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**TRANSCRIPT - GR 07 15 22 “To D or not to D: Understanding the Musculoskeletal & Non-musculoskeletal Benefits of Vitamin D” – Sherri-Ann Burnett-Bowie, MD MPH**  
from the Massachusetts General Hospital

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- 00:44:05 Okay, great Hello everyone hello, everyone in person and the people out there and zoom today we have a great honor today we're hearing from Dr Sherry and Burnett buoy.
- 00:44:17 and Dr Bernabeu is an internationally renowned endocrinologist specializing in Austria process and mineral bone disorders, she completed Medical School at the University of Pittsburgh.
- 00:44:29 In her medical residency and fellowship at mass general hospital having off with a master's in public health from Harvard University.
- 00:44:37 she's remained at mass general hospital since finishing her training and has created a name for herself, not only as a powerhouse of clinical and basic science, research.
- 00:44:46 but also in art and advocate and ally for those who are underrepresented in medicine, she is currently the chair at mgh department of medicine, diversity and inclusion board dedicated to advancing equity and inclusion through teaching investigation scholarship and mentorship.
- 00:45:05 Dr Burnett movie was instrumental in generating generating organizational change at mgh based both on the science of implicit bias training.
- 00:45:15 but also on our own scientific investigations into the field of equity and compensation and representation.
- 00:45:22 What struck me most, when I was reading about Dr brennan movie is her scope and her compassion she's provided the medical community with truly practice changing research driven.
- 00:45:34 basic science insights into the fields of us to process but also has immerse yourself in the town of the moral struggle our age is how to improve representation and equity in medicine.
- 00:45:46 She has done so not only systematically through equity and inclusion inspired research but also relational to her dedication to mentoring and Community engagement.
- 00:45:56 In fact, our own our very own Tyson bell has the honor being listed amongst her impressive list of mentees.
- 00:46:04 And I think we can all agree that if someone has the patience and the moral will and the to mentor Tyson bell she is certainly a special individual and so without further delay, I present to you sherry and burnett buoy.

**Sherri-Ann Burnett-Bowie**

00:46:23 Thank you so much, Dr Khan call for that very kind and generous.

- 00:46:29 Introduction one clarification, it was truly a privilege, in the very easy.
- 00:46:37 To care.
- 00:46:38 bell who has been a superstar from his days interested in seeing onwards so i'm really excited my younger daughter kind of chuckled when she saw my slide table when I was looking at my slides this morning he said.
- 00:46:53 You come up with that title mana I felt like I know I see if some parental chops, so we are going to be really digging deep into vitamin D some physiology but really kind of put into context, how clinicians can.

- 00:47:13 Well, how they should advise patients in terms of what are really the benefits of vitamin D or not, and then I think, maybe, hopefully, there will be some.
- 00:47:23 Research questions that you are inspired to pursue based out of the assignments, so I have no disclosures and we're going to start with a case, but before then.
- 00:47:34 Just as a reminder that you will be able to have a better sense of the pros and cons of screening provider and D deficiency to describe.
- 00:47:42 The goal vitamin D levels for musculoskeletal and non musculoskeletal health so to start with a case, this is a 50 year old postmenopausal patient.
- 00:47:53 The past medical history of pre diabetes, hypertension and low bone density T scores of minus 1.5 at the spine, in particular, who had been referred for low vitamin D and overall bone management.
- 00:48:07 Patient really was quite clear that she did not like this philosophy therapy, because she probably that it pleases your bones.
- 00:48:15 Maybe i'll have the good fortune of coming back on another day to describe why that's not the case she was on antihypertensive medication pretty minimal dietary calcium.
- 00:48:26 her family and social history are notable for her mom having breast cancer multiple sclerosis will come up later and her sister having died of colon cancer, other than it being mildly hypertensive and having a BMI of 29 her exam was unremarkable sold her guard to her laboratory findings.
- 00:48:47 Her surname phosphate was a little bit decrease this was an afterthought, she was supposed to do so, that was not.
- 00:48:56 Too surprising for parathyroid hormone level was elevated and in the context of her having a low dietary calcium intake fat plus her her inviting her urinary calcium of 20 of 50 milligrams over consistent with.
- 00:49:17 Having.
- 00:49:19 A low dietary calcium intake but then you know what What about her 25 K dot C vitamin D so is she vitamin D deficient, how would you treat here and, again, what are the benefits when you think about her globally, of increasing vitamin D.
- 00:49:38 We really have had an experience that are really whole landscape change over time, in terms of what constitutes a normal vitamin D cell.
- 00:49:46 In the 1970s, that was a level of nanograms per ml focus on that, but if you have a say units President as well, but level 10 nanograms per ml or less was considered.
- 00:49:59 Low and then over time, it was creeping up and with that there is also this explosion in sales of vitamin D supplements the sunshine of hormone was seen as the cure all.
- 00:50:12 There was also than a distinction between what's considered low vitamin D and then insufficient vitamin E, where there was it was posited that.
- 00:50:22 Less than 20 was low 20 to 30 was insufficient by keeping in mind that that lifeguards have 25 bucks vitamin D levels of about 80 milligrams per ml.
- 00:50:35 And then in 2011 Institute of medicine, now the National Academy of Medicine turn things over in the bonehead world like coming up with these recommendations and they very explicitly said that.
- 00:50:51 If you're 25 on a population health level if you're 25 the level is 20 nanograms per ml or higher that's normal if you are 12.5 nanograms per ml or less that's deficient.
- 00:51:04 And then there were recommendations mean in terms of what's considered a standard daily intake of vitamin E 600 units if you're a one to 70 years old.
- 00:51:14 A little bit more if you're 70 years old, and they were really pretty emphatic that there were no there was no evidence for different thresholds for different endpoints.
- 00:51:24 I would posit that this was informed by what we've learned about hormone replacement therapy aware.
- 00:51:30 And the nurses health study which isn't epidemiologic study it seemed as if by hormone replacement therapy could only be a good thing.

- 00:51:39 And then in women's health through the women's health initiative, we learnt more that there were pros and content.
- 00:51:46 For me, I saw this as a call to arms for us to really study vitamin D to understand what the benefits are.
- 00:51:54 I think the challenge of studying vitamin D is that most NIH grants the standard if you're so fortunate to have your work plug it it's a five year plan and then potential for renewal.
- 00:52:06 But you could do have to wonder, do we actually have to have for longer periods of observation of at someone's vitamin D level to understand what the benefits truly are so i'll put that out there.
- 00:52:22 In terms of who's at risk for low vitamin D levels, whether you consider that a level of 20 nanograms per ml or the 12 grams per ml.
- 00:52:32 If there's any limit in your sun exposure, so if you're living in Boston as compared to beautiful charlottesville.
- 00:52:41 there's less sun exposure just by virtue of my latitude.
- 00:52:44 And then, if you factor in anything that decreases the likelihood of being able to make vitamin either skin, whether that is skin pigmentation sunscreen or clothing.
- 00:52:54 On these are all risk factors for vitamin D, which puts a lot of us in that space, if your BMI is increased.
- 00:53:02 And there's an increase in likelihood of vitamin D deficiency and there's a lot suggested about why this is true, but.
- 00:53:09 I would argue that we really don't know why there is this association between fits pmi and loads he and it's not that the fat soluble little filmic.
- 00:53:21 vitamin is being stored in fat stores, because there is actually no strong data to support that any form of Mel absorption if you were breastfed baby.
- 00:53:31 And then, for these other causes of vitamin D deficient some of these are causes of low 25 hypoxia vitamin D, which is the dietary measuring that might be a panic failure.
- 00:53:43 or certain medications that increased the metabolism of 25 bucks the vitamin D.
- 00:53:49 And then, when you have chronic kidney disease you can't do that important second I thought solution, and at the level of the kidney and therefore you can't make the activated form of vitamin D 125 times the vitamin D.
- 00:54:01 And then, if you have granuloma forming disorders, where the one alpha headlights lasers present in the granulomas similar to macrophages you can actually have this an increased use of substrate as the cost for the deficiency and 25.
- 00:54:19 As I covered most of this already vitamin D is either meeting by the sun in the skin or if you end up coming up in the Caribbean.
- 00:54:29 Also cod liver oil never get anyone brawling except for the recurring tickets that, but it was a great source of vitamin D So those are the main dietary sources of vitamin D.
- 00:54:40 For terms of foods that are not supplemented the first time I got solution in the liver, a second hand oscillation enter the kidney.
- 00:54:47 Remembering that began 25 D represents dietary stores 125 at the activated farm and this is a nuclear transcription factor and what allows for some of the.
- 00:55:03 explanation for why vitamin D has such a widespread effect and it's known that extra 23 is an important modulator of the generation of 125 I have got C vitamin D with regards to.
- 00:55:23 This stories remembering that it's very imbalance on the concentrations of vitamin D, we have for lower stores have 125 E but that's far more.
- 00:55:38 Have a higher affinity to the vitamin D receptor and then the half life of 125 bag what's the vitamin D is very short, which makes it challenging to measure.
- 00:55:50 It in with regard to identifying who might be at risk for low vitamin D, an additional challenge or the.

- 00:56:01 vitamin D assays with there being significant variability and what's measured, so in this study, there was samples, who are given by 10 different.
- 00:56:15 individuals and measured at these six different laboratories and for each individual there is quite the range of whether they were identified as having a vitamin D level.
- 00:56:31 above or below the threshold which at that point in time was 30 nanograms per ml was the goal that we were hoping to achieve and patients but, as you can see here for each of the individuals, with the exception of maybe have.
- 00:56:48 Individual 10 and individuals, three and four.
- 00:56:53 And two they could either be considered above that threshold or below so this led to the creation of the task group, which is a group that is created at external vitamin D calibration.
- 00:57:10 Quality Control that can be circulated so that we don't have this degree of variation in vitamin D between flaps.
- 00:57:19 So what, in terms of thinking about our first patient and what tests me support a clinical diagnosis of vitamin D deficiency, there are a few of them and i'm going to wash them.
- 00:57:29 All now so if your parathyroid hormone is elevated that can support vitamin D deficiency but anytime you're assessing parathyroid hormone, you have to do it in the con.
- 00:57:42 You have to also consider what someone's calcium intake is whether it's dietary or supplemental because that can influence it.
- 00:57:50 If you have a low urinary calcium, as I mentioned earlier that supportive of a diagnosis of vitamin D deficiency your 125 by HIV vaccine vitamin D can be any level so it's really not clear that.
- 00:58:03 you're that you can sense, it can be any level in vitamin D deficiency there's not much that I anchor on when I think about 125 in terms of what the 125 level should be.
- 00:58:17 Our bodies really do not like being Hypo cal scenic and you have to have pretty profound vitamin D deficiency and potentially impaired.
- 00:58:29 parathyroid hormone function for Hypo kelsey nia to develop, because the body Defense against typo kelsey nearby elevating parathyroid hormone and drawing calcium from the skeleton to supply.
- 00:58:43 A nerve cell signaling etc hyperphosphatemia is something that can often occur in the setting of vitamin D deficiency.
- 00:58:51 And the pathway to the hypervisor timmy is the elevation and parathyroid hormone, so I at the case I I attributed the patient's slightly decreased.
- 00:59:02 Some phosphate to the time of day, so to be able to distinguish is a time of day trading hyperphosphatemia is that postprandial status driving it or is it hyperparathyroidism.
- 00:59:16 Measuring some phosphate when someone is fasting and edm is the best way to do it, and then, if someone has long standing vitamin D deficiency and or calcium deficiency, they can develop element and alcohol and ferocity secondary to an underlying all stimulation.
- 00:59:37 But I think well they're all of these are tests that can be supportive of a diagnosis of vitamin D deficiency, as I mentioned dietary calcium and taking influence it.
- 00:59:47 As a as an influence, and also, if you have any in the way of decreased go mariel filtration right back and also influence the levels.
- 00:59:58 There are a number of epidemiological data showing the prevalence of vitamin D deficiency in different groups on this and haines analysis looking over all at the percentage of people who is 25 bucks the vitamin D levels are less than 20 it was more likely when the study was done for.
- 01:00:19 You males to have.
- 01:00:24 put up flip it was more likely for females or women to have load 25 K dot C vitamin D that men they didn't measure individuals who identified as non binary.
- 01:00:35 And then, as over time, you also see that children are least likely to be efficient and then there's an increase in prevalence of vitamin D deficiency of with aging.

- 01:00:53 In this now we're looking at the actual measure to 25 bucks the vitamin D and three groups from n haines in non Hispanic white participants in Hispanic participants and in black participants in with as we look at the population aggregate data, keeping in mind that this is.
- 01:01:18 Still in the context of the social contract nature of rates and, but there are some trends that we can see here where on average.
- 01:01:28 There were higher vitamin D levels in individuals classified as white person's individuals classified as black with individuals who are classified as Hispanic Mexican Americans specifically being intermediate in between, and again that vitamin D levels decrease with aging.
- 01:01:50 This is a study that we performed ha, taking advantage of 600 plus subjects who would come in healthy volunteers for research subjects, because we were very curious.
- 01:02:01 In individuals who are being recruited for help, what is the prevalence of 2500 C vitamin D across different thresholds and what we observed using that 20 milligram per ml threshold is that.
- 01:02:15 46% of our male of participants 31% of our female participants again and we did not have the option for participants to choose non binary when this the studies were done.
- 01:02:30 There was a flip of what i've shown you before where there is a lower percentage of women who were vitamin D deficient and this is right now to be a reflection of increase supplement news.
- 01:02:43 We were able to have more data around the prevalence of vitamin D deficiency individuals who identify as Asian and this is a little bit of a still.
- 01:02:58 very much an aggregate level measure, because in this study we're combining individuals who might originate from Southeast Asia with those who originally from East Asia or Asia at large, but really significant.
- 01:03:18 prevalence of vitamin D deficient are low vitamin D and we did not necessarily report out on clinical measures only have served of the testing that I mentioned beforehand of.
- 01:03:29 BBC hyper parathyroid ISM or not, and we did officer of the known seasonal variation in vitamin D deficiency with.
- 01:03:38 The lowest prevalence of vitamin D deficiency happening and people who came in during the summer, after all, of the wonderful exposure to something.
- 01:03:47 So, with regard to the benefits associated with normal or increase 25 hypoxia vitamin D, now that we have a sense of the fact that this is something that's very prevalent if you use a 25 K Black Sea level of 20 nanograms per ml or less to define low vitamin D.
- 01:04:06 What are the benefits associated with it, the demonstrated benefits associated with either normal or increasing vitamin D so much of this work was informed by the identification of vitamin D receptor in 1987, it is a.
- 01:04:24 Important in cell signaling.
- 01:04:27 activating when 125 I had roxy vitamin E binds to it, then there's activation of multiple nuclear transcription factors as pretty ubiquitous.
- 01:04:37 And that its President, most just use with a few exceptions, red blood cells straight in muscle on some highly differentiated brain brain cells, do not have the vitamin D receptor.
- 01:04:48 Other vitamin D receptor is required for here and I actually had a chance to work with some of these myself Dr Murray, to me, is a colleague and.
- 01:04:59 She developed with vitamin D receptor knockout mouse that has a very distinct you know type it has it has alopecia for the homeless, I get knocked out the heterozygous while it has here, it does have the large dermal system that are part of the presentation for of the knockout mouse.
- 01:05:27 So this table is supposed to be difficult to read, but what it's representing is that once the vitamin D receptor knockout mouse is generated by.
- 01:05:39 me there is this ability to look and determine the phenotype of these mice and there was a bone phenotype there was.

- 01:05:52A scanner phenotype that I showed you there was an immune phenotype as well as a cardiovascular phenotype so This again is how this this over time, expanding Australia, the influence of vitamin D how that.
- 01:06:08evolved.
- 01:06:10So, with regard to vitamin D and cancer so i'm going to start with the non muscular skeletal benefits of vitamin D and, if you remember.
- 01:06:20Our case of the patient had a sister who died of colon cancer.
- 01:06:28125 bucks a vitamin D, the activated form does have Antonio plastic effects that have been demonstrated in vitro.
- 01:06:38Where there's either inhibition of growth induction of a pop justice or promotion of differentiation in different cancer cells there's also some data that 125 day actually vitamin E may be anti angiogenic.
- 01:06:56When i'm in the setting of vitamin D receptor deficiency, there is in there, an evil data related to increase in skin and pulling tumors as well as a induced leukemia.
- 01:07:14But when we think about bringing it to humans, the first major signal and just to point out, this was published in 1980.
- 01:07:23that there was a connection between vitamin E and cancer was this epidemiologic assessment of colon cancer mortality rate per hundred thousand population.
- 01:07:36And what you observe here in those states where there's less and the way of solar radiation to Massachusetts is right here i'm.
- 01:07:49versus states that have increased solar radiation so Virginia, is not here, but my assumption is that it should be here and that there was a real difference in who was dying from colon cancer with there being for lower colon cancer mortality in the sunnier states.
- 01:08:13So this was a.
- 01:08:17major part of the women's health initiative trying to understand the role of vitamin E and calcium supplementation on the risk of developing colorectal cancer so as a reminder.
- 01:08:32In the women's health initiative which studied 36,000 women over 40 sites, the intervention was 1000 milligrams of elemental calcium and 400 units of vitamin D versus placebo, so what would sound like a relatively low dose.
- 01:08:58Over the eight years of the study.
- 01:09:03There were.
- 01:09:05Advanced invasive colorectal cancer in particular that occurred, but what you can see here is that there was overlap of the intervention group.
- 01:09:18And the placebo group until about year five and then it seemed to separate with the intervention group actually having a higher rate of invasive cancer so with regard to the findings of this study, there was no evidence of.
- 01:09:39calcium and vitamin D, reducing the risk of developing colorectal cancer.
- 01:09:49I think it's hard when you go into a study and you do not find what you're hoping to find so and remember what I said earlier about maybe eight years is not long enough to see if the effective intervention, the women in the study we're not recruited for vitamin D deficiency.
- 01:10:11So they went back and they looked at participants at their baseline vitamin D.
- 01:10:19and looked at those who have 2500 C vitamin DS have told nanograms per ml or less at the baseline of the eight Year study versus those who's 25 payback C vitamin D is 23 nanograms per ml on one.
- 01:10:37And what they observed in this post hoc analysis was that there was a higher rate of invasive colorectal cancer, if your vitamin D was low when you started to study so very provocative.



- 01:10:55 This is sitting on the nasher some important work from Dr Kenny ang where she studied 1000 patients 1000 plus patients with advanced or metastatic colorectal cancer and again looked at their vitamin D levels.
- 01:11:15 At baseline this was not a vitamin D intervention and she looks the majority that something quite striking were.
- 01:11:29 63% of the group had vitamin D levels of less than 20 and then she prepared those who had their 25 hypoxia vitamin D level eight nanograms per ml as a median versus 27.5 nanograms per ml and what she observed was that, even after adjusting for.
- 01:11:57 chemotherapy race, age, those who were in the highest.
- 01:12:06 quintile vitamin D had the longest survival so 33 months versus 25 months of overall survival, then in terms of looking at progression free survival again being in this highest category conferred of protection.
- 01:12:28 The next steady and i'll just show you that this was the kaplan Meier curve, this was that highest quintile of vitamin D level and survival.
- 01:12:39 distressingly there was.
- 01:12:42 Poor overall survival, with the majority of people dying over the course of follow up but There does seem as if there is some advantage conferred by having a hierarchy at baseline.
- 01:12:57 So, Dr King also the team stratified by the different categories that we use less than 10 10 to 20 greater than 20 and again.
- 01:13:09 There was this.
- 01:13:12 A now of benefits related to the highway 25 feet.
- 01:13:18 So the team then studied giving high dose versus standard dose vitamin D, in addition to chemotherapy for patients with advanced your manuscript colorectal cancer.
- 01:13:33 And by high dose.
- 01:13:37 Those randomized 139 overall participants those who roughly half to the high dose they received 8000 international units daily.
- 01:13:47 For two weeks, and then 4000 international units daily plus keen on 4000 international units is the guilt that's considered the upper range of normal or the upper limit of normal on dietary or daily intake versus 400 international units daily plus to them.
- 01:14:06 And here, you see again tremendous mortality i'm forced to be morbidity associated with this, I was sitting, I was correct before in terms of progression free survival, starting at 139 and ending it.
- 01:14:25 Only 17 was progression free survival and then the Multi variable hazard ratio after multi variable it did seem as if there might be still a slight benefit to the intervention, but not, it was not seen prior to the Multi variable analysis.
- 01:14:47 So I think very suggestive that it might be helpful, but definitely not a slam dunk.
- 01:14:55 So, with regard to now thinking about the immune system, a little bit more broadly outside of cancer.
- 01:15:02 The first signal that vitamin D might be important for the immune system came from these what was observed, if you were living in the city and you develop tuberculosis, you were sent to the country.
- 01:15:19 And you literally sat outside in the sun and lot better, and this was taking advantage of the fact that when you're making vitamin D you increase.
- 01:15:34 Your capital aside and levels within the macrophages and then they are able to kill mycobacterium TV, so the underlying.
- 01:15:44 physiology that i'm going to really fly by the vitamin D receptor is a precedent in many immune cells and then the one alpha had box lays which we often think of as President and the kidney it's also present and macrophages in particular.
- 01:16:03 it's known that vitamin D deficiency may impair an effect of.
- 01:16:12 vitamin E that turns off.

- 01:16:15The.
- 01:16:17auto immunity.
- 01:16:20or when your vitamin D deficient you're more likely to attack your own tissues, because of the impaired effect of 125 the on a 10 year leading that he helped her one immune responses.
- 01:16:39So there have been these associations of vitamin D deficiency, and these immune conditions on for our patient her sister had her excuse me her mother had multiple sclerosis.
- 01:16:53So this was a study, so the women's health initiative, I didn't mention it earlier, but the women's health initiative had some degree of racial and ethnic diversity in this particular finished study.
- 01:17:06There was pretty limited diversity, it was a very homogeneous population which.
- 01:17:14has therefore it, it raises, how much we can generalize to other populations, but what it did allow for us having a very being able to understand something when I think it's a real.
- 01:17:27Which is the ability to provide them indeed to lower the risk of type two diabetes in a very high risk population.
- 01:17:37So it's been one, there are very high rates of type one diabetes, they study 12,000 plus live births and actually included 10,000.
- 01:17:49Plus children and analyses and they were followed on through each one and in that time at one individuals developed type one diabetes.
- 01:18:01The recommended dose of vitamin D, there is a not the 600 units that I mentioned for the US and the Institute of medicine, but 2000 units daily.
- 01:18:15And what was observed was that when you took that daily versus taking lower levels, there is a significant reduction in the likelihood of developing type one diabetes.
- 01:18:33With regard to multiple sclerosis, this is a study that was done in members of the military and they were looking not.
- 01:18:44At an intervention, but again looking at baseline vitamin D levels prior to the diagnosis of multiple sclerosis and the data are provided for both white and black.
- 01:18:57army and navy members, but when you look at the findings, there is an association of higher vitamin D specifically a level of 14 nanograms per ml.
- 01:19:11and higher with lower rates of multiple sclerosis, but the challenge with this is that we're seeing in the white participants, but not observed in black participants, but I think the devils in the detail, there are only the highest the.
- 01:19:29While the data work cut in quintiles for white participants that are cut into Troy tiles for black participants and that last total.
- 01:19:43Was 22 essentially 40 nanograms per ml so there were there are significant differences are the vitamin D levels of participants space really get curious.
- 01:19:54I mentioned this earlier, this is the basic science data related to achieve capital side and it being produced within the macrophages after the macrophages generate 125 D.
- 01:20:09And then.
- 01:20:11With regard to call it 19 the data really have not been there was intensely investing in it, but there really have not been data to support that higher vitamin D.
- 01:20:25decrease decreases your likelihood of susceptibility to kill the 19 or two you're hospitalized your hospital, of course, if you were hospitalized provided for coordinating so one of my interest is always been the relationship between vitamin D and diabetes, I had one beer.
- 01:20:46In certain populations and, in particular, and populations of color the higher rates of vitamin D deficiency and the higher rates of type two diabetes or insulin resistance, so I wondered if.
- 01:20:58That might be connected, the first signal regarding vitamin D and diabetes came from the nurses health study, where in this study patients women who had both high vitamin D intake and high calcium intake the spot on this column in the back had, for they were for.



- 01:21:28 Sydney says, the only people who have low vitamin D and low calcium, as opposed to high vitamin D and high calcium, there is a higher risk of type two diabetes, if you are low in intake and reduce risk of diabetes, if you had high intake.
- 01:21:48 And this was also demonstrated in a cross sectional studies were just looking at 25 hypoxia vitamin D versus insulin sensitivity low vitamin D associated with.
- 01:22:02 Increased insulin sensitivity with a hyper glycaemic clamp so we actually studied this recruiting for individuals who were low Vedic who had low vitamin D.
- 01:22:17 Get recruited 90 individuals who had 50% or more history of type two diabetes, so this is very motivated group, it was also a very diverse group in terms of who was represented some of the imbalances that you see here had to do with the more that you stratify.
- 01:22:40 In your enrollment.
- 01:22:44 process, it can lead to some of these imbalances.
- 01:22:48 Our participants, had we measured by amino acid their vitamin D levels were on average 15 nanograms per ml only repeated by the gold standard.
- 01:22:58 A little bit higher at nanograms per ml and individuals majority of whom had normal glucose tolerance, we had a few who had impaired glucose tolerance and we.
- 01:23:11 repeated their vitamin D over 12 weeks once weekly ergocalciferol with the plan for treatment of the placebo group at study completion.
- 01:23:23 So we beautifully improved vitamin D levels in the treatment group that they said was in the placebo group.
- 01:23:31 And there was absolutely no impact on insulin resistance or insulin secretion or sensitivity by the glycemic crap that we performed, so this 12 week steady on did not show any benefit to.
- 01:23:51 Repeating vitamin D, with regard to insulin resistance or or secretion we also looked at a number of other metabolic parameters only publisher so if anyone ever wants to look at.
- 01:24:04 This again they have the delta, which is so important for viewing power calculations.
- 01:24:13 And what I will sort of skip through for the next few slides is that there is a major Meta analysis that also showed no improvement in insulin resistance or progression to take two diabetes with vitamin D.
- 01:24:26 And then the task, or a doctor, because it all had we were actually recruiting roughly at the same time, where they were recruiting individuals who are at higher risk for type two diabetes mellitus.
- 01:24:38 And here, you have to have pre diabetes, they had different ages for different groups and you could not come in on vitamin D or much calcium, and they were randomized 4000 international units of the daily versus placebo.
- 01:24:59 And again very diverse cohort again this has to do with intentionality around study design and that can't be said enough so that we can have a better representative of our patients and, unfortunately.
- 01:25:15 Over the course of this four plus year study, there was no benefit of vitamin D on developed or development or progression to take to take to Davies so it's hard to make the argument that you will prevent diabetes with vitamin D, but at the same time it's a vitamin, so there is.
- 01:25:44 there's not a whole lot of harm with cake.
- 01:25:47 With regard to the various of studies of Bible study, and this was a two by two study where men and women were given either vitamin D or Omega three.
- 01:26:01 or double placebo.
- 01:26:04 For five years No Entry vitamin D.
- 01:26:09 Because of the challenge of recruiting this number of people with their this timeframe, with the high end points in cancer, heart disease and stroke.
- 01:26:19 And again, this ends up being very representative, but real benefit.
- 01:26:26 No change in basic cancer, no difference in cardiovascular that it's um and with the breakdown, or maybe it seems like there's a little bit of data digging.

- 01:26:40 So there might be a little bit of a decrease in cabbage, but if you think about a P value is 0.05, and that means that one out of 20 times it's going to be rammed ever that you find something the fact that this could be just a random finding and not a true benefit.
- 01:26:59 When they then did post hoc analyses to look at 25 be on versus under 20 nanograms per ml there was also no benefit seen.
- 01:27:11 So i'm going to switch now, so I also have I put together what I shared just now, potentially, if you are.
- 01:27:19 finished in background, and if you notice as medical backgrounds in that pediatric grand rounds, but maybe they're submit pii providers, maybe for individuals who are finish you might want to achieve higher vitamin D and to burn down.
- 01:27:34 Children developing type one diabetes, I think the is still pretty provocative and I think there's a rationale to cancer prevention to think about.
- 01:27:46 Increasing your vitamin E but we're going to switch to bone which is i'm proud to be a bonehead.
- 01:27:51 And this is actually an image that I share with patients and that has to do with the fact that osteoporosis, is seen as a benign disease, whether in fact.
- 01:28:00 The disability associated with either years last sale help disability or or early death from your product factor is similar to pull rectal cancer.
- 01:28:12 So this is the strongest data that we have regarding vitamin E.
- 01:28:17 And for much of these studies and get his point to be vitamin D with calcium so some of the early studies by that Chris shipley and dustin he's aware, there was a reduction in vitamin D.
- 01:28:31 reduction in risk or fracture for the vitamin D and calcium is not sure if that was you know, treating Austin Malaysia or direct effect on us to your private bone.
- 01:28:41 And the record trial or participant Scott, calcium 1000 plus vitamin D 800 vs Mano therapy or placebo, there was no empty fracture efficacy.
- 01:28:54 i'm Dr Heikki the shop floor is really led the way and through Meta analyses first and a cohort of just under 10,000 patients shown that a combination of vitamin D 800 units.
- 01:29:07 and achieving a 25 feet of 40 nanograms per ml led to 26% reduction in hip fracture keep in mind that that's a higher vitamin D annotate them currently recommended however it's below that what's considered the upper limit of normal for vitamin D and take.
- 01:29:25 And then in women's health initiative, there was no or all any fracture Africa system or to the colorectal cancer findings, however, there is about those who are fully compliant post hoc a 30% decrease in hip fractures.
- 01:29:41 This is something that you do not want to do so, there is such a thing as too much of a big things on vinyl the.
- 01:29:48 Women were given a single dose of 500,000 units of vitamin D annually for three to five years.
- 01:29:57 And they actually saw an increased incidence of falls and fractures and it's likely that their subsequent data showing that there was some hyper kelsey nia that occurred with that single mega dose of vitamin D.
- 01:30:12 out Dr Heikki the shelf, for I did a second city now extending prefer study was just under 10,000 the second study was just over 31,000 patients the 11th or CTS with a much greater number of hip fractures and again showed that with that vitamin D 800.
- 01:30:33 Units daily on, there is a 30% reduction hip fracture and a 10% reduction in the number T bone fracture which was significant.
- 01:30:44 In swan so i'm privileged to be the site principal investigator for the sun setting it is a 25 plus year study of the men applause for longer to know.
- 01:30:54 there's seven sites across the country and in each site half of the cohort was intentionally enrolled to be white and the other half.

- 01:31:01 Like Chinese Japanese or Latina to be able to understand how many balls all of the different potential impact that letter plus how that the similar and different across groups.
- 01:31:13 And then, this swan were able to demonstrate that when you're 25 he is over 20 nanograms per ml.
- 01:31:21 There is a 45% reduction in the risk of fragility fracture over 10 years but that this was not associated with bone density change so keep in mind that, with their bones, while we focus a lot on bone density.
- 01:31:33 There are many treatments that will have stable bone density, but will still reduce rapturous.
- 01:31:43 And this is that, in the same data for non in terms of the hazard for fracture.
- 01:31:50 So these are the studies that.
- 01:31:53 You know, there is the time on the end, I would say, there still is a lot of concern, whether you can or should you be taking a calcium, does it cause heart attacks so number one I would I share a patient is that.
- 01:32:09 You need both calcium and vitamin D to reduce fracture it's not just vitamin D, so you do need to have some calcium, and that if you're really worried, so the goal the dietary calcium cake is about.
- 01:32:24 1000 milligrams.
- 01:32:26 For men or premenopausal women 1500 up to 1500 milligrams for postmenopausal woman, and if you have concerns look between your dietary and supplemental calcium, please don't eliminate calcium from your diet, because it's needed to reduce fracture especially here.
- 01:32:51 Okay, and this was just another study from Dr Michelle throwing showing that vitamin D have indicated of 700 to 1000 units daily can decrease your risk of falling by about 20%.
- 01:33:06 So, in terms of returning back to our patients, in addition to her mother having breast cancer her mother had had a recent hip fracture which increases the patients risk for factoring herself, and so what did we advise so.
- 01:33:25 One that she met meets the Institute of medicine criterion for vitamin D deficiency, and that there are.
- 01:33:35 There is a benefit associated with increasing her 25 year will allow her to increase calcium absorption of course yeltsin's direct to consumer calcium.
- 01:33:45 I So this was the recommended that we pursued also talked about raloxifene because, in addition to its benefits for Osteoporosis, it is a.
- 01:33:59 A approved for reducing expressive of breast cancer and she did have that family history, so, then the other part, that's honestly saying that they're unclear benefits around.
- 01:34:10 glucose intolerance multiple sclerosis and colon cancer in terms of taking vitamin D, but, most importantly, that she should pursue regular colonoscopy.
- 01:34:20 So I am always more exuberant about what I think I can cover versus what time allows so i'm going to pause with the last slide.
- 01:34:33 Our last two slides and it gets shared that when the US preventive services task force or released the recommendations around spinning for Easter kinetic vitamin D deficiency So these are not patients who have bone.
- 01:34:51 disorders, where you would want to scream to ensure that they're getting enough vitamin D, so that they can absorb their calcium, because of the importance for their belt help these are population.
- 01:35:03 General population health recommendations are there was a recommendation to not screen in I have the privilege of writing the editorial with the polar bear and the polar of you pen and one of the.
- 01:35:19 Suggestions was maybe we can make when we're taking care of patients, maybe we can just ask them to consider like taking a multivitamin.
- 01:35:30 or a vitamin D supplement without screening because of the data of how prevalent vitamin D deficiency is and the fact some of the data that we've had from swag tonight.

- 01:35:43 don't have a chance to show you that regular everyday use of vitamin gear or multivitamins has in our cohort increase circulating 25 hypoxia vitamin D levels.
- 01:35:56 Over a 10 year period so maybe we just had a common sense approach encourage everyone to take a vitamin or cod liver oil or fatty wild fishes and then screen, the people who are most at risk is with regard to their own outcomes and this is a cartoon that I had.
- 01:36:15 sort of put together that you know it again without all of this is in the context of calcium intake but you tend to see pete parathyroid hormone increase when you're 25 K Betsy vitamin D levels are 50 nanograms per ml or lower.
- 01:36:31 Also, of course, your gsr impacts that 22 based on a doctor, for his data This offer is 20 anagrams for me at least is the magic number for fractures there are some data from cadavers that you need at least 30 nanograms per ml appointment ID to.
- 01:36:51 not have a simulation to fully mineralized your bone and then from the colon cancer studies, maybe having it be a little bit higher so with that, let me stop the screen share and what questions can I answer.

### **UVA Internal Med**

01:37:08 I try and position myself, so you can see me but I don't think you can.

- 01:37:16 Stand right here, there you go Hello.
- 01:37:22 So it sounds like in correct me if i'm wrong, but you feel like a lot of the you know, have all these studies, looking at different health outcomes you believe.
- 01:37:31 The biggest bang for its buck is kind of in this area of mineral mineral bone disease it didn't really affect diabetes it didn't really affect cancer necessarily.
- 01:37:42 But it also you also mentioned it doesn't necessarily demonstrate that it actually makes our bones look stronger or or actually become less asked to.
- 01:37:53 melodic or less less asked to Malaysia last osteoporosis, do you think that there's.
- 01:38:00 A separate mechanism and you alluded to the mechanism of maybe too much vitamin D get your calcium so high, and those people fall.
- 01:38:09 But is there a separate mechanism by which vitamin D may be helping strengthening our bones, or just reducing our risk of fracture that's not necessarily related directly to the bone.

### **Sherri-Ann Burnett-Bowie**

01:38:19 So, thank you very good question I I don't know.

- 01:38:25 I even though we weren't able to demonstrate it my assumption is that.
- 01:38:31 Where the effect of vitamin D on bonus most proper probably through the.
- 01:38:37 Addressing Austrian Malaysia or treating our simulation even if it's not able to be shown so that would be my assumption I don't know that people have ever studied any other role for vitamin D or don't help but it's a very interesting question and something that.
- 01:38:57 I will i'll look up in and share and see if I can find anything but I think, even though it was not demonstrated the assumption is that there is hyperparathyroidism.
- 01:39:08 Maybe there's hyperthyroidism without trusting alicia that may be still problematic for bone health.
- 01:39:16 Or, there may be a component of off similarly share either way if you can take away the secondary hyperparathyroidism or you can really always skeleton that that is associated with the decrease in the factual.

- 01:39:30 And i'm.
- 01:39:32 Sure i'm going to read, so can you comment on who are good candidates for vitamin D testing most was testing sending us your process, for example, but i've also.
- 01:39:41 seen some conditions test for potentially unfounded indications example fatigue depression, so I to have seen this I would really encourage.
- 01:39:56 Limiting more to the austere process face if you screen, so one thing that I recognize that people sometimes feel when you feel as if there's nothing else to explain why a patient is having a symptom or has a diagnosis, the data for vitamin D and fatigue.
- 01:40:21 As a source of low vitamin D as a source of fatigue is really.
- 01:40:27 does not exist, and I think the challenges that because our normal range is still sometimes list of vitamin D of.
- 01:40:39 24 is being low i've had patients come in and say you know my i'm depressed i'm fatigued because my vitamin D is 28 and I it's heartbreaking to sort of have to say to them, I actually don't think that's the case.
- 01:40:54 If you're going to try to.
- 01:40:58 You know, do that test to see an increase in vitamin D improves symptoms I wouldn't have a goal vitamin D, have any higher than 40.
- 01:41:08 or 50 nanograms per ml because otherwise I think again it's setting up a false reality if there's a placebo effect from having a higher vitamin D, maybe that's not a bad thing, but I doubt very much that.
- 01:41:24 Little vitamin D contribute so tikka tikka the question.
- 01:41:35 Any other questions we may be at the hour.

#### **UVA Internal Med**

01:41:38 i'm just going to ask one more curious, so I also is just reading and kind of became aware of vitamin D's role and multiple sclerosis, so you referenced that here.

- 01:41:49 It didn't look like vitamin D help people with coven unfortunately Is there anyone do their research that's happening looking at other either autoimmune or just the immune immune deficiencies in the realm of vitamin D supplementation.

#### **Sherri-Ann Burnett-Bowie**

01:42:07 I think, since the vital D steady was pretty much ambassador, that was a hundreds of millions of dollars study um.

- 01:42:16 I it's it's not clear to me that people will continue down the path of looking at vitamin D and immune system or there was some very compelling data that treating vitamin D made it less likely to develop asthma.
- 01:42:32 In children, but it just was below the myth significant so it's I think it's hard, I think that.
- 01:42:45 yeah I don't know majors studies will can't infection now, in the aftermath of the no findings from vitamin D or the immune system.
- 01:42:58 So i'll just say this one quickly, are you recommending routine vitamin D supplementation as opposed to screening for all asymptomatic adults are targeting high risk individuals example Perry and postmenopausal women um.
- 01:43:13 So, again I I received some negative feedback from this recommendation or rewrote the editorial I think it makes sense for someone who is does not have any bone.

- 01:43:29 Indications it's not clear to me that we should be screening, I think we should just tell or suggested patients, you know very much in the shared decision making, that there are some data that they may.
- 01:43:43 have long term benefits to taking a vitamin D supplement and because it's so hard to get vitamin E based on decrease sun exposure, I think it makes sense, just to have someone.
- 01:43:58 Take a vitamin D supplement or a multivitamin because in our swan study that's what happened in patients who are hiring so if someone who has mal absorption and someone who might wear complete.
- 01:44:15 Covering based on religious reasons for patients who we have or portion for us your process I do or osteopenia I do think we should screen them.
- 01:44:27 Because they're not they're not the same as the general population who don't have who are not at as high risk and then for our.
- 01:44:39 obstetricians I bet if anyone may be attending there are some pretty significant findings related to rickets that can be demonstrated in utero which, in the context of improved vitamin D results, so I do think that there's much more work to be done in the.
- 01:45:01 obstetrics world regarding vitamin D, there are also some signal that higher vitamin D makes it less likely to to develop preeclampsia.

#### **UVA Internal Med**

01:45:17 Great does a wonderful job Thank you so much.

#### **Sherri-Ann Burnett-Bowie**

01:45:20 Thank you for the honor.