuals with thalassemia should not wait to exercise until they feel they have enough energy; regular exercise will create the energy to continue. The benefits of exercise may actually be greater in thalassemia as studies have shown patients have reduced muscle mass and are at higher risk for osteoporosis. Exercise can stimulate both muscle and bone growth and increase bone strength.

For regularly transfused patients who are able to exercise safely, exercise intensity may need to vary if fatigue is a factor. Hemoglobin has a direct impact on exercise capacity, and patients who have frequent fatigue may benefit from a maintaining a higher hemoglobin level.

How Much Exercise do you Need?

For children and adolescents, the Center for Disease Control (CDC) recommends 60 minutes of physical activity per day. For adults, the CDC recommends a minimum of 150 minutes of moderate activity every week. Time spent engaging in physical activity should be split

between aerobic, muscle strengthening, and bone strengthening activities. These recommendations for aerobic activity have been translated into the number of steps per day for children and adults. For adults, a minimum of 10,000 steps/day is recommended. Girls and boys need more: a minimum of 12,000 to 15,000 steps/day, respectively, for the same level of physical activity.

Guidelines like these are not always applicable for individuals with chronic illnesses; the extent to which physical activity can be performed should be determined on a case-by-case basis. For individuals experiencing severe pain or fatigue, or those with a history of fracture, consultation with your healthcare provider is recommended to reduce risk of injury.

How Can You Track Exercise Goals?

To ensure you are meeting your exercise goals, there are many different types of activity monitors that can be used track your progress. Wrist worn activity monitors all have health applications that can track your daily steps and energy expenditure, monitor your heart rate, and allow you to set personal exercise goals. If you choose to purchase a fitness tracker, it's best to read up on which device suits your needs before buying. There are also free apps for your smartphone that can track your steps if you carry your phone with you throughout the day. Alternatively, you can simply record the amount of time you spend exercising every week.

Those who incorporate exercise into their daily routine and identify friends to keep them accountable to the routine will have greater success at making exercise a daily part of their life.

What Can You Do?

You should select daily activities or sports that you enjoy — maximizing the likelihood of continued physical activity. Some exercises can be done from a sitting position; seated running, leg extensions or heel raises can all be performed in a chair. Another accessible type of physical activity is isometric exercise. Isometric activities are performed in a static position using muscle contractions to stay in the same position; examples include the plank or wall squats. Isometric exercises improve muscle tone, can be performed in the comforts

HIKE WITH THE THALASSEMIA TEAM!

Come put your best foot forward and join us on a hike with the Thalassemia team! We will be planning a hike on **March 24th, 2018** in the Berkeley Hills. Our team will be hiking together and inviting families and patients to join for a morning of some exercise and fresh air! Please monitor our website for details to follow.

of your home, and don't require fancy weight equipment. Your local club is also a great resource for recreational classes of all types (e.g. swimming, ballet, basketball). For adults, joining a gym or taking a yoga or dance class can be a fun way to engage in physical activity. For kids, daily participation in P.E. and after school sports is encouraged.

Wherever you decide to exercise, doing so with a group, family, or friends can promote adherence to physical activity and add to the fun!

Summary

- Exercise is important.
- Frequently engage in light and moderate intensity activities; these have numerous benefits for individuals with thalassemia.
- Experiment with exercise, and find activities that work for you.
- Make exercise a priority in your life; you will be rewarded through a healthier body and a happier mind.
- If you have questions about exercise, ask your healthcare team about how to get started!

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Interview with Kim

Hi! I'm Kim. I'm a petite beta-thalassemia major patient who is asleep the minute the first unit of blood is hanging. I've been working out since I was a sophomore in high school and can't imagine ever giving up. I'm a mom to a four-legged Maltese Mix pup who loves to play fetch and be spoiled with hugs and kisses. As a little kid, I always wanted to be a nurse and made that dream come true a few years ago. Now, I'm a pediatric hematology/oncology nurse, I am loving every minute of it, and often have a private giggle at how funny life can be. I'm somewhat of a globe trotter: every year I try to go somewhere overseas and explore other cultures.

When did you start incorporating exercise into your daily lifestyle?

I started seriously exercising when I was a teenager in high school. Being a teenager and feeling the pressure to "fit in", I started to work-out to manage my weight. That time has passed and now I work out to maintain weight and stay healthy.

What type of exercises do you enjoy?

For me, I always like exercises that change constantly. I'm not the type to sit on a bicycle or run for 30+ minutes. Luckily, I found a private gym that provides personalized group training with a mix of circuit training, boot camp, and HITT. I absolutely love it!

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Interview With Kim, continued:

What benefits have you experienced from exercising regularly?

Weight and Diet! Since working out, my body doesn't crave the sugary and salty foods as much. I still love my French fries. But it's easier for me to say no to sweets and salty foods.

Bone Density. Although thalassemia can cause early onset osteoporosis, my bone density scans have been consistent over the years.

Mental Relief. I treat my work out time as MY TIME. It's my time to just relax.

Strength. I've gained muscle mass, core strength, and flexibility. I lift weights that don't make sense if you look at my size. My trainers don't know about my thalassemia. That's my choice, because I want them to push me as hard as anyone else and not feel hindered because of my condition.

Youth. I look younger than my age.

What would be your best advice for someone looking to start exercising?

My best advice and what I tell all my friends: Don't overdo it! Start off easy and simple. Just like you, your body has to learn and adjust to this new demand. Take it easy, slowly build up your strength and then challenge it slowly.

Additionally, start off with something you ENJOY doing...whether it is hiking, dancing, yoga, biking, playing ping pong, frisbee, rock climbing, etc. Try something new, or what you have always though would be fun.

Have you ever experienced any setbacks or barriers to exercise? If so, how did you overcome them?

When I was little, my parents were always afraid of me over-exerting myself because of my thalassemia. They didn't let me do anything physically demanding as a child (no dance classes, sports, or playing outside). I think my mom thought that I should have been excused from PE in school altogether and at one point I almost got my doctor to write me an excuse letter until he found out that I was getting an A in PE. So when I started to consistently work out, my parents were cautious and worried. My mom tried to dissuade me but I'm incredibly stubborn. My dad recognized the need for it, saw the determination in me, and would from far away oversee my work-outs and show me lifting techniques.

Another set-back that I experience is dealing with the ever changing hemoglobin. For the most part, in my day-to-day activities, I don't notice a difference in energy level between right before and after transfusion. The only way I know it's time for a transfusion is when I hit the gym. As my transfusion date gets closer, I'll notice that I'm slightly breathing harder, taking longer breaks between sets, or having more difficulty to lift the same weight compared to when I just get transfused. Sometimes I don't notice any difference. But when I do, I just adjust and allow myself that additional second or two to keep going. I never allow myself the excuse "I'll just not go today because I have transfusion in 2 days". I have BAD days. There are days when I'm too exhausted and I am debating with myself if it is even

worth going. Those are the days where I keep repeating to myself "It's better to have a bad workout day than to not work out at all". At the end of it, I'm glad that I went.

One more set-back that I'm dealing with is a weak right knee, which came about slowly over time. When I first started working out, I did not have any issues with my knees. But as I kept working out, I noticed that I was favoring my left knee. I've had scans to see if something was wrong structurally, but everything came out normal. So now, unfortunately, there are days when I'm at the gym and when I do isolated moves, my right knee feels weak and can't bear it. My trainers are well aware of this, ask me how my knee is for that day and will

adjust the exercise if needed for me. It doesn't stop me from working out; it just means I have to do an alternative exercise.

Read the full interview online.

PATIENT SUPPORT GROUPS FOR THALASSEMIA: A PERSPECTIVE

By Robert Yamashita, PhD
Outreach Director

The biggest obstacle to achieving a successful long-term outcome in thalassemia is patients' adherence to iron chelation therapy (ICT). Before oral chelators were introduced, subcutaneous infusion of deferoxamine (Desferal®, "Des") made adherence to therapy a challenge. These problems drove the need for patient-led support groups in the 1980's and 1990's.

With sponsorship from Cooley's Anemia Foundation, patients started the Thalassemia Action Group (TAG), which empowered them to advocate for themselves. It also provided patients a platform to network and share experience of living with thalassemia. It quickly became apparent that the quality of thalassemia expertise and care varied greatly at different facilities. The development of the standard of care guidelines for thalassemia by Oakland was largely driven by such realization, and the assessment of needs of patients living across the country.

Things changed with the advent of oral chelators in the 2000's, which were felt to resolve all issues with adherence. These had a real and highly significant impact on the lives of all individuals with thalassemia. It seems that, at the same time, the need for a patient support group decreased, and TAG ceased to exist.

Thalassemia may appear different today, but some old challenges remain, and some new challenges continue to emerge. Life expectancy is much longer, which brings the need to plan for still being healthy and to maintain good quality of life for a long time. The oral chelators are not without their limitations, so that adherence remains a central issue. The changes in the healthcare environment have made patients more aware of the community that they had, and the work that needs to happen to recapture it. There are signs of change, with increased avenues for interaction between patients of different generations. There are nascent efforts to restart conversations. All of these suggest that there is strength in the idea for patient support groups.

WELCOME, VIKTORIIA KOLOTOVSKA

I moved to the US in 2011 from Kiev, Ukraine where I was born and raised. I graduated from the National Technical University of Ukraine with a dual Master's degree in Material Science and Computer Science.

I started my research journey in Material Science by developing point-of-care diagnostic biochips. I had an opportunity to immerse in the world of biotechnology and learn about its medical applications.

I joined the growing Iron Overload Program team at Benioff Children's Hospital in September 2017. I was enticed by the hospital's and the team's culture and their interdisciplinary perspective approach to care for patients with high risk iron overload. As a Study Coordinator, I perform SQUID measurements and assist with the program's projects. I am also excited to be a part of the thalassemia community because the field offers endless opportunities to learn and grow.

In my free time I enjoy being active. My favorite activities are climbing, running and exploring California outdoors.

INTERVIEW WITH JENNIFER FERGUSON

FROM CLINICAL PRACTICE TO CLINICAL RESEARCH

By Jennifer Kim

Welcome Jennifer Ferguson. Jennifer graduated from UCSF School of Nursing with a master's in nursing and family nurse practitioner degree in 2003. She has worked most of her career with vulnerable populations in women's health and with teens at the Alameda County Juvenile Justice Center. In 2014 she joined the hematology research team and began working with patients with rare diseases, most recently focusing on thalassemia. She currently coordinates several trials in thalassemia, brain iron accumulation, Niemann-Pick, and sickle cell disease. In her free time, she loves spending time with her 12 and 9 year old boys, hiking, backpacking, skiing and reading. She and her husband hiked the Pacific Crest Trail together, a 2700 mile trail from Mexico to Canada. This fall, they hiked the Tahoe Rim Trail, covering 300 miles in the mountains surrounding Lake Tahoe.

JK: What made you decide to pursue a nursing degree?

JF: I always knew I wanted to go into healthcare. I was deciding between medicine and nursing school. I decided that I like the holistic view of nursing and I felt like the nurse practitioner route would be perfect for me because I can work autonomously and still be able to treat patients and the families as a whole.

JK: What drove you to work with vulnerable populations in women's health and with teens at the Alameda County Juvenile Justice Center?

JF: I always knew I wanted to work with vulnerable populations. I felt that was where the most needs were. The program at UCSF also focused on working with vulnerable populations, and it was always my goal to work where the most need was.

JK: What made you decide to transition into hematology and specifically thalassemia?

JF: When I first transitioned into research, I worked with a rare disease called PKAN within the Hematology Department. As I got to know the hematology team, I also got to know more about sickle cell disease and thalassemia. Then interesting projects came up in thalassemia. Through those, I got to really know the patients, families, and the broader community of thalassemia. I have really enjoyed that process.

JK: What made you decide to go into research?

JF: What I like about research is that I get to know families in-depth over a long period of time. I felt that the work I was doing in juvenile justice was very episodic. So I didn't get to know the families as in-depth as I would've liked. In research, in the studies that I have been involved in, I get to know families over a long period of time and get to know all of the different aspects of their lives, which I find to be very important when you are trying to provide good comprehensive health care.

JK: Do you also see patients regularly in clinic?

JF: No, not right now. I'm just focusing on clinical research.

JK: What has your experience been like working with individuals with thalassemia?

JF: I find that there is an incredible resilience in the thalassemia community. Patients are living full and active lives. Despite challenges that come with living with a chronic disease, individuals and families are extremely positive and enthusiastic about life, which I find really inspiring.

JK: How has your experience caring for patients with chronic illnesses differed from those with acute symptoms?

JF: In my work before, I was mostly working with individuals who were not dealing with chronic diseases. Therefore, I was seeing people at snapshots in time and caring for one particular thing that would then resolve, whereas my work with chronic diseases and rare diseases has allowed me to work in broader range of healthcare. I get to see the continuity and long term impact of what we are doing to help people living with chronic disease.

JK: What are your goals and aspirations for working with individuals with thalassemia?

JF: We are always working towards finding cures, but I think as a shorter term goal, we should be improving the patients' and families' quality of life on a day to day basis. I don't think this will always occur through big breakthrough drug trials, but also just in our day to day interactions with our patients.

JK: Is there anything else you would like to add ?

JF: It's been truly inspirational working with the team here. I've learned so much from all of the providers and teams in all different areas of hematology and research. I love meeting new families and patients through my work in research and look forward to continuing and building on these relationships for many years.

5th ANNUAL THALASSEMIA ADOPTION CLINIC

By Wendy Murphy, LCSW
Social Worker, Northern California Comprehensive Thalassemia Center

On July 13th and 14th, 2017, the Northern California Comprehensive Thalassemia Center hosted the Fifth Annual Adoption Clinic. The first clinic was held in July 2013 to accommodate the needs of families who had recently adopted a child from China or India with transfusion-dependent thalassemia. Our center decided to have the five families come on the same day for a comprehensive clinic visit and the chance to meet the other families. It was a successful day filled with activities for the children and a lunch talk for the parents with Dr. Nancy Curtis of the International Adoption Clinic at UCSF Benioff Children's Hospital Oakland.

We have continued to host the Adoption Clinic since July 2013. In 2015, we expanded the program to two days as well as including a dinner talk. With the most recent clinic in July 2017, the following experts presented at the dinner talk for the parents:

- Dr. Ellen Fung - "Bone Health in Patients with Thalassemia"
- Dr. Nancy Olivieri - "How Thalassemia as a Disease has Changed in Developing Countries over the Past Decade"
- Dr. Elliott Vichinsky - "Updates on New Therapies in Thalassemia"

The families appreciated hearing from these experts and having the opportunity to ask questions. It was also very important for the families to have the chance to socialize with each other. Most of the families come from states other than California, and many live in a community where their child may not know any other children with thalassemia.

We are looking to expand the clinic this coming year and we hope that more families will be able to attend the dinner talk. The dinner talk will be on Wednesday, July 18th. More details are to come about the presenters. We welcome suggestions and would like to hear from the families to better understand their needs.

VITAMINS, MINERALS, AND YOU

What are the frequent questions about the supplements you are taking?

Talking Nutrition with Connie Schroepfer, MS, RD

There are many reasons why the right vitamin and mineral supplements are important for your health:

- ⇒In thalassemia some vitamins and minerals may be used up at a faster rate.
- ⇒Extra vitamins and minerals are needed to protect cells from damage when you have iron overload.
- ⇒Extra vitamins and minerals are needed for bone health.
- ⇒For children and teens, extra vitamins and minerals are needed to reach full growth potential.
- ⇒It is important that the supplement(s) you are taking have the right amount of nutrients (enough but not too much).

What Multi-Vitamin/Mineral (MVI) supplement to choose:

Your thalassemia team reviews available multi-vitamin/mineral combinations to choose those which have the right amounts of vitamins and minerals to meet your needs.

The recommendation may change if the formulation of the MVI has changed.

It is important that you always check the label to make sure that iron has not been added since the last time you purchased it.

If you find a supplement you would like to take instead of the specific one the medical team has recommended, a good idea is to take a picture of the content label to show the team before you purchase it.

What the medical team looks for in a multi-vitamin/mineral supplement:

1. No iron in any form
2. Enough, but not too much of essential vitamins; not more than 100-250% of RDA (recommended dietary allowance)
3. Essential trace minerals (zinc, copper, selenium) in balanced amounts. NOTE: "gummie" vitamins don't contain copper, and most have a low amount of zinc.
4. Calcium may or may not be included.
   - ⇒ If calcium is not included in the multi-vitamin/mineral, a separate calcium supplement may be recommended if your daily sources from food (mainly milk, cheese, yogurt) are not sufficient.

How to assure you are taking the right supplement(s) and that you take it!

Take a picture of the label(s) front and back to bring with you to your appointments, or better yet, bring the container(s) with you.

And take a picture or bring with you any other nutritional supplements you take, e.g. Omega 3, fish oil, herbal supplements

When you purchase your vitamin, mark on the calendar a date to purchase the next one which is about 2 weeks before the number of pills in the container will run out. Most containers are a 2-3 month supply.

Check the label: is it one, or two, or three of these that will give the amount of nutrients on the label? This isn't a problem with most regular vitamins, but "gummie" types often require 2-3 of them to equal the label amount.

Suggested use: As a dietary supplement, parents may give each child up to two (2) gummy bears per day. Instruct child to chew each gummy bear carefully and thoroughly.

Supplement Facts

Serving Size 2 Gummy Bears

Amount Per Serving		% Daily Value 2-4 Yrs. 4 & Up	
Calories	15		
Total Carbohydrate	4 g	**	1%†
Sugars	3 g	**	**
Vitamin A (as retinyl palmitate)	2100 IU	84%	42%
Vitamin C (as ascorbic acid and sodium ascorbate)	20 mg	50%	33%
Vitamin D (as cholecalciferol)	400 IU	100%	100%
Vitamin E (as dl-alpha-tocopheryl acetate)	16.5 IU	165%	55%
Vitamin B-6 (as pyridoxine HCl)	2 mg	286%	100%
Folic acid	140 mcg	70%	35%
Vitamin B-12 (as cyanocobalamin)	6 mcg	200%	100%
Biotin	60 mcg	40%	20%
Pantothenic acid (as calcium d-pantothenate)	5.2 mg	104%	52%
Iodine (as potassium iodide)	42 mcg	60%	28%
Zinc (as zinc chelate)	2.7 mg	34%	18%
Choline (as choline bitartrate)	40 mcg	**	**
Inositol	40 mcg	**	**

† Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established.

Other ingredients: Glucose syrup, sucrose, water, gelatin; less than 2% of: citric acid, colors (annatto extract, purple carrot juice concentrate, turmeric), fractionated coconut oil (contains beeswax and/or carnauba wax), lactic acid and natural flavors. **Contains: tree nuts (coconut).**

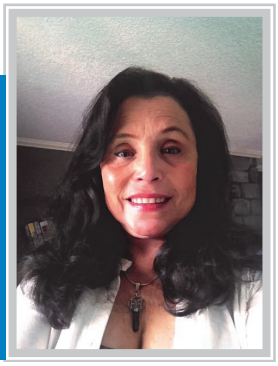
When to take: If the Vitamin C amount is >60 mg, it's best to avoid taking it with meals. You might put the container by your toothbrush to remember to take it in the morning or at night before bedtime.

It might be useful to put the supplements that are recommended for you in a weekly or monthly pill planner.

INTERVIEW WITH SUSAN WINNER

By Jennifer Kim

Susan has been a patient at UCSF Benioff Children's Hospital Oakland for many years. She was extensively involved in a patient-led support group called Thalassemia Action Group (TAG) in New York. She is interested in beginning a similar support group for patients here at UCSF Benioff Children's Hospital Oakland.



Susan Winner

JK: Please tell me a little bit about yourself.

SW: I'm 57 years old. I was diagnosed with thalassemia when I was 2 and I started transfusion at age 3. I started Desferal in 1977. I have educational background in graphic design and in art history.

JK: How did having thalassemia impact your life outside of the hospital?

SW: Well, basically, it was really hard as a child. Because I was iron overloaded, I had dark skin and I was teased and bullied. When I began dating, I didn't know how to tell them that I had thalassemia. I never had a hard time telling it to my girlfriends. When I was 19 I met my husband. I didn't need to tell him that I had thalassemia. He figured out [on his own] that I had genetic disease. I was married at 21 and we have been married for 36 years. He's been super supportive of me.

JK: Can you describe your past experience with support groups for the thalassemia community?

SW: In 1985, I and five other patients started the Thalassemia Action Group [supported] by Cooley's Anemia Foundation in New York. We used to have yearly conferences and Friday night get-togethers with [thalassemia] patients. During the conferences, we used to also have physicians come in to speak about thalassemia. We traveled to other states and got patients involved across the country because we recognized that people from the middle states in the U.S. did not have the same support system as we did.

JK: What made you decide to start the support group? What were your aspirations?

SW: The idea of creating a thalassemia support group started from a patient coordinator at Cooley's Anemia Foundation. She invited me and five other patients from different areas to meet at the Foundation office and start the Thalassemia Action Group.
Our major goal was to reach out to isolated patients and those who were not regularly going to the infusion centers that other patients with thalassemia were at. We also hoped to teach the parents of young children with thalassemia that there is hope for their children. We allowed the parents to have conversations with older patients with thalassemia. Actually, I spoke with this couple who was expecting a baby with thalassemia. Later, they emailed me back thanking me that I spoke to them because without our conversation and my support, they would have aborted their baby. Overall, I just hoped to create a support network for everyone.

JK: Do you have plans for another support group in the near future? What do you hope to get out of it?

SW: Nothing is official yet, but I want to start having activities for adults with thalassemia and try to regroup the community again. I'm planning to ask around to see what types of activities that patients like to engage in.

JK: Lastly, do you have any advice or words of encouragement for youth and young adults with thalassemia?

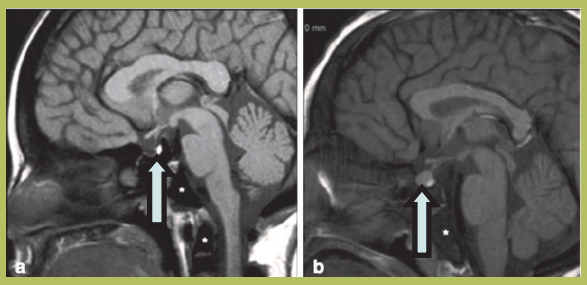
SW: I would say that, it's about patients accepting what they have. If they don't beat themselves up, others won't either. Just feel good about yourself. They are meeting their challenges with their diseases. It's like having a second job; I would advise them to have a positive outlook and attitude. I'm all for early education with the kids and to be honest with them.

IRON AND THE PITUITARY GLAND

Can we diagnose it early and prevent dysfunction?

By Sylvia Titi Singer, MD — Pediatric hematologist/oncologist

The pituitary gland is a small organ that secretes several hormones including growth hormone (GH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). When the iron concentration gets too high in the pituitary, it can cause serious problems in our body's growth and reproductive system, such as delay in onset of puberty. With recent advancement in MRI technology, it is becoming possible to measure the pituitary iron overload and the size of the gland. Intensive chelation and close monitoring of the pituitary function are needed to maintain the appropriate hormone levels.



a. Low signal intensity of the pituitary gland (arrow) with a smaller than normal gland size for age (3.5mm height) in a TDT 12 year old with severe iron overload.

b. Normal signal intensity of the anterior pituitary lobe with a normal pituitary size for age (6mm height) in a TDT 11 year old with mild iron overload.

Most individuals on regular transfusions have their liver iron and cardiac iron measured yearly, and they pay close attention to these numbers, recognizing the importance to their health and longevity. Less is known in clinical practice about iron accumulation in hormone-producing organs, pancreas (which produces insulin), thyroid, and the pituitary gland.

The pituitary gland is a small organ at the base of the brain that secretes several important hormones. Among them are luteinizing hormone (LH) and follicle stimulating hormone (FSH), which regulate the reproductive system. LH/FSH stimulate the ovaries in females and testes in men to produce estrogen and testosterone, respectively. These hormones are involved in pubertal development, and in the ability to produce sperm in men and induce ovulation of oocytes (eggs) in women, thus enabling men to father a child and women to get pregnant. When iron accumulates in the pituitary, after a certain concentration, it reduces the secretion of hormones. When severe enough, this causes a condition called hypogonadotropic hypogonadism, where children have a delay in starting puberty, women do not get a menstrual period (or stop having one), and men produce less than the normal amount of sperm.

Hypogonadism is the most common endocrine problem in patients with transfusion-dependent thalassemia (TDT), with a prevalence rate of over 50% in several large studies. It is believed that the hormone-producing cells of the pituitary are particularly sensitive to iron toxicity. Early recognition of iron loading of the pituitary and low hormone secretion is very important because hypogonadism is only partially reversible by intensive chelation. Unfortunately, pituitary dysfunction is difficult to measure before puberty because of immaturity of the hormone producing system.

In recent years, MRI technology has advanced to enable measurement of iron level in the pituitary (in the same way that iron is measured in the heart), as well as the dimensions and size of the gland. These results can be compared to normal values by age and gender. Though a helpful tool, MRI of the pituitary is not done routinely for clinical assessment at this time.

With this in mind, we conducted a study in Oakland on patients over 10 years of age who were on regular transfusions. We wanted to determine the age and progression of pituitary iron deposition and understand when the gland starts to shrink in size. We checked how these findings on MRI affect the reproductive hormones (LH, FSH, estrogen and testosterone). In women, an additional hormone called anti-Müllerian hormone (AMH) was also measured to estimate the fertility potential. We also examined how iron overload in the liver and heart relates to the iron deposition in the pituitary.

The study showed that patients with transfusional iron overload begin to develop abnormal pituitary iron load in the first decade of life. However, the critical time is between 10-20 years of age as many patients can rapidly accumulate pituitary iron, and pituitary volume loss first becomes evident. The volume loss is then more significant during the third decade of life.

Many women in this age range (25-40 years old) have no menstrual period and have very low AMH levels, suggesting that spontaneous pregnancy will be difficult. Similarly, in men at this age range, low LH/FSH resulted in very low testosterone levels requiring replacement therapy; some that were analyzed, had low sperm counts.

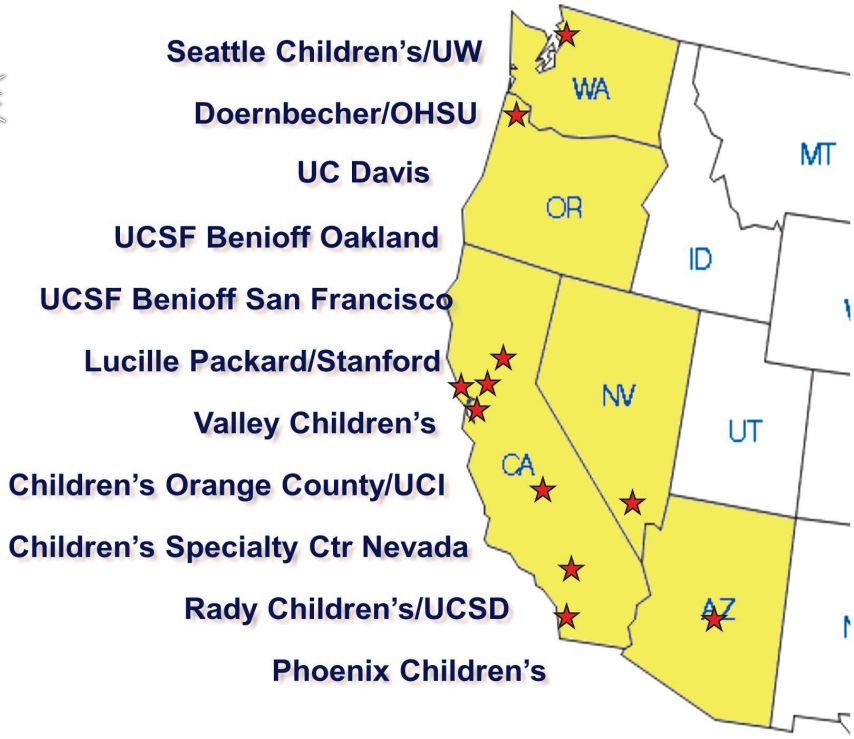
We found that higher pituitary iron level was related to reduced gland volume; meaning that increased concentration of iron causes the gland to shrink, probably due to a direct toxic effect of iron on these sensitive cells.

This stage is important to recognize; it is possible that if the increased pituitary iron is recognized early enough and more intense chelation is given, further permanent cell damage and gland shrinkage can be prevented. There are some exceptions, as some patients even with moderate-to-severe pituitary iron overload retain normal gland volume and function.

Pituitary iron deposition is related to cardiac iron and liver iron concentration. We found that high cardiac iron (T2* less than 20 ms) and high liver iron (over 10 mg/gram dry liver weight) are highly associated with a level of pituitary iron that can cause loss of gland volume and hypogonadism.

In summary, pituitary iron deposition accelerates in adolescence and later. Both pituitary iron overload and presence of volume loss are independently associated with low hormones levels, hypogonadism and low fertility. If treated early enough with intensive chelation, it is likely that further damage and irreversible volume loss can be prevented. The study also suggests that maintaining good control of liver and cardiac iron reduces the risk of pituitary iron deposition. There is a need to conduct a longitudinal study and monitor these parameters over time to understand these important relationships between pituitary iron, iron in the other organs, and chelation therapy.

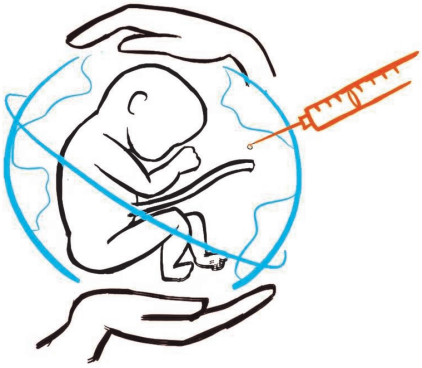
Ollie, Halloween 2017



The *Thalassemia Western Consortium* is a network of specialty thalassemia centers to improve access to comprehensive care for individuals with thalassemia.

ALPHA THALASSEMIA MAJOR CLINICAL TRIAL

By Billie Lianoglou,
LCGC Genetic Counselor at UCSF Fetal Treatment Center



The UCSF Fetal Treatment Center and UCSF Benioff Children's Hospital Oakland have opened the first FDA approved phase 1 clinical trial to perform *in utero* stem cell transplantation. Alpha thalassemia major causes severe anemia in the fetus, and is usually fatal in utero. The only current treatment for supporting the fetus through pregnancy is fetal blood transfusions. Newborns continue to need chronic transfusions to treat the severe anemia. Stem cell transplant after birth can cure the disease completely but there can be significant complications and it is often difficult to find a suitable stem cell donor.

Our team has developed a new strategy of in utero stem cell transplantation with the goal of curing the fetus before birth. By using the mother as the stem cell donor, this therapy takes advantage of the natural immune tolerance that occurs in pregnancy between the mother and developing fetus.

Ten women with a diagnosis of alpha thalassemia major during pregnancy will be enrolled. The stem cell transplantation takes place once in the pregnancy at the same time as a needed *in utero* red blood cell transfusion between 18 and 25 weeks gestation. Participants will continue to receive *in utero* blood transfusion approximately every 3 weeks until close to term delivery.

This study is supported by a grant from the California Institute of Regenerative Medicine and is led by pediatric and fetal surgeon Tippi MacKenzie, MD, of the UCSF Fetal Treatment Center, and Elliot Vichinsky, MD, Northern California Comprehensive Thalassemia Center at UCSF Benioff Children's Hospital Oakland. This is the first stage in developing an effective, minimally risky therapy for inherited blood disorders with plans to expand to other disorders in the future.

For information about the trial, please call:

1-800-RX-FETUS
(1-800-793-3887)

Study contact at the UCSF Fetal Treatment Center:

Billie Lianoglou, LCGC
(415) 476-1004.

Send email to fetus@ucsf.edu.

To learn more about alpha thalassemia, families or providers can call the Northern California Comprehensive Thalassemia Center at 510-428-3347 or visit our web site thalassemia.com.

More information:
thalassemia.com/services-intrauterine-therapy.aspx
fetus.ucsf.edu/research/intrauterine-therapy-alpha-thalassemia-major

Open Research Studies

Title	Abstract
2002-075 Natural History of Iron Burden and Risk of Organ Injury as Assessed and Predicted by Non-Invasive Measurement Techniques	Longitudinal assessment of whole body iron burden is essential for managing chelation and phlebotomy therapies and may be effective in predicting risk of organ injury. Biomagnetic susceptibility measurement of liver iron concentration using SQUID technology. We will assess iron burden by biosusceptometry and serum ferritin at CHRCO and evaluate the clinical evidence of cardiac, hepatic, endocrine and orthopedic dysfuntion, and relate it to total iron burden as assessed by biosusceptometry and other non-invasive techniques.
2016-073 Evaluate the Efficacy and Safety of RBCs Derived from Mirasol-treated Whole Blood Compared with Conventional RBCs in Patients Requiring Chronic Transfusion Support (PRAISE Trial)	Thalassemia is the most transfused syndrome worldwide. The risk of transmitting pathogens is reduced by pre-screening of blood donors and testing of the blood. The Mirasol System offers a means to make transfusions significantly safer by targeting unscreened and undetected pathogens. This is a prospective, multi-center, randomized, crossover trial to evaluate the clinical effectiveness of RBCs derived from Mirasol-treated WB versus conventional RBCs in transfusion dependent thalassemia patients.
2016-082 Towards the Development of a Noninvasive Prenatal Testing for Beta-Hemaglobinopathies	The goal of this project is to show proof of concept for a non-invasive prenatal test (NIPT) for beta-hemoglobinopathies utilizing a novel DNA probe capture assay and next generation sequencing (NGS). Our preliminary data have shown that our probe capture/NGS system can overcome the challenges implicit in the analysis of cfFDNA for NIPT: low DNA amount. The final proof of principle for this NIPT assay requires blood samples from pregnant couples, confirmed to have mutations in the beta-globin gene. For this work we are collaborating with our Indian colleagues at the Postgraduate Institute of Medical Education and Research, Chandigarh.
2017-002 Evaluation of Human Erythroferrone in Thalassemia	The purpose of this research study is to learn more about proteins that regulate iron in the blood in patients with thalassemia. Blood transfusions are used to treat thalassemia which leads to excess iron in the body. Studies have shown that individuals with thalassemia can develop iron overload even if they are not receiving transfusions. Protein signals in the blood affect the way iron moves through, and how iron is stored in, the body.
2017-065 Standardizing techniques to measure pancreas volume and identify head, body and tail with MRI in transfusion dependent thalassemia.	Patients with thalassemia require frequent blood transfusions, putting them at high risk for loading iron into their pancreas. As a result, patients can develop endocrine and exocrine aberrations, abnormal pancreatic growth patterns, and the onset of diabetes mellitus. In contrast to non-iron overloaded patients with diabetes, the excessive amounts of iron and diabetes mellitus cause significant variations throughout the pancreatic geometries of our patients, especially after a splenectomy. The purpose of this study is to develop standardized measurement techniques that will define the geometry of the pancreas in our patients with thalassemia. Using MRI technology, we retrospectively analyze scans to develop and standardize techniques to measure pancreatic volume and length in this population.

Title	Abstract
2016-032 A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent -Thalassemia, who do not have 0/0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral A-T87Q-Globin Vector in Subjects 12 - 50 Years of Age	This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with β-thalassemia major. Patients must be at least 12 years of age with transfusion dependent β-thalassemia who do not have the β0/β0 mutation and are clinically stable to undergo transplantation but who lack a suitable matched family member donor.
2017-050 A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent B-Thalassemia, who have a 0/00 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral Globin Vector in Subjects 12 - 50 Years of Age	This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with transfusion dependent β-thalassemia. Patients must be at least 12 years of age with the β0/β0 mutation and be clinically stable to undergo transplantation but who lack a suitable matched family member donor.
2017-075 Longterm Follow-up of Subjects with Hemoglobinopathies Treated With Ex Vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced With a Lentiviral Vector	This gene therapy follow up study is a multi-center trial aimed at providing continued review and reporting on patients with transfusion dependent β-thalassemia or sickle cell disease who have received the bluebird bio LentiGlobin® BB305 Drug Product and who have completed that therapeutic study. This long-term follow up study is designed to monitor patients for 15 years post gene therapy product administration to evaluate long-term safety of the gene therapy drug product used and to monitor long-term efficacy of the therapeutic effects.

We appreciate Brent Bonfiglio for bringing gelato to the holiday party!

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Oakland

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If you no longer wish to receive our newsletter, please email info@thalassemia.com.