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Quantifying Compliance to Vitamin D Supplementation: Preference for the Salient and Compliance Incentives to Prevent Osteoporosis in a Pediatric Fracture Population

A Thesis in Biology

By

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ABSTRACT

The following three-part analysis addresses the question of how to improve compliance with a vitamin D supplementation protocol in a pediatric population and aims to validate the role of supplementation in preventing risk of fracture and poor bone mineralization. Part I utilizes an economic modeling system to address whether health insurance serves as a compliance incentive for pediatric fracture patients. The model concluded that health insurance had no effect on compliance level and that compliance level determined osteoporosis-related costs and expected labor income. Part II uses a retrospective analysis of a pediatric population to determine which factors impact compliance to a vitamin D supplementation protocol following a fracture. The results showed that patients with lower levels of baseline vitamin D were more likely to comply to the regimen. Part III uses a prospective longitudinal intervention study approach in a pediatric population to address how to improve compliance with a vitamin D supplementation protocol following a fracture. The study follows patients with dual x-ray absorptiometry (DEXA) scans at three time points during the healing processes in addition to vitamin D levels. Preliminary data indicate that the DEXA scans help promote compliance to the vitamin D supplementation protocol and that patients following the protocol show significant improvements in bone mineral density (BMD) relative to expected changes in bone mineral content (BMC).

Results from all three parts of the analysis indicate that making silent illnesses, such as fracture risk and poor bone mineralization, more salient improves the likelihood that patients will comply with a vitamin D supplementation protocol following a fracture.

DEXA scans have been able to increase compliance rates, and the results from the follow up scans are promising. The American Academy of Pediatrics (AAP) should take a formal stance on the preventive role of vitamin D in pediatric bone health, requiring physicians to annually monitor levels and to include vitamin D monitoring in sports physicals. Adolescence is a critical time to maximized peak bone mass to stave off future osteoporosis risk.

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Patient Medical Compliance: Implications for the treatment of chronic diseases

"increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" [1]

Patient compliance to medical regimens may be an important variable to improve patient outcomes and reduce overall medical costs. Medical patient compliance can be defined as "the extent to which the patients' behavior (including medication-taking) coincides with medical or healthcare advice" [2]. For the scope of the analysis presented below, patient medical compliance will be framed within the context of osteoporosis risk prevention in a pediatric population. I will use an economic model, retrospective analysis of a pediatric population, and a prospective longitudinal intervention study of a pediatric population to assess incentives for compliance with a vitamin D supplementation protocol following a fracture. Additionally, this analysis aims to validate the Minkowitz vitamin D supplementation protocol (Figure 9) as a preventive approach to compromised bone health acutely and osteoporosis long-term.

Challenges arise in compliance research because the definition appears to be binary, but compliance is more complex than that. It becomes even more challenging to define compliance when the scope is opened beyond medications; lifestyle changes, such as improvements in diet and exercise, are often introduced as part of the treatment. If a patient with high cholesterol takes statins but does not follow the physician's diet and exercise plan, are they compliant? Additionally, if the patient follows the exercise and medical regimen on weekdays but not on weekends, are they compliant? In order to

clarify the complexities behind defining patient compliance, I will describe a three-part study of medical compliance to vitamin D supplementation.

The accountability of medical compliance falls heavily on the patients, where it is directly their own responsibility to align with the instruction provided. Medical patient adherence is defined slightly differently by the World Health Organization (WHO), as "the extent to which the persons' behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider" [1]. The definitions of adherence and compliance include all stages of patient care and can account for patients that fall in several categories: those who do not start medication, do not continue treatment, solely take pharmaceutical measures, solely take non-pharmaceuticals measures, and those who inconsistently take pharmaceutical and non-pharmaceutical measures. The literature divides nonadherence and noncompliance into primary initiation or secondary continuation [3]. Scholars and medical practitioners justifiably use the terms adherence and compliance interchangeably. The primary difference between the two terms is the relative roles of the patient and physician. For the purposes of the research provided in this three-part study examining pediatric populations, I will be using the phrase compliance to describe patient behavior.

The WHO reported that only 50% of chronic disease patients in the developed world would be considered compliant[1][1]. In an analysis of the clinical implications of helping patients follow prescribed treatments, Dr. Haynes with the Department of Clinical Epidemiology and Biostatistics, McMaster University Medical Center made the

[1] Data was drawn from a meta-analysis of scholarly research about compliance and adherence.

claim repeated by the WHO report on medical adherence that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" [1]. Although hyperbolic at first glance, Haynes' statement raises an excellent point about the necessity of medical compliance as it pertains to health outcomes. All the resources and labor dedicated to developing drugs and finding cures are wasted if patients do not comply with prescribed treatment and preventive regimens. For this reason, among many others, the dangers of poor compliance should be of great concern for those battling and treating chronic diseases.

Medical patient noncompliance is far from a novel phenomenon but may not spark concern as a noteworthy chronic cause of morbidity in developed countries. For example, the Centers for Disease Control (CDC) lists heart disease, cancer, and chronic lower respiratory diseases as the leading causes of death, followed by Alzheimer's Disease, unintentional injuries, stroke, diabetes mellitus, pneumonia/influenza, kidney disease, and suicide [4]. With chronic conditions that require a multifaceted treatment approach over a long period of time (often indefinitely), improving patient compliance may yield significant widespread benefits. Poor compliance may be a latent contributor to the top causes of morbidity.

Patient noncompliance is a complex problem, especially in the realm of chronic diseases. Physicians treating cardiovascular disease see difficulty with patient compliance both in the primary preventive and secondary treatment stages of the disease. There are serious medical consequences of noncompliance at both the primary and secondary

stages, such as exacerbation of disease, failure to gain preventive benefits from a treatment, or failure of future protection (i.e., not finishing a course of antibiotics) [5]. Primary prevention refers to actions taken before the onset of a disease or condition, and secondary prevention refers to intervention measures taken to ameliorate the intensity of a disease or condition. Analysis of the efficacy of treatment strategies shows that close to 50% of individuals do not start treatment (identical to WHO estimates of overall medical compliance [1]) and that compliance declines after a year but not at such a drastic rate [5]. Citing a couple of Lipid Research Clinic-Coronary Primary Prevention Trial (LRC-CPPT) studies, the major takeaway from the pattern of patient compliance is that patients experienced long-term benefits from the cardiovascular medications [5]. The medications in the study do not have immediate benefits, like one would see when taking pain medication. Patients who expected, but did not see, instant benefits were likely to stop taking the prescribed medications. There may be something specific about the nature of detection and treatment of chronic diseases, like those of the cardiovascular system, that could be responsible for the decrease in noncompliance from the primary to the secondary stage. Why are patients becoming noncompliant in lower numbers in the secondary stage to prevent exacerbation of the condition, rather than in the primary stage before the manifestation of the disease? It is necessary to uncover patient motivations for compliance in preventive versus treatment stages of a disease.

Patients with high cholesterol can visualize their LDL and HDL levels with blood tests periodically before and during treatment. Patients suffering from HIV/AIDS can monitor their CD4 count over the course of treatment. Consistent monitoring of a

biomarkers of a disease may impact the way patients view the severity of their condition and thus, make decisions about medical compliance. The ability to visualize biomarkers of a disease that are not as noticeable as a rash or back pain plays a role in the level of patient compliance. Osteoporosis may be equally as rampant as immunological diseases and cardiologic disorders at some point in individuals' lives. Based on a 2010 estimate with data from the National Health and Nutrition Examination Survey 2005–2010 and the 2010 US Census, 53.6 million adults in the US would be classified as either having osteoporosis or low bone mass (10.2 million osteoporosis; 43.4 million low bone mass) [6]. Although cardiovascular disease is the leading cause of mortality globally, osteoporosis may lead to other secondary illnesses and infections that are listed as the primary cause of death (i.e., osteoporotic fracture leads to hospitalization and pneumonia in the hospital) [4]. Perhaps physicians tackling and preventing the consequences of osteoporosis can take advantage of the strides made for patient compliance in other related specialties that have utilized medical tests to make their conditions more salient and trackable.

Examining the compliance rate successes in treatments of other chronic diseases may reveal clues for improving compliance to osteoporosis prevention and treatment. Focusing on the pharmacotherapeutic aspect of hypertension treatment, the familiar 50% noncompliance in the primary stage is evident, resulting in approximately 75% of patients formally being treated for hypertension unable to appropriately lower blood pressure [7]. Proper medical compliance has been shown to reduce consequences of hypertension. The primary reasons for poor compliance to anti-hypertension medications

are “the asymptomatic and lifelong nature of the disease” [7]. Proposed compliance interventions are behavior-oriented, suggesting that patients periodically monitor their own blood pressure as a way to hold themselves accountable to pharmacological treatment and lifestyle alterations. Checking blood pressure for fluctuations provides physical evidence of compliance for the patient and physician.

Focusing on the pharmacotherapeutic aspect of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) treatment, approximately one-third of patients comply with the prescribed treatment, a significant decline from the overall WHO projection of 50% for chronic diseases [8]. One of the most serious consequences of poor compliance to HIV treatments is viral resistance to the medicinal cocktail. Highly active antiretroviral therapy (HAART) has proven to be effective, but the complicated medical instructions may contribute to poor compliance [8]. Perfect compliance is key for achieving long-term viral suppression. Additionally, there is evidence to suggest that more symptomatic patients are increasingly likely to comply to treatment regimens. Social factors like stress and poor support systems negatively impact HIV treatment compliance [8], so physicians should address these factors when prescribing medications. Physicians may be able to address these social inhibitors to compliance by verbally checking in with patients during regularly occurring visits. Another way to improve compliance with HIV treatment is to confirm that patients understand the complicated relationship between treatment, viral load, and disease progression [8]. For dependent patients (such as children), it is critical that the caregiver (i.e., parent) believes in the efficacy of the treatment regimen [8].

In the pediatric fracture population, risk of future fractures may not seem as life-threatening as hypertension or HIV/AIDS; framing future osteoporosis risk as a warning after an initial fracture may not be as effective in a pediatric population than it would be in an older adult population. Utilizing lessons from hypertension and HIV/AIDS treatment compliance, how can pediatric physicians convince parents that poor bone mineralization is both dangerous immediately and long term (i.e., osteoporosis)?

Compliance in Preventive Treatment

Medical compliance varies by the type and duration of treatment. Patients avoid or fail to comply with prescription medication at variable rates. Compliance rates may depend on whether the treatment is short-term curative medication, preventive treatment, or involves making long-term behavioral and lifestyle adjustments. Vitamin D supplementation counseling falls into the last two categories: preventive and long term. Compliance is an integral part of preventive health, as it may improve the patient's quality of life and could mitigate future health care expenses. In their comprehensive analysis on achieving medical compliance, DiMatteo and DiNicola describe three levels of prevention to understand noncompliance. Primary prevention occurs before the disease state, secondary prevention occurs when a patient is identified as "at risk", and tertiary prevention is designed to slow down the progression of a disease [9]. Current osteoporosis-oriented care lies in the tertiary prevention stage towards susceptible populations (i.e., postmenopausal women) trying to mitigate the subsequent fracture and refracture risk for osteoporotic patients. What if practitioners could identify patients earlier and provide intervention at the primary and secondary prevention stages? In the

case of osteoporosis, pediatric fracture cases present an opportunity to intervene earlier in the bone health cascade.

In the case of osteoporosis, debilitating fractures can have serious ramifications on quality of life. Weycker et al. employed a retrospective analysis to address correlations between healthcare costs, resource utilization, and osteoporosis-related fracture outcomes [10]. Of the 268,4777 subjects admitted to the hospital for osteoporosis-related fractures, the mean hospital cost was $12,839 and the average length of stay was 5.1 days (5.6 for men and 4.9 for women) [10]. Additionally, the study identified exacerbated comorbidities (pain, basic functional impairment, and death) as possible clinical consequences of osteoporosis-related fractures. Looking narrowly at hip fractures, 20% of patients report some level of medical complications post-surgery in the following areas: cognitive and neurological, cardiac and vascular, pulmonary, gastrointestinal, urinary, hematologic, and endocrine-metabolic (consolidated in [11]). While a debilitating hip fracture could result in permanent residence in assisted living, minor fractures that lead to cessation of exercise also have a high impact on future health outcomes. Exercise cessation is also linked to increased risk of cardiovascular disease and Alzheimer's Disease [12]. It is evident that the positive and negative consequences of compliance with lifestyle and pharmacotherapy components of osteoporosis care have far reaching effects.

Compliance with pharmacotherapeutic and lifestyle alterations potentially could provide financial and medical help for those predisposed to poor bone health. An alarming finding from a study exploring fracture patients' decision-making processes for

bisphosphonate treatment from the School of Public Health at the University of Alberta found that "less than 20% of people are treated for [osteoporosis] in the year post-fracture…of those written a prescription for [osteoporosis] treatment, 30% will not fill their prescription (primary non-adherence) and of those who do fill their first prescription, at least half will stop treatment within 1 year" [13]. Based on the previous statistic, only 3% of people with an osteoporotic fall continue compliance with medications after one year.[2] The most noteworthy aspect of this finding is the group that started medications but stopped within the first year. Twelve patients (n=7 persisted and n=5 stopped) were interviewed prospectively regarding variations in bone mineral density (BMD) to determine attitude shifts regarding their osteoporosis diagnosis and bisphosphonate treatment (taken with recommended lifestyle changes). What caused the shift in patient medical compliance? Wozniak et al. attribute this behavior to patients reevaluating the severity of osteoporosis and the impact of treatments over time.

An interview-based study questioned women who filled a bisphosphonate prescription to determine motives for noncompliance [14][3]. Compliance was binary and described as greater than or equal to 140 days of usage over a 7-month prescription period. McHorney et al. hypothesized that potential side effects would be the primary obstacle to medical compliance. The main differences between the compliant and noncompliant groups were that adherers were more likely to report a diagnosis of osteoporosis, rather than osteopenia (a "pre-osteoporosis" state) or normal bone mineral

[2] 20%* 30%* less than half= 2%
[3] Sample size (n=1015)

density (70% vs. 61%) and that adherers were more likely to report noticeable height loss (58% vs. 45%) [14]. Both a formal diagnosis and noticeable height loss make osteoporosis more striking. The results from this study suggest that the female participants were more likely to comply with their bisphosphonate regimen when the disease became more salient.

The analysis presented in this three-part study aims to observe and classify human behavior with vitamin D supplementation for reducing subsequent fracture risk, and by effect, to maximize peak bone mass to reduce the future risk of osteoporosis. The results from this analysis provide stronger evidence for the benefits of vitamin D supplementation in pediatric bone health, will suggest a tool for improving patient compliance to the vitamin D supplementation, and will provide a policy recommendation for how to thoroughly address compromised pediatric bone mineralization and heightened fracture risk. For the purposes of addressing this challenging question, I will explore patient behavior from various disciplines: economics, public health, and biology. These three disciplines in conjunction create a more holistic framework from which to derive recommendations designed for how to improve compliance and to improve bone health.

Background on osteoporosis

Clues about the etiology of a disease in an older demographic may lurk in a younger pediatric demographic. Osteoporosis is colloquially known as the disease of elderly women, characterized by decreased bone mineral density and increased fracture risk. According to the World Health Organization (WHO), osteoporosis is classified as a

bone mineral density (BMD) reading with a t-score of at least 2.5 standard deviations below the average for a given age/gender demographic [15]. The current standard for determining BMD is with a dual X-ray absorptiometry (DEXA) scan. BMD specifically measures the density of calcified material of the bone, including the cortical and trabecular regions. Once an individual's BMD reads below normal for a given demographic, therapeutic intervention is likely advised.

In order to further to study vitamin D as a preventive approach to future osteoporosis risk in the pediatric population, I will discuss compliance in the context of vitamin D in three parts. Part I will model patient incentives in osteoporosis from an economics perspective. This analysis addresses the relationships between health insurance, medical and lifestyle treatment compliance, expected labor income, and expected lifetime osteoporosis costs. With this model, compliance will be defined on a trinary scale: compliant, partially compliant, or non-compliant. Health insurance provides cost sharing for patients to influence the affordability of care. Four models will be compared against each other to determine the relative strength of health insurance incentives on the level of compliance, on expected labor income, and on costs related to osteoporosis prevention and treatment. The first part of the analysis yields observations about the nature of human behavior in response to "invisible diseases" and health insurance cost sharing principles. I hypothesize that patients with insurance (more cost sharing) will not be any more compliant with treatment than patients without health insurance, and I hypothesize that compliance level will play a larger role in expected future labor income and osteoporosis-related costs than the presence of insurance.

Part II will examine the relationship between baseline vitamin D level and patient compliance in a pediatric fracture population from a public health perspective. For the purposes of information recall, compliance will be defined in a binary manner: either compliant or not compliant. This retrospective study will examine compliance trends in a pediatric fracture population to identify variables associated with compliant behaviors. The second part of the analysis supports the observation found in part I and provides suggestions for further research in improving patient compliance to the vitamin D supplementation regimen. I hypothesize that most of the patients will present with a vitamin D deficiency, and a majority of the patients will not be compliant to their supplementation. Additionally, I hypothesize that patients with more severe deficiencies will be more likely to comply to vitamin D supplementation.

Part III will examine the relationships between baseline vitamin D level, body mass index (BMI), measurements of bone mineralization (bone mineral density and bone mineral content), and patient compliance in a pediatric fracture population from a biological perspective. A secondary aim of this study is to visually quantify bone strength and fracture risk as a proposed method of improving compliance to the vitamin D supplementation. The study is in the pilot stages, but the compliance component will be defined on a scale similar to that of part I: compliant, partially compliant (broken into primary and secondary), and noncompliant[4]. The final part of the study will culminate in predictions for the full version of the study with policy recommendations on vitamin D supplementation for pediatric bone health for the American Academy of Pediatrics

[4] This distinction will be made in the full version of the study, not in the pilot stage.

(AAP). I hypothesize that most patients in a pediatric fracture population will present with low vitamin D and low BMD, but dual x-ray absorptiometry (DEXA) scans will make them more compliant; patients compliant to vitamin D will show increase in BMD relative to bone mineral content (BMC).

PART I: Modeling Patient Incentives in Osteoporosis Treatment and Prevention

In the context of medical compliance, health insurance potentially could be lauded as a tool to make medication and health care utilization more accessible. Under cost sharing conditions, all goods (health-related or not) that are not covered by health insurance will become relatively more expensive when compared to products and services that are covered. Modeling scenarios in which patients make decisions about medication and medical care consumption may be a useful way to observe this phenomenon. Behaviors that deviate from what may be considered rational within the economic discipline, such as preference for the salience, time inconsistencies, and probability weighting, may explain the trends from economic modeling of medical compliance and health insurance. Health insurance is lauded as a way to increase affordability of care by providing cost sharing for patients. I hypothesize that patients with insurance (more cost sharing) will be no more compliant with their treatment than patients without health insurance, and I hypothesize that compliance level will play a larger role in expected future labor income and osteoporosis-related costs than the presence of insurance.

Health Insurance May Hinder Medical Compliance

There is limited literature about the relationship between health insurance and compliance. From a sample of nonelderly diabetics from the Medical Expenditure Panel Survey (2000-2011), Fout and Gilleskie [16] sought to determine whether there was a relationship between compliance with medicinal treatments and the presence of health insurance. The primary conclusion of the study was that insurance which provides drug

coverage may result in better compliance with medicinal diabetes treatment. Consequently, health insurance with drug coverage may disincentivize regular exercise [16]. The observations from Fout and Gilleskie's study align with the Neoclassic economic model of moral hazard, which demonstrates how individuals act during lowered levels of risk. Moral hazard is a response to risk that can be seen across many markets and everyday situations. A common example of moral hazard is the observed response to lowered risk under insurance. Uninsured drivers may be more cautious on the roads than insured drivers, who have a lower risk of financial responsibility for the consequences associated with an accident. The same principle applies to health-related behavior when individuals are covered by health insurance.

Moral hazard was a key concept missing from Kenneth Arrow's seminal work, *Uncertainty and the Welfare Economics of Medical Care*. Arrow made the claim that the unique medical care industry will experience market failure from the vast amount of uncertainty, since insurance cannot account for the uncertainty [17]. Mark Pauly critiqued Arrow's work in *The Economics of Moral Hazard: Comment* by observing that the characterstic uncertainty is not to blame, but rather the increased consumption of medical care with health insurance [18]. Individuals may consume more medical care while insured with the corresponding decrease in the marginal cost, or rather the additional cost for and additional unit of consumption. Pauly identifies this consumption behavior as consistent with rational decision making.

Consequently, changes in consumption (i.e., medical care covered by insurance) may have an inverse effect on the consumption of health-related care that is not covered

by health insurance. For example, individuals may be more prone to stop exercise regimens once enrolled in a health insurance plan that lowers the cost of medical expenses associated with obesity (statins, hypertension medication, etc.). Fout and Gilleskie explain this phenomenon by claiming that patients consider medicinal treatments and lifestyle alterations to be substitute goods [16]. As the price of medicine decreases, the demand for healthy lifestyle alterations (goods associated with healthy eating and regular exercise) decreases. Moral hazard explains how insured individuals may act in ways that will increase the demand for medical care; moreover, the presence of insurance increases the consumption of medical care.

Health care utilization can be divided into the extensive and the intensive margins. The extensive margin refers to the decision to see a doctor (i.e., go to the urgent care center, go to an annual doctor appointment, etc.), while the intensive margin refers to "what happens once a person is in the [health] system" [19]. For the purposes of patient compliance, the intensive margin is more relevant. Patient medical compliance does not simply mean going to visit a doctor. Compliance does not solely mean getting an x-ray or a prescription, rather it requires the act of going to the doctor, getting a prescription filled, and then actually following the physician's instructions regarding how and when to take the medication and how to properly integrate the suggested lifestyle adjustments.

Patients recognize and cope with illness in various ways. David Mechanic concedes that recognition of a symptom is a necessary, but not sufficient, variable to persuade patients to pursue care [20]. Mechanic suggests that patients will seek medical care under ten conditions:

> "(1) visibility and recognition of symptoms; (2) the extent to which the symptoms are perceived as dangerous; (3) the extent to which the symptoms disrupt family, work, and other social activities; (4) the frequency and persistence of symptoms; (5) amount of tolerance for the symptoms; (6) available information, knowledge, and cultural assumptions; (7) basic needs that lead to denial; (8) other needs competing with illness responses; (9) competing interpretations that can be given to the symptoms once they are recognized; and (10) availability of treatment resources, physical proximity, and psychological and financial costs of taking action" [20].

Mechanic's ten conditions detail reasons why patients would accept a change in their health status significant enough upon which to act (with proper medical advice). Patients must recognize the problem, deem it serious enough to seek attention, then acknowledge that seeking care is a viable option for their situation. Patients' acknowledgement and recognition of these ten conditions based on health perceptions is understandably variable. Health itself is extremely variable, hard to define, and, therefore, not measured well. One definition of health provided by the WHO, is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [21]. Health should be defined on a spectrum. If defined binarily, the implied assumption would be that people are either completely healthy or completely unhealthy (dead).

The Rand Health Insurance Experiment (RHIE) examined the relationship between health insurance and medical care utilization and found that cost sharing reduced the consumption of medical care, but the researchers were unable to deduce any relationship to health outcomes [22]. A major flaw of the RHIE was that researchers examined the extensive and intensive margins of health care utilization in an aggregated fashion. A disaggregated study potentially could show how cost sharing has more of an effect on the extensive margin, which alludes to the problem cited earlier about insurance encouraging excessive consumption of health care. A more recent study addressing the impact of the Affordable Care Act (ACA) on insurance coverage, access to care (specifically affordability and access to a personal physician and to medication), and health (health status and activity limitations) reported successful increases in all three measures [23]. However, the measures about lower cost sharing and access showed steeper improvements than self-reported health. It is challenging to define health, so there were likely variations between how health was defined by the subjects in the RHIE. The significance of the health utilization on health outcomes may be skewed from variable definitions of health. Increased medical care does not necessarily mean better health for the population. Additionally, unnecessary consumption of medical care can contribute to the exorbitant costs that overburden the system.

The intensive margin explains what individuals do once in the health care system (i.e., after they go visit a doctor). Although patients may be seeing a general physician on a yearly basis, one cannot assume that they are receiving the necessary tests and that they are utilizing their prescribed medications properly and regularly. Additionally, the

intensive margin is a more accurate way of measuring compliance, as visits to a physician or a hospital for care (extensive margin) do not guarantee that individuals will subsequently comply with treatments.

Preference for the Salient, Time Inconsistency, and Probability Weighting

Behavioral and Neoclassical economics provide two different ways of analyzing human behavior. Neoclassical economics deduces behavior starting with assumptions; whereas, behavioral economics induces predictions from data and observations. A prominent issue with osteoporosis risk is that patients can neither see the problem, nor the impact of prevention, nor the impact of treatment. Stefano DellaVigna's analysis of behavioral economics sheds light on a type of behavioral inconsistency: preference for the salient effect. Preference for the salient explains how individuals make choices based on what stands out [24]. According to preference for the salient, individuals prefer to act upon conditions that are more noticeable. Salient preferences can apply to medical conditions and commercial purchases alike. Back pain stands out more than asymptomatic osteoporosis. Acknowledging and treating the back pain may take precedence over taking multivitamins to prevent potential future fractures.

Time inconsistencies and probability weighting are other behavioral phenomenon related to preference for the salient. Individuals exhibiting time inconsistencies value today more than tomorrow, or the present more than the future. For example, patients may decide to exercise tomorrow or to start taking their vitamins tomorrow. Alternatively, physician persuasion may be strong enough to encourage initial treatment, but the impact of treatment is invisible prior to a DEXA imaging scan. A patient's

inconsistencies in the utility of treatment over time reflect imperfectly rational behavior. Patients still understand the value of the treatment or lifestyle recommendations but cannot seem to prioritize making those changes immediately. Probability weighting explains why people weigh more obvious salient diseases, such as cancer and heart disease, as riskier than less salient diseases like osteoporosis. Poor bone mineralization and high bone porosity are not traits that can be easily seen. Additionally, we are not surrounded by alarming news stories regarding the latest scare in osteoporosis as we are for cancer and infectious disease. Therefore, people may weigh the probability of a debilitating osteoporotic fracture less than cancer, heart attacks, and Alzheimer's Disease.

In the pediatric population, a vitamin D level under 40 ng/µl is considered insufficient, and a level under 20 ng/ml considered deficient (see Figure 9). Based on this theory of preference for the salient, one could hypothesize that children presenting at lower levels of insufficiency or deficiency would be more likely to take therapeutic measures seriously than those presenting a baseline level closer to sufficient levels of 40 ng/ml. Lower baseline levels may be more likely to provoke a more compliant response. Additionally, parents are likely to warrant a stronger reaction in response to alarmingly low vitamin D levels. Depending on the age of the pediatric patient, parents may have a greater sense of agency and take control of and responsibility for their child's medical compliance.

Compliance incentives such as quantifying and visualizing markers of the disease for vitamin D supplementation have implications for future policy changes relevant to pediatricians and pediatric orthopedic physicians. Compliance studies provide clues for

how to best ensure that patients will take vitamin D supplements in response to a deficiency. A comparative case study model could be helpful for studying the costs and benefits of osteoporosis treatments, levels of compliance, the role of health insurance in decision making, and the long-term consequences of treatment or lack thereof.

The model presented below allows for manipulations that mimic realistic scenarios and yields information about compliance incentives in osteoporosis care. To perform this analysis, I created four models to look at variances in compliance and insurance and how those variables affect positive and negative cashflows as well as the present and future value of expected labor income minus osteoporosis-related treatment. In isolation, the four models do not mean anything; it is when the models are compared with each other that they start to tell a story about the relationships between compliance, insurance, and expected osteoporosis-related expenses.

Methods:

I used reasonable medical scenarios to develop the four model patients: Tara (compliant and insured), Tina (non-compliant and insured), Cam (partially compliant and uninsured), and Stacy (partially compliant and insured). I generated positive and negative cashflows from osteoporosis-related expenditures, incomes, and scholarships that are impacted by the presence or absence of osteoporosis-related health outcomes. I used the following formulas to calculate present value (PV)[5] and future value (FV)[6] of expected labor income[7]. The PV (time 0), FV (time 60), and FV (projected to end of life) for all

[5] $PV(M_T)= C_0/ (1+i)^n$

[6] $FV(M_T)= C_0* (1+i)^n$

[7] *i*= the discount rate of 0.03; *n*= number of years since time 0

four cases took the following variables into account: age, positive cashflows, negative cashflows, injury cost, probability of injury (resulting in a fracture), and expected labor income (Figure 1). I calculated positive cashflows for all four cases with expected athletic scholarship and salary as a CPA. Tara's college athletic scholarship in case 1 was valued at $20,000. I calculated negative cashflows for all four cases with expected medical expenses (DEXA scans, x-rays, surgery, vitamin D supplements, bisphosphonates, etc.), priced with and without insurance. The remaining negative cashflows are detailed in Figure 1.

Table 1: Positive and Negative cashflows for osteoporosis and fracture care

Description	Cost
Social Security during retirement[8]	$1,360/month or $14,320/year
Expected CPA salaries[9]	$50,500 (baseline for out of college), $73,800 (average salary), and $124,000 (exceptional CPA
DEXA scan with insurance (copay and 30% of bill)[10]	Copay= $50 $125 (0.3)= $37.50 =$87.50
Non-surgical treatment of broken arm with insurance (copay and 30% of bill)[11]	Copay= $50 $2,500 (0.3)= $750 = $800
Non-surgical treatment of broken arm without insurance	$2,500
Surgical treatment of broken hip with insurance (copay and 30% of bill)[12]	Copay= $100 $26,912 (0.3)= $8,073.60

[8] https://www.ssa.gov/news/press/factsheets/basicfact-alt.pdf

[9] http://www.investopedia.com/articles/investing/051415/how-much-do-cpas-make.asp

[10] www.choosingwisely.org/patient-resources/bone-density-tests/

[11] http://health.costhelper.com/broken-arm.html

[12] http://health.costhelper.com/hip-fracture.html

	=$8,173.60
Surgical treatment of broken hip without insurance	$26,912
Surgical treatment (vertebroplasty) of broken vertebrae with insurance (copay and 30% of bill)[13]	Copay=$100 $9,837 (0.3)= $2,951.10 =$3,051.10
Surgical treatment (vertebroplasty) of broken vertebrae without insurance	$9,837
Atorvastatin (generic Lipitor) with insurance[14]	($9.95/ month) (year) $119.40
Atorvastatin (generic Lipitor) without insurance	($126.40/ month) (year) $1516.80
Average cost of care following heart attack (90 days) with insurance[15]	$38,501
Cost of bisphosphonates (Alendronate 70mg-generic) with insurance[16]	($41/month) (year) $492.00 $492.00 (0.1) = $49.20
Cost of multivitamin (Vitamin D, calcium, phosphate, etc.)[17]	2 months= $9.99 1 year= $59.94

I calculated utility of expected labor income by taking the square root of the net cash flows[18]. The proposed population will be risk averse on matters related to health, so that the modeled population is one that is generally interested in being healthy. Probability represents the likelihood of fracture and compounds after every fracture. Age

[13] http://health.costhelper.com/spinal-compression.html

[14] https://www.goodrx.com/atorvastatin

[15] http://www.nber.org/digest/oct98/w6514.html

[16] http://www.consumerreports.org/cro/2013/09/osteoporosis-medications/index.htm

[17] http://www.vitacost.com/productResults.aspx?N=0&ss=1&Ntt=calcium%20and%20vitamin%20d

[18] individuals make decisions based on utility, which is represented by a concave utility function

10 was set at time zero where the first fracture occurs for all four cases. Probability of a fracture is a cumulative risk that increases with subsequent fractures, menopause, and genetic predisposition. Compounded risk doubled with every subsequent increase in risk (starting at a base of 0.1 because all patients started with a fracture at age 10).

Case 1 (Figure 1a) models the positive and negative cashflows in a female insured patient who is compliant with treatment. Tara fractures her radius at age 10 playing soccer. She has insurance, so her family only has to pay the copay and 30% of the fracture treatment costs. Because of early influence of her parents, Tara decides to take multivitamins (vitamin D, calcium, phosphate, etc.) from the point of her fracture until the end of her life. Tara is able to completely recover, stay in soccer, and get a generous athletic scholarship to a good four-year college. Tara enters menopause at age 55, does well in her career as a CPA, and she is able to retire at age 65 without any serious health complications. Tara dies of natural causes at age 85.

Case 2 (Figure 1b) models the positive and negative cashflows in a female insured patient who is non-compliant. Tina fractures her radius at age 10 during gymnastics. She has insurance, so her family only has to pay the copay and 30% of the fracture treatment costs. Because of the early influence of her parents, Tina decides to never take multivitamins (vitamin D, calcium, phosphate, etc.) from the point of her first fracture till the end of her life. Tina refractures at age 15 (wrist) and again at age 50 (pelvis) when she is eventually diagnosed with osteoporosis. Tina drops out of gymnastics and chooses to never exercise again. Tina develops high cholesterol and

obesity and has to start taking statins at age 25. After completing college, Tina performs mediocrely in her career as a CPA because she has to take many days off for her poor health. Tina goes through menopause at age 55, and her last fracture is in her vertebrae at age 60. Tina eventually succumbs to a heart attack in the hospital and dies shortly after her fourth fracture.

Case 3 (Figure 1c) models the positive and negative cashflows in a female uninsured patient who is partially compliant. Cam fractures her radius at age 10 playing soccer, but her family does not have health insurance. Because of the early influence of her parents, Cam decides to take multivitamins (vitamin D, calcium, phosphate, etc.) from the point of her first fracture until she leaves for college. Cam goes to college, studies to be a CPA, and remains relatively active for her entire life. Osteoporosis runs in her family. Cam goes through menopause at age 50. When Cam fractures her wrist again at age 60, she goes in for a DEXA scan and is prescribed a bisphosphonate and multivitamins. Without insurance, Cam is unable to afford both bisphosphonates and multivitamins, so she just takes the multivitamins. Cam suffers from a debilitating hip fracture at age 75 and dies shortly after in the hospital.

Case 4 (Figure 1d) models the positive and negative cashflows in a female insured patient who is partially compliant. Stacy fractures her radius at age 10 playing soccer. She has insurance, so her family only has to pay the copay and 30% of the fracture treatment costs. Because of the early influence of her parents, Stacy decides to take multivitamins (vitamin D, calcium, phosphate, etc.) from the point of her

first fracture until she leaves for college. Stacy goes to college and studies to be a CPA, and she remains relatively active for her entire life. Osteoporosis runs in her family, and Stacy goes through menopause at age 50. When she fractures her wrist again at age 60, she goes in for a DEXA scan and is prescribed a bisphosphonate and multivitamins. With insurance, Stacy chooses the cheaper option (viewing bisphosphonates and multivitamins as substitutes), so she just takes bisphosphonates. Stacy suffers from a debilitating hip fracture at age 75 and dies shortly after in the hospital.

(A.)

Age	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85
Postitive cashflows	$0.00	$0.00	$20,000.00	$50,500.00	$73,800.00	$73,800.00	$124,000.00	$124,000.00	$124,000.00	$124,000.00	$124,000.00	$124,000.00	$14,320.00	$14,320.00	$14,320.00	$14,320.00
Negative cashflows	-$800.00	-$139.94	-$139.94	-$139.94	-$139.94	-$139.94	-$139.94	-$139.94	-$139.94	-$219.94	-$219.94	-$307.44	-$219.94	-$219.94	-$139.94	-$139.94
Probablity fx	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
net cash flow	-$800.00	-$139.94	-$139.94	$45,310.06	$71,330.06	$71,330.06	$118,840.06	$118,840.06	$118,840.06	$113,740.06	$113,740.06	$113,652.56	$36,036.06	$36,036.06	$37,548.06	$37,548.06
labor income	$0.00	$0.00	$0.00	$45,450.00	$71,470.00	$71,470.00	$118,980.00	$118,980.00	$118,980.00	$113,960.00	$113,960.00	$113,960.00	$36,256.00	$36,256.00	$37,688.00	$37,688.00
expected utility labor income (utils)	0.00	0.00	0.00	191.87	240.60	240.60	310.44	310.44	310.44	270.06	270.06	270.06	152.33	152.33	174.72	174.72
PV time 0	-$800.00	$0.00	$0.00	$29,172.63	$39,571.21	$34,134.47	$49,018.18	$42,283.52	$36,474.13	$30,135.43	$25,995.08	$22,423.59	$6,153.84	$5,308.36	$4,759.89	$4,105.93
PV	**$328,736.25**															
FV time 60	-$4,713.28	$0.00	$0.00	$127,890.05	$149,642.31	$111,347.93	$137,930.43	$102,633.19	$76,368.73	$54,427.93	$40,499.49	$30,135.43	$7,133.99	$5,308.36	$4,105.93	$3,055.20
FV	$845,765.68															
FV (discounted till end)	**$888,354.35**															

(B.)

Age	10	15	20	25	30	35	40	45	50	55	60
Postitive cashflows	$0.00	$0.00	$0.00	$50,500.00	$73,800.00	$73,800.00	$73,800.00	$73,800.00	$73,800.00	$73,800.00	$73,800.00
Negative cashflows	-$800.00	-$800.00	-$240.00	-$359.40	-$359.40	-$359.40	-$359.40	-$359.40	-$8,380.50	-$5,023.56	-$41,759.00
Probablity fx	0.1	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.6	0.6	0.8
net cash flow	-$800.00	-$800.00	-$240.00	$34,990.60	$66,450.60	$66,450.60	$66,450.60	$66,450.60	$21,139.50	$54,796.44	-$26,999.00
labor income	$0.00	$0.00	$0.00	$35,350.00	$66,810.00	$66,810.00	$66,810.00	$66,810.00	$29,520.00	$59,820.00	$14,760.00
expected utility: labor income (utils)	0.00	0.00	0.00	131.61	180.93	180.93	180.93	180.93	68.73	97.83	24.30
PV time 0	-$800.00	$0.00	$0.00	$22,689.82	$36,991.08	$31,908.83	$27,524.84	$23,743.16	$9,049.56	$15,818.72	$3,366.86
PV	**$170,292.86**										
FV time 60	-$4,713.28	$0.00	$0.00	$99,470.04	$139,885.30	$104,087.80	$77,451.10	$57,630.89	$18,947.76	$28,570.37	$5,245.46
FV	$526,575.44										
FV (projected till end)	**$526,575.44**										

(C.)

Age	10	15	20	25	30	35	40	45	50	55	60	65	70	75
Postitive cashflows	0	0	0	50500	73800	73800	124000	124000	124000	124000	73800	73800	14320	14320
Negative cashflows	-$2,559.94	-$559.94	-$559.94	-$750.00	-$750.00	-$750.00	-$750.00	-$750.00	-$1,000.00	-$1,000.00	-$2,684.94	-$1,559.94	-$1,559.94	-$26,912.00
Probablity fx	0.1	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.6	0.6	0.6	0.8
net cash flow	-$2,559.94	-$559.94	-$559.94	$34,600.00	$66,060.00	$66,060.00	$108,190.00	$108,190.00	$102,920.00	$102,920.00	$91,195.06	$92,320.06	$48,448.06	-$24,048.00
labor income	$0.00	$0.00	$0.00	$35,350.00	$66,810.00	$66,810.00	$108,940.00	$108,940.00	$103,920.00	$103,920.00	$93,880.00	$93,880.00	$50,008.00	$2,864.00
expected utility: labor income (utils)	0.00	0.00	0.00	131.61	180.93	180.93	231.04	231.04	193.42	193.42	122.56	122.56	89.45	10.70
PV time 0	-$2,559.94	$0.00	$0.00	$22,689.82	$36,991.08	$31,908.83	$44,881.84	$38,715.47	$31,857.39	$27,480.46	$21,414.69	$18,472.50	$8,488.01	$419.33
PV	**$280,759.47**													
FV time 60	-$15,082.15	$0.00	$0.00	$99,470.04	$139,885.30	$104,087.80	$126,291.32	$93,972.60	$66,702.29	$49,632.77	$33,363.39	$24,825.50	$9,839.93	$419.33
FV	$733,408.13													
FV (projected till end)	**$756,275.98**													

(D.)

Age	10	15	20	25	30	35	40	45	50	55	60	65	70	75
Postitive cashflows	$0.00	$0.00	$0.00	$50,500.00	$73,800.00	$73,800.00	$124,000.00	$124,000.00	$124,000.00	$124,000.00	$73,800.00	$73,800.00	$14,320.00	$14,320.00
Negative cashflows	-$859.94	-$219.94	-$219.94	-$240.00	-$240.00	-$240.00	-$240.00	-$240.00	-$320.00	-$320.00	-$936.70	-$529.20	-$529.20	-$8,173.60
Probablity fx	0.1	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.6	0.6	0.6	0.8
net cash flow	-$859.94	-$219.94	-$219.94	$35,110.00	$66,570.00	$66,570.00	$108,700.00	$108,700.00	$103,600.00	$103,600.00	$92,943.30	$93,350.80	$49,478.80	$3,282.40
labor income	$0.00	$0.00	$0.00	$35,350.00	$66,810.00	$66,810.00	$108,940.00	$108,940.00	$103,920.00	$103,920.00	$93,880.00	$93,880.00	$50,008.00	$11,456.00
expected utility: labor income (utils)	0.00	0.00	0.00	131.61	180.93	180.93	231.04	231.04	193.42	193.42	122.56	122.56	89.45	21.41
PV time 0	-$859.94	$0.00	$0.00	$22,689.82	$36,991.08	$31,908.83	$44,881.84	$38,715.47	$31,857.39	$27,480.46	$21,414.69	$18,472.50	$8,488.01	$1,677.31
PV	**$283,717.46**													
FV time 60	-$5,066.43	$0.00	$0.00	$113,680.04	$144,763.81	$107,717.87	$132,110.87	$98,302.90	$66,702.29	$49,632.77	$33,363.39	$24,825.50	$9,839.93	$9,063.57
FV	$784,936.52													
FV (projected till end)	**$812,183.67**													

Figure 1: Spreadsheet of variables impacting present and future values of expected labor income (A.) Tara case 1, (B.) Tina case 2, (C.) Cam case 3, (D.) Stacy case 4; data about multivitamin and osteoporosis treatment costs were obtained from Vitacost 2017 and from Consumer Reports Best Buy Drugs 2013

Results:

There are distinct differences in positive and negative cashflows with modifications to the level of compliance (compliant, noncompliant, or partially compliant). The presence of insurance was held constant for the comparison between cases 1 and 2. Case 1 shows perfect compliance, while case 2 shows no compliance to neither the multivitamin nor bisphosphonate regimens. The key difference in positive cashflows is that there is a greater maximum (at $124,000) for case 1, while case 2 only maximizes at $73,800 (Figure 2). Case 1 lives the longest (85 years), and therefore shows a continued positive cashflow that represents Social Security benefits. Case 1 shows a constant low cost ($59.94 for the multivitamins) for negative cashflows, and case 2 shows a dramatic final negative peak at -$41,148.88. A final key difference is in lifespan, as case 1 represents 25 more years of life than the lifespan presented in case 2.

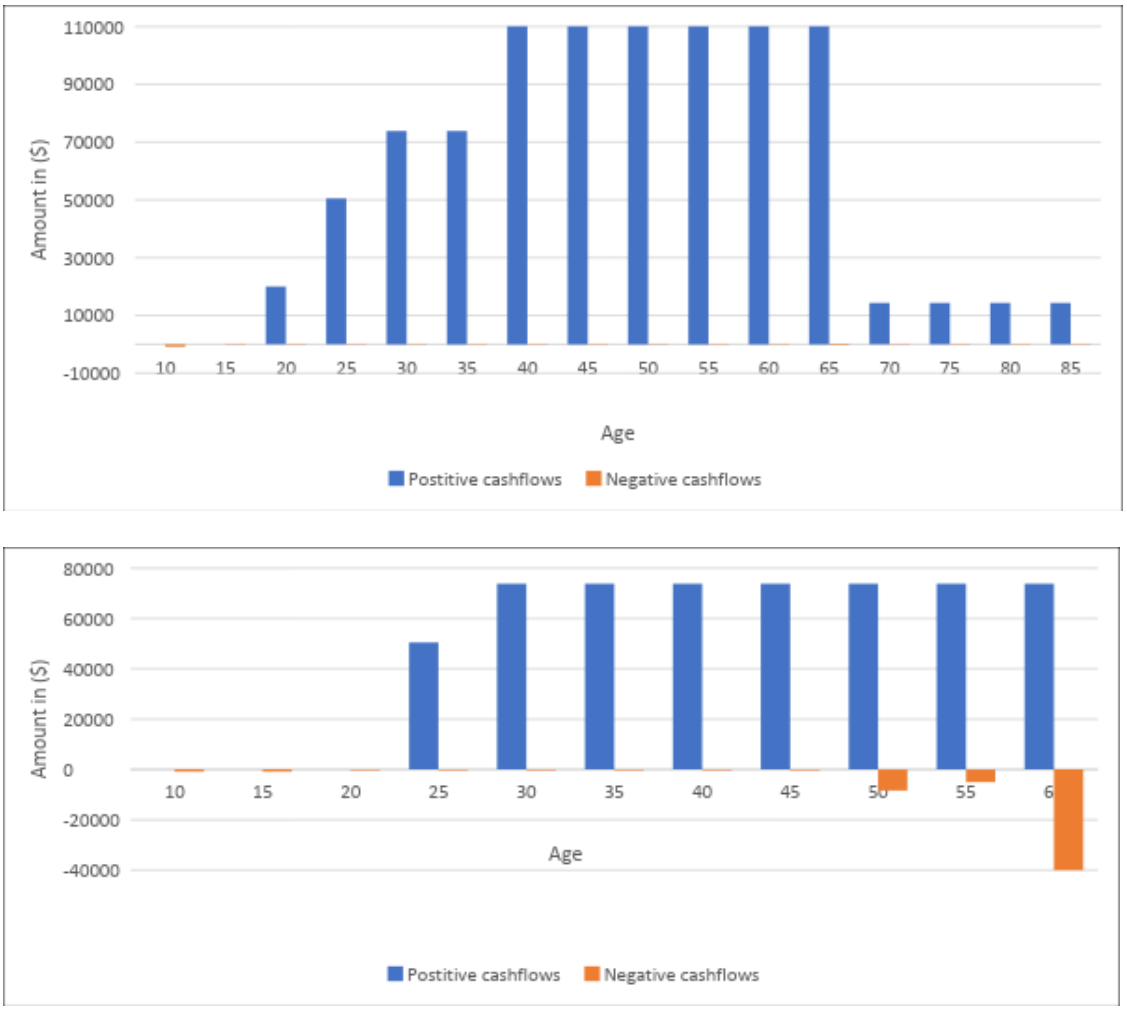


Figure 2: Positive and negative net cashflows for case 1 (top) and case 2 (bottom) calculations derived from Figure 1

There are differences in positive and negative cashflows based on level of compliance and presence of health insurance. The primary difference between cases 3 and 4 is the presence of insurance. The level of compliance was held constant at partially compliant (inconsistently takes treatment) for this comparison. Case 3 represents no insurance and case 4 represents insurance. There is no difference between either case in positive cashflows. While there is a slightly larger negative cashflow at age 10 for case 3, the primary spike is at age 75 (-$21,529.60 for case 3 and at -$6,538.88 for case 4)

(Figure 3). The data indicate that insurance has a greater influence on negative cashflows rather than positive cashflows. Both of the cases represented females who have a family history of osteoporosis and entered menopause relatively early (increasing probability of fracture independent of compliance level).

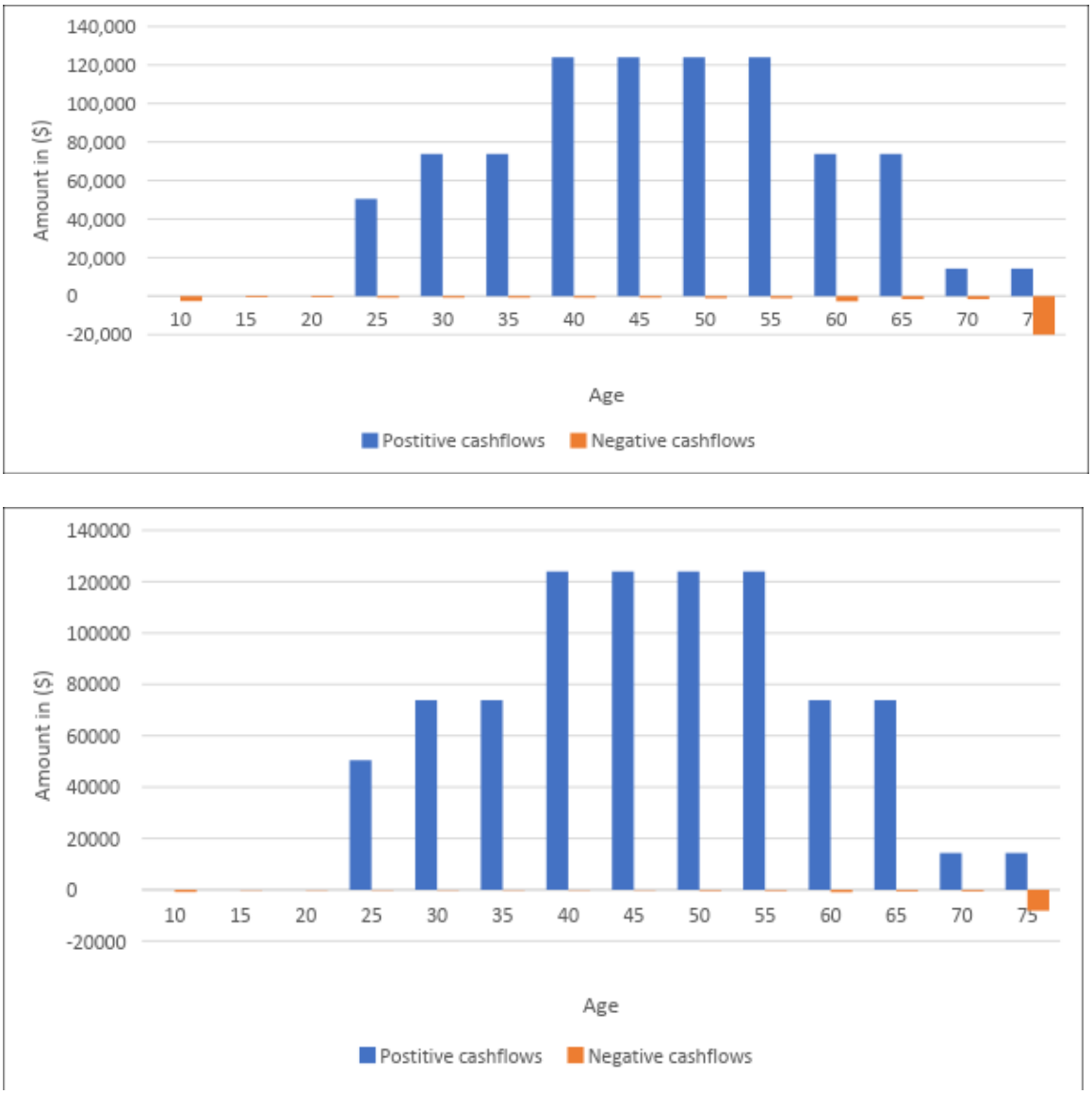


Figure 3: Positive and negative net cashflows for case 3 (top) and case 4 (bottom)
calculations are derived from Figure 1

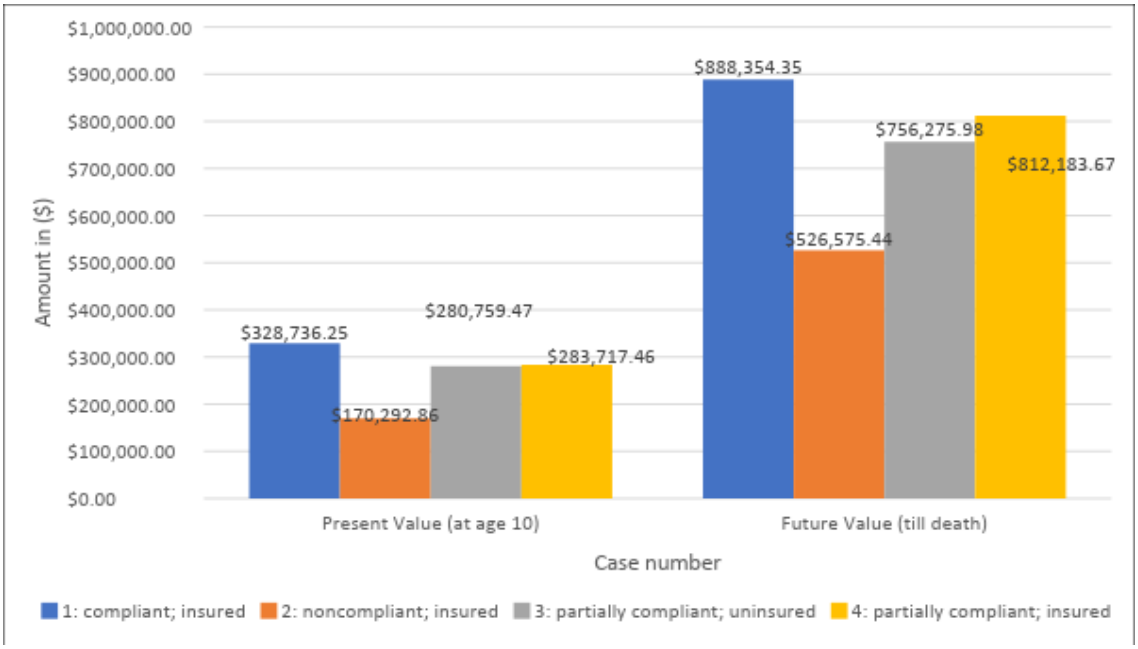


Figure 4: Present and future values of expected labor income-expected osteoporosis treatment costs future value was discounted to the end of life

Looking at the present value and future value of expected labor income minus osteoporosis treatment costs reveals a new area of comparison between the four models. Case 1 (compliant with insurance) has the greatest present and future values of expected labor income minus osteoporosis treatment costs, while case 2 (not compliant with insurance) has the lowest present and future value (Figure 4). Cases 1 and 2 represent the extremes for compliance (fully compliant and fully noncompliant), while holding the presence of insurance constant. Compared to case 2, the present value of case 1 is greater by 93.04% and the future value is greater by 68.70%. Case 3 (partially compliant without insurance) and case 4 (partially compliant with insurance) are almost identical in terms of present and future values of expected labor income minus osteoporosis treatment costs. Compared to case 3, the present value of case 4 is greater by 1.05% and the future value is greater by 7.39%. The expected utility of labor income (Figure 5) mirrors the trends

seen with the present and future value of expected labor income. All four cases plateau until age 20. Case 1 shows the largest sustained spike, while case 2 shows the lowest sustained peak. There is no significant difference between in values at all time points for cases 3 and 4.

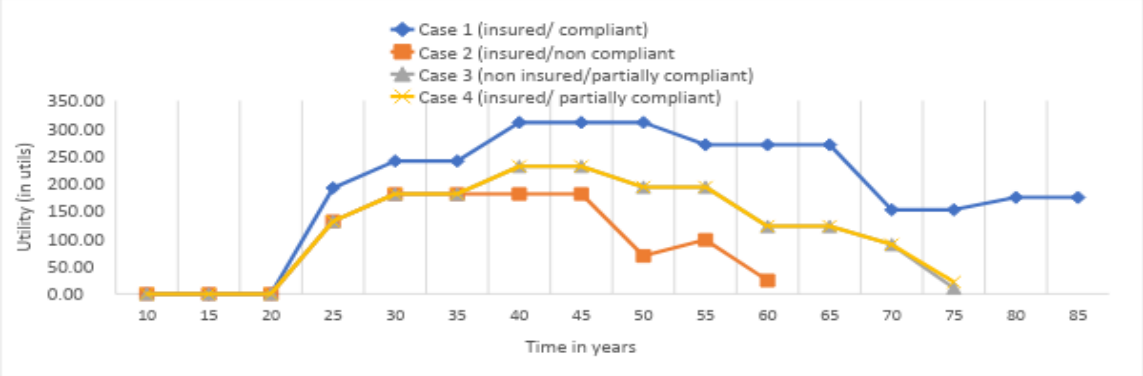


Figure 5: Expected utility of labor income

Discussion:

Behavioral economics provides a framework for understanding how Tara, Tina, Cam, and Stacy chose their level of compliance. Did these individuals maximize the utility of the osteoporosis drugs and multivitamins in addition to other lifestyle behaviors? Tara ends up living the longest, has the highest present value at age 10, and the highest future value at time of death. Tina made the decision to remain noncompliant for the entirety of her lifetime and suffered from four fractures as a result. Tina did not maximize the utility of the medications nor of the multivitamins (Figure 4). Tina likely falls prey to time inconsistency, preference for the salient, and unrealistic probability weighting. Cam and Stacy take either medications or multivitamins for portions of their lifetime (partially compliant), but do not maximize their utility as well as Tara in case 1. Some potential explanations for why Cam and Stacy stopped multivitamin usage once

they started college could be that their parents were enforcing the multivitamin use, time inconsistency, or they held a general misunderstanding of continued preventive benefits of multivitamin use during the period of peak bone mass development. By the second fracture at age 60, both Cam and Stacy chose to partially comply to one segment of the treatment (either bisphosphonates or multivitamins) based on which treatment was cheaper. Between the two fractures at ages 10 and 60, there was no significant difference in the level of severity. Time inconsistency best explains Cam and Stacy's patterns of behavior.

The case model analysis of the benefits and costs of osteoporosis care over time, with manipulations to the level of compliance and presence of health insurance, demonstrates the need to identify better tools to improve compliance since health insurance clearly is not a significant motivator. Health insurance is no magic bullet, since cases 3 and 4 are almost identical in terms of expected labor income and likelihood to comply while they vary in insurance (Figure 5). The similar behavior is likely a rational response to price with the substitution effect of insurance between bisphosphonates and vitamin D. Additionally, the trend is a behavioral response to salience, time inconsistency, and probability weighting of both children and parents.

Future studies should monitor the extent to which parents aid or impede complete compliance and the extent to which the asymptomatic nature of metabolic bone health impacts children's decision making. Every case in this model begins with a fracture at age 10 to demonstrate the potential for preventive action in adolescence before reaching peak bone mass. Ideally, every child could be like Tara (case 1) and would value the

importance of supplementation to completely heal fractures and to prevent further refracturing. As the future of health insurance in America is changing drastically with uncertain costs, understanding the interactions between medicine, insurance, and compliance in chronic diseases is of the utmost importance. Americans may be more effectively persuaded to take preventive action against chronic diseases whether or not they have an adequate amount of health insurance. There is also a need to make osteoporosis risk more salient through DEXA visualization of the bone mineralization in younger populations that have a greater chance of preventing the economic and medical costs associated with osteoporosis.

PART II: Compliance to Vitamin D Supplementation in a Pediatric Fracture Population

While Part I provided valuable information about compliance incentives in hypothetical pediatric patients over the span of their lifetimes, Part II will address compliance incentives in an actual pediatric population. In adolescence, vitamin D can promote bone healing and prevent future fracture risk. Pediatric patients are not given a clear "pre-osteoporotic" label, but there may be early signs for which to look. In this retrospective study, I hypothesize that a majority of the patients will present with a vitamin D deficiency and a majority of the patients will not be compliant. Furthermore, patients with more severe deficiencies will be more likely to comply to vitamin D supplementation.

The role of vitamin D in calcium absorption

Vitamin D is a fat-soluble molecule colloquially known as the "sunshine vitamin". Historically, vitamin D came to the public's attention through the discovery of the connection between inadequate childhood sunlight exposure, smog associated with the Industrial Revolution, and rickets in 19th century England. In 1922, biochemist Elmer McCollum was able to determine the beneficial fat-soluble vitamin compound within cod liver oil and gave it the name vitamin D [25]. McCollum's discovery led to a deliberate connection between vitamin D as a supplementary tool and bone health for children with rickets disease, a metabolic bone disorder quite similar to osteoporosis. Although the general public may merely associate calcium with bone health, vitamin D is a key player in the metabolism and utilization of calcium.

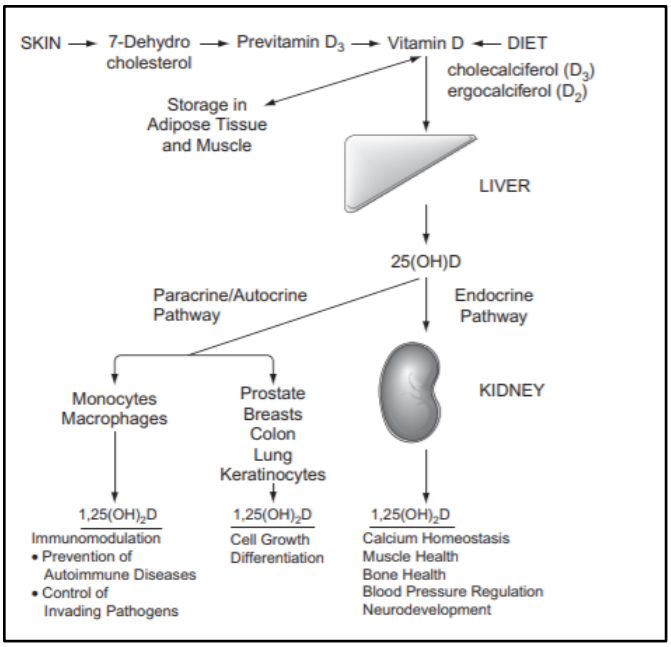


Figure 6: Vitamin D Metabolism (derived from [26])

Vitamin D is obtained either through dermal synthesis or from the diet, including supplementation. Several metabolites are produced in the synthesis process with two noteworthy metabolites being 1,25-dihydroxyvitamin D and D_3 (25(OH)D) [26]. Upon interaction with UVB rays, pre-vitamin D_3 is activated into a biologically useful form of vitamin D, cholecalciferol (Figure 6). The stepwise reactions and melanin in the dermal layers contribute to the blocking of potential vitamin D_3 synthesis. Therefore, not all sun exposure results in the formation of metabolically useful vitamin D. There are also seasonal variations in the amount of vitamin D available [26]. In summer months with greater sun exposure and vitamin D absorbance potential, there is a tradeoff with an associated increased risk for skin cancer. This compromise is a notable point of disagreement between physicians who promote exposure for vitamin D absorbance and those who prioritize skin cancer prevention.

Cholecalciferol (either from ingestion via the intestines or dermal synthesis) travels through the blood to the liver and the kidney (Figure 6). Cholecalciferol is eventually converted from 1,25-dihydroxyvitamin D to the 25(OH)D form that can easily circulate throughout the body. Vitamin D has the endocrine function of encouraging the release of (or suppressing) Parathyroid Hormone (PTH), which allows for resorption of bone minerals to be released into the bloodstream, reabsorption of calcium in renal tubules, and the upregulation of 1-hydroxylase to stimulate the production of 1,25-dihydroxyvitamin D [26]. It is this metabolically active form that promotes the absorption of calcium ions in the intestines. The compound 25(OH)D, as opposed to 1,25-dihydroxyvitamin D, is the more reliable form of the metabolite to track an individual's vitamin D status. Although it is not the more biologically active form (1,25-dihydroxyvitamin D), 25(OH)D circulating levels are what determines an excess or deficiency [26].

Risk factors: What are we looking for?

Amidst concern regarding vitamin D deficiency, studies have evaluated supplementation compliance in children known to be 25 vitamin D (25VitD) deficient after fracture. While fractures do not occur as a direct result of the 25VitD level, the severity of the fracture is related to the severity of the 25VitD deficiency [27]. The trend observed in Minkowitz et al.'s retrospective study was a motivating factor for the compliance study detailed below in Part II. Osteoporosis is generally associated with postmenopausal women, but similar characteristics of low BMD and increased fracture risk can be seen in the pediatric population. Adolescence is a critical period for peak bone

mass development, with 80-90% of bone mass acquired by age 20 [28]. A 10% increase in peak bone mass is estimated to decrease future risk of osteoporosis by 50% [29]. Serum 25VitD level is a factor related to bone acquisition and peak bone mass through its role in facilitating calcium absorption. Maximizing peak bone mass is acutely important in order to prevent further fractures and or refractures in children. The healing process can be easily interrupted, oftentimes as a result of returning to sports prematurely. Thus, to stem the prevalence of osteoporosis, diagnosis of hypovitaminosis D (deficient or insufficient amount) and treatment should start in childhood.

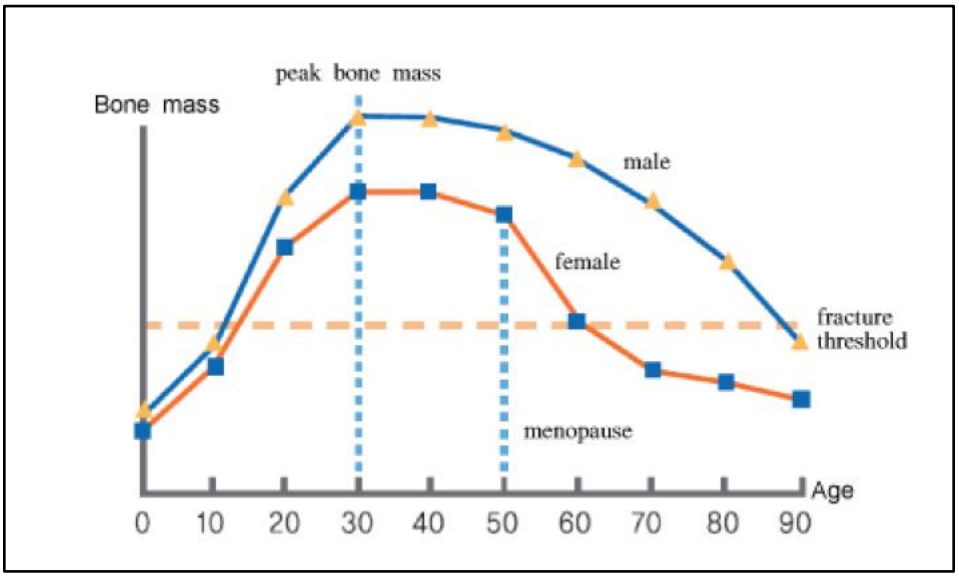


Figure 7: ***Changes in peak bone mass in respect to aging*** [30] Peak bone mass is maximized between ages 20-30, and it starts to decline thereafter. Adolescents and postmenopausal women present comparable levels of fracture risk past the fracture threshold. Males present with consistently higher BMDs on average throughout their lifetimes.

Physicians, researchers, and public health officials should be concerned about patient compliance to medicinal regimens and lifestyle adjustments. The general public may not understand the necessity of consistent compliance or may not understand that a full dosage is more than one pill (i.e., complex medical regimens). According to the

literature, approximately 40%[19] of patients do not correctly adhere to treatments, but this can reach up to 70% when there is a greater reliance on lifestyle adjustments [31]. While the consequences of noncompliance may seem to fall solely on the patient, there are more widespread ramifications. Improving patient compliance is crucial to improving outcomes, economic efficiency of the health care industry, and general public health. The principle of medical compliance can be applied to a population of children with hypovitaminosis D. Treatment for low 25VitD in addition to preventative measures in children start with Vitamin D_3 supplementation with calcium. Other nutritional factors include, but are not limited to, magnesium, phosphorus, boron, silicon, and vitamins (A, D, E, C, and certain B[20]) [32].

The American Academy of Pediatrics (AAP) only advocates checking 25VitD levels in "at-risk" children (typically those with 25VitD absorption or production issues), but not in the general healthy population. Consequently, most children never have 25VitD levels checked [33]. Some physicians deviate from the AAP norm to regularly monitor the vitamin D levels of pediatric patients. Dr. Barbara Minkowitz, a pediatric orthopedic surgeon, regularly checks healthy pediatric patients that present with fractures or other indications of compromised bone integrity. Minkowitz studied fracture patients in the multi-ethnic Morris-Essex community who had comparable 25VitD demographics to a non-fracture control population representative of the same community [27]. Sixty-five percent of healthy pediatric fracture patients in this group were deficient in 25VitD,

[19] Different than the World Health Organization's estimate of 50% [1]
[20] Often found in common multivitamins over the counter

which was shown to impact fracture severity [27]. The current study seeks to identify compliance patterns in the Morris-Essex population of patients with fractures who were counseled to start taking Vitamin D_3 supplementation with calcium.

Methods:

The retrospective study includes pediatric patients from a previous study with fractures who were tested for 25VitD level regardless of fracture severity [27]. Dr. Minkowitz instructed patients to take vitamin D_3 supplementation with calcium based on their 25VitD levels. Dr. Minkowitz used her protocol for supplementation (Figure 9) for these patients using Endocrine Society recommendations [34]. We analyzed compliance patterns to see if fracture severity, lower 25VitD, or age affected supplementation compliance. We reviewed patients' medical records, bone health history and follow-up surveys. A Sussex County health group contacted patients and asked about supplementation compliance using an IRB-approved telephone survey after 48.6 months average follow-up [27]. Sample questions included: "sex, age, body mass index (BMI),…skin tone,…ethnicity, multivitamin intake, dairy intake, healthy eating habits, sun exposure, sunscreen use, season in which patient presented with the fracture, seasons in which child plays outdoors, 25(OH)D, calcium, phosphorus, intact parathyroid hormone…injury location, history of fractures before index case, fracture pattern severity, and mechanism of injury" [27].

Patients were counseled in a single physician pediatric orthopedic office practice by a pediatric orthopedic surgeon and certified medical assistant (CMA) regarding supplementation dosage based on baseline 25VitD level. Counseling included a

discussion regarding bone health needs, a personalized supplementation sheet encouraging the use of a calcium counter app, and a vitamin D brochure written at an appropriate reading level (for pediatric patients). Patients were asked to bring their supplementation bottles to the office to ensure appropriate supplement dosage. At each office visit (2 to 4 visits per patient), the medical team asked patients about supplementation use and reminded patients to take their vitamins. We obtained a repeat serum 25VitD level 2 to 6 months after initial labs while patients were instructed to take supplementation. We compared patients' initial and follow-up serum 25VitD levels. We compared demographics of this study population to the initial study. The statistician performed independent sample *t* tests and univariate and multivariable ordinal regression analyses to identify associations.

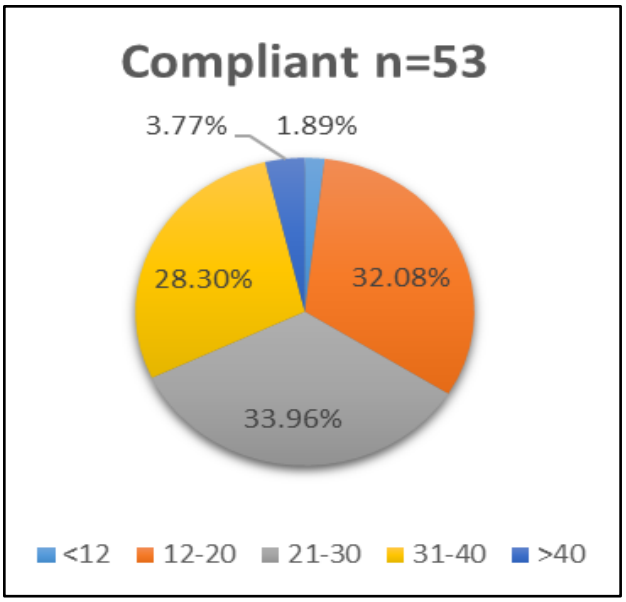
Results:

Table 2: Number of patients in each Vitamin D baseline group *Fisher's exact; *significant*

Baseline D25 group	n	Compliant n=53	%	Non-Compliant n=188	%	p-value*
<12	3 (0.01)	1	1.89%	2	1.06%	0.527
12-20	47 (0.20)	17	32.08%	30	15.96%	0.017*

21-30	104 (0.43)	18	33.96%	86	45.74%	0.158
31-40	65 (0.27)	15	28.30%	50	26.60%	0.861
>40	22 (0.09)	2	3.77%	20	10.64%	0.177

Patients in the five baseline D25 groups were subdivided by a binary division of compliance (Table 2). The largest percentage of compliant and non-compliant patients were in the 21-30 baseline group. Based on relative percentages, the 12-20 baseline group was most likely to comply ($p=0.017$). The <12 baseline group was too small to determine statistically significant results. Compliance percentages are broken down by baseline 25D group to represent the level ranges within the compliant and non-compliant groups (Figure 8).



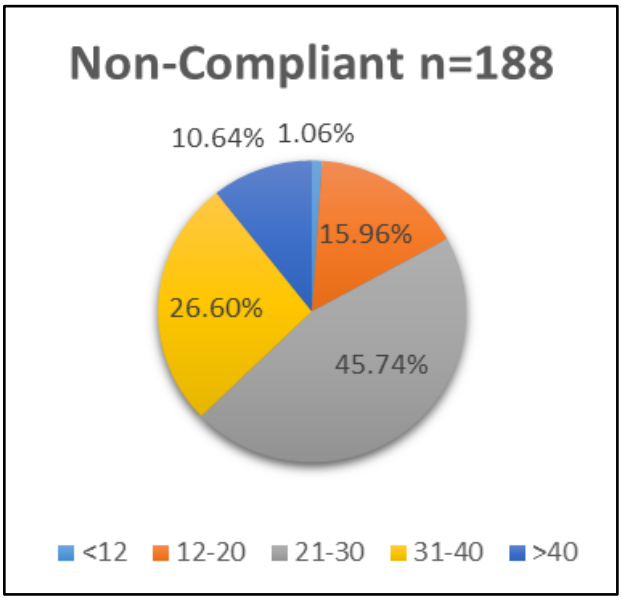


Figure 8: Compliance by baseline D25 group

Bone Health Protocol- Pediatric Orthopedics

Barbara Minkowitz, MD, Atlantic Health Systems, Morristown, NJ

Vitamin D and Calcium are daily supplements needed by everyone, everyday

Daily Vitamin D guidelines to obtain serum levels 40-60ng/ml in children without liver/ kidney dysfunction (predicated on serum 25-OHVitamin level).

0-1 **year:** 400U Vitamin D, **1-8 years:** 600-1000U Vitamin D, **9-13 years:** 1000-2000U Vitamin D, **13-18 years:** 1500-2000U Vitamin D, **Adult:** 2000U Vitamin D

20-50 lbs: 500-1000U Vitamin D, **50-90 lbs:** 1500U Vitamin D,**90+ lbs:** 2000U Vitamin D

•Vitamin D taken always with calcium; 1000 mg daily except 1-4 years old= 700mg daily

No Fracture present: Supplementation guidelines based on serum 25-OH VitD level used when fractures are not present. Labs must be repeated 2-6 months after supplementation, depending on amount given and to validate amount being used for maintenance. Some people are non-absorbers, and will require higher maintenance levels.

30-40ng/ml: considered normal by lab, however by Endocrine Society, 40-60ng/ml is optimal.	Add 500U VitD + calcium
20-30 ng/ml: considered VitD insufficient	Add 1000U VitD + calcium
12-20 ng/ml: considered VitD deficient	Add 2000U VitD + calcium
<12 ng/ml: considered VitD deficient	7000U VitD + calcium (If < 10 may give 14,000 VitD) and then repeat labs at 2 months, decrease if value in range, or send to endocrine This is equivalent to 50,000U or 100,000U per wk

Fracture present: With a fracture present, higher initial supplement can be used (dictated by serum level and not age or weight), for 2-3 months then repeat labs and decrease VitD or send to endocrinologist if not responsive. This is most important for bone fractures that can take a long time to heal, even in the best situation.

30-40 ng/ml: considered normal by lab, however by Endocrine Society, 40-60ng/ml is optimal	Add 500-1000 units VitD + calcium
20-30 ng/ml: insufficient for healing	Add 4000 units VitD + calcium
16-20 ng/ml: insufficient for healing	Add 4000 units VitD + calcium
<15 ng/ml: deficient	7000U VitD + calcium (If < 10 may give 14,000 VitD) and then repeat labs at 2 months, decrease if value in range, or send to endocrine This is equivalent to 50,000U or 100,000U per wk

Fracture present but no serum25-OH VitD is available: Patients are empirically started on supplementation while awaiting serum level. VitD is then adjusted up or down as dictated by lab values:

≤12 years of age or < 90 lbs: 2000 units VitD + calcium

≥12 years of age or > 90 lbs: 4000 units VitD + calcium

Plan B: The Noncompliant Child: A weeks worth of VitD can be given once a week and calcium given daily.

•Some children have absorption problems that are recognized and some are not. They may need up to 7000 units of VitD daily for maintenance (equivalent 50,000 units per week). Serial 25-OH VitD levels help discovery and allow customization of supplements.

Figure 9: Minkowitz Bone Health Protocol recommendations for daily vitamin D and calcium supplementation based on age, weight, and presence of fracture to obtain serum levels 40-60 ng/ml

Discussion:

The pediatric compliance data revealed insights about the relationship between baseline vitamin D level and the likelihood to comply with the vitamin D supplementation protocol. As seen in Table 2 and Figure 8, patients in the 21-30 baseline 25D level range made up the largest percentages of both the compliant and non-compliant groups. The statistical analysis revealed that patients with lower levels of baseline 25D were more likely to be compliant (the lowest group of <12 was too small for analysis). For every increase in baseline 25D (by 1 ng/ml), likelihood of compliance decreased by 5%. As the severity of the vitamin D deficiency decreases, so does the likelihood of compliance with a supplementation protocol that may help prevent future fractures. Although noncompliant patients made up the majority of the study group (regardless of baseline 25D level), of those who were compliant, 68% presented with deficient levels under 20 ng/ml.

The data obtained from this study may make a vitamin D deficiency more salient to a patient. Although patients cannot physically feel a deficiency, a lower test result may ignite fear to comply with any form of treatment that could bring the vitamin D levels back to 40 ng/ml. A higher test result (i.e., 35 ng/ml) may not influence the same level of fear, resulting in a less effective incentive to comply to a vitamin D supplementation protocol to bring the level up to 40 ng/ml. There is possible variability in how the health care provider is describing the deficiency based on the level of severity, with more severe

deficiencies being described more harshly. Bone health can be quantified by vitamin D level but more visibly through scanning images. A visual depiction of the bone health state may create more salience for fracture risk and early compromised bone health.

Limitations of this study lie in the limited scope of questioning. The data about compliance was self-reported, and blood work was not obtained to validate the results. Errors in patient reporting are likely to reflect false claims about compliance. Therefore, the potential bias could exaggerate the effect of baseline vitamin D level on patient compliance. The data also reflect a response bias, since subjects included in the study were either responsive to the phone call surveys or had updated medical records. Another limitation of the study is the binary definition of compliance; either yes or no. Future compliance studies will address the previous limitations by only using data within medical charts. Although this methodology cannot eliminate self-reporting bias, the information will be derived from doctor-patient interactions rather than from phone interviews. Future research initiatives should focus on strategies for improving compliance to the vitamin D supplement protocol. Based on the principle of preference for the salient, physicians should conduct thorough follow up monitoring with scanning techniques and other measures that provide tangible proof of compromised bone health to create a more pronounced sense of urgency in the pediatric fracture population.

PART III: Clinical Evaluation of Pediatric Bone Mineral Density and the Role of Vitamin D Supplementation in Fracture Prevention: A Pilot Study to Quantify Compliance

Part II validated to the claim made in part I about preference for the salient. With better understanding of patient compliance with vitamin D supplementation, we can now explore strategies to improve compliance rates. Within the parameters of this intervention study, I hypothesize that most patients in a pediatric fracture population will present with low vitamin D and low BMD, but DEXA scans will make them more compliant; patients compliant to vitamin D will show increase in BMD relative to BMC.

The data derived from a DEXA scan is an areal BMD measurement, meaning that it is unable to differentiate between the cortical (thick outer layer) and trabecular (inner porous layer) regions [35]. Cortical and trabecular bone exhibit different porosity, so the future of osteoporosis scanning technology may pursue methods that can differentiate between porosity differences within the two regions. DEXA scans can provide the BMD and the BMC for specific regions of the bone, particularly in high impact regions of interest: femoral heads, lumbar vertebrae (L1-L4), and wrists. These specified areas tend to be common osteoporotic fracture sites. Osteoporosis is initially characterized asymptomatically because BMD is only known once a DEXA scan is performed. Additionally, BMD and BMC cannot be detected with a simple blood test. The noticeable physical manifestation of osteoporosis is a fracture, which is a salient indicator of bone fragility.

The four cells primarily responsible for bone metabolism are osteoblasts, osteocytes, osteoclasts, and osteoprogenitor cells [36]. Throughout a lifetime, osteocytes are constantly being resorbed by osteoclasts and formed by osteoblasts. This continuous homeostatic negative feedback loop is designed to prevent bones from becoming too dense or too porous. Osteoporosis is a metabolic imbalance where the amount of bone matrix being resorbed by osteoclasts is greater than the amount that can be formed by osteoblasts [36].

Peak bone mass is the critical amount of bone mass acquired while an individual is still growing. Maximizing peak bone mass is a tool for staving off future risk of osteoporosis (Figure 7). If an individual reaches a higher peak bone mass, then it will take a longer amount of time to cross the fracture threshold. Individuals can attempt osteoporosis prevention through actions and lifestyle choices that promote the build-up of bone, including but not limited to: a healthy diet rich in calcium, sufficient vitamin D absorption or supplementation, and high-impact exercise. Wolff's Law explains how high-impact exercise promotes bone mineralization, primarily in load bearing skeletal regions. Specifically, the physical stress placed on load bearing bones creates signals that can be sensed by other bone cells [37]. Wolff's Law can be applied to healing fractures (thus preventing subsequent refractures), because high-impact exercise stimulates osteoblasts, the key players in bone healing during modeling and remodeling [37]. However, the strain must be minor enough that it does not prevent bone remodeling while in a compromised state. Athletes are encouraged to apply a median amount of pressure

with lighter forms of high-impact exercise, like walking as opposed to running, to promote healing after the initial callous has formed over the fractured bone.

Fracture severity may also provide information about an individual's compromised bone. The Abbreviated Injury Scale (AIS) ranks fracture severity on a 1-4 scale, with a 1 representing fractures that require minor interventions (dislocations, contusions, etc.) to a 4 representing severe fractures requiring surgical intervention [38]. An observational pediatric study on patients with fractures requiring surgical intervention found that higher AIS levels are associated with lower levels of Vitamin D, with these patents falling into the deficient and insufficient ranges [27].

Parts I and II indicated the need to make the risks of fracture and poor bone mineralization more salient through quantification of the conditions. The purpose of the following pediatric fracture observational study is to determine the relationship between compliance to a vitamin D supplementation regimen and changes in the quantification of BMD and BMC. From this pilot study, we hypothesize a positive relationship between initial vitamin D level and levels of bone mineral quantification (BMD and BMC). Additionally, we hypothesize that patients who receive the DEXA scans will be more compliant to the supplementation regimen.

Methods:

The study design is a prospective longitudinal intervention study under the leadership of Dr. Barbara Minkowitz, MD and Jennifer Ristic, PA at Atlantic Health System's Department of Sports Medicine. The overall duration of the study is approximately three years but only one year per participant. The estimated date of

completion is April 2020. The data for part III will be on the first round of DEXA scans, X-rays, and blood panel information.

Source of Patients: We will screen 600 fracture patients with the goal to enroll 250 between the ages of 4-18 years of age who are interested in participating in the study and can lay still for the DEXA scan. Repeat DEXA will be checked after six months one-year post fracture. We will monitor patients with phone reminders to encourage compliance with their supplementation and that their serum vitamin D levels are within the 40-60 ng/ml recommended range. The source of study participants is from the Children's Orthopedic and Sports Medicine group in Atlantic Health System. The pediatric patients will already have been treated for fractures and will be able to have the DEXA performed within the first nine weeks after fracture. In the summer months, only subjects with a low vitamin D level can be included to avoid false high levels often seen during the summer time. During every other month, subjects with any vitamin D level will be included. Children with the following conditions will be excluded from the study:

> *amyloidosis, ankylosing spondylitis, collagen vascular diseases, congenital porphyria, epidermolysis bullosa, prior gastrecTaray, hemochromatosis, hemophilia, homocystinuria, idiopathic juvenile osteoporosis, idiopathic scoliosis, inflammatory bowel disease, insulin-dependent diabetes, leukemia, lymphoma, bone cancer, malabsorption, nutritional/eating disorders, organ failure/transplantation, osteogenesis imperfecta, parenteral nutrition, severe liver disease, thalassemia, thyrotoxicosis, acromegaly, adrenal atrophy, Cushing's*

syndrome, gonadal insufficiency, hyperthyroidism, hyperparathyroidism, and hypophosphatasia.

Only participants who give assent and whose parents give consent can be included in the study. The materials being used to recruit patients are the consent form, assent form, an informative brochure about DEXA scanning, and a $25 stipend in the form of a gift card (given at each DEXA, $75 per participant).

Consent and Assent: Those obtaining consent will use respectful and child-friendly language to the prospective participants or their legally authorized representatives. We will give participants and their parent(s) sufficient opportunities to ask questions throughout the entirety of the study. We will tell participants and their parent(s) that they can withdraw from the study at any time for any reason with no consequences. Research investigators will refrain from any language or body language that may be perceived as coercive to either the patient or their guardian(s). We will document the consent (assent) of the participant in writing in language suitable for their age group. We will also document the consent from the parent(s) in writing.

Standard Practice: X-ray and Bloodwork: Upon consent and assent, we will ask the patient to have an x-ray performed as part of the orthopedic care, blood drawn early on in fracture care, and a DEXA at the time of his/her fracture or within nine weeks. Further blood draws may be required to address vitamin D serum levels. The blood draws will be done at an appropriate lab, with approximately 15 ml (about ½ an ounce) obtained. A series of tests initially drawn will include complete blood count (CBC), comprehensive metabolic panel (CMP), phosphorus, parathyroid hormone (PTH), calcium, and 25

hydroxyvitamin D. 25 hydroxyvitamin D draws will be repeated at 6-month intervals depending on serum 25(OH)D level and response to supplementation. The goal is to optimize the serum 25(OH)D level to 40-60 ng/ml. Serum 25(OH)D levels under 40 ng/ml are considered insufficient or deficient, and those over 60 ng/ml are considered hypovitaminosis (high levels of a vitamin to the point of toxicity).

Hand Grip Strength: We will test patient grip strength using a Jamar Dynomometer gripper. The Gripper uses the mechanical effort needed to move the bar within the hand pump as an indicator for musculoskeletal capacity. We will perform the test three times to get an average strength score (presented with a standard deviation).

DEXA Scanning: The radiologist will perform the DEXA at 111 Madison Avenue, Morristown, NJ on a Lunar DEXA machine. The first DEXA scan must be performed within the first 9 weeks after the fracture. The vertebral DEXA takes 1 minute, and a whole body DEXA (less head) takes 5-6 minutes. Although callus formation, bone remineralization, and muscle atrophy may be problematic for the vertebral scan, they will not affect the whole body DEXA (less head). There cannot be a cast in place at the time of DEXA scanning. A second DEXA will be required six months later and a third one year later. The radiologist will analyze these DEXA results using z-scores, since pediatric body mass will likely change over time.

DEXA Analysis: A radiologist with Atlantic Health Systems analyzed the results from the DEXA scans. The DEXA provided bone mineral content (BMC), bone mineral density (BMD), and z-score for the lumbar spine (L/S) region, the total body less head "TBLH" region, and the left and right femoral heads. For the purposes of analysis, the results were

separated into two racial categories: African American/Black and White/Asian because of skin tone-based differences in UVB absorbance.

Follow-up and Compliance: The patients will be able to get information about supplementation and reminders for visits and lab draws from Dr. Minkowitz and her staff. We will remind the patients by phone (as frequently as needed to get a response when it is time to schedule a follow up) that they are part of this study and advised to continue taking vitamin D and calcium supplementation as per the Minkowitz protocol (see attached). We will tell patients if any further blood testing is required and when to return for follow-up DEXA.

Patients may decide not to continue in the research study at any time without it being held against them. If patients decide to leave the research study, they must contact the investigator so that the investigator can ensure that the removal process is complete. The person in charge of the research study or the sponsor can remove them from the research study without approval from the coordinator of research data. Possible reasons for removal include inability to sit still for a DEXA scan or blood draw.

Results:

We are currently conducting a pilot study including 14 patients with median age of 11 (range 7-18), 4 (28.57%) female and 10 (71.43%) male (Figure 3). The ethnic distribution is 5 (35.71%) Hispanic or Latino and 9 (64.29%) not Hispanic or Latino. The racial distribution is 9 (64.29%) white, 4 (28.57%) African American, 1 (7.14%) Asian. Mean initial vitamin D level is 19.88$\pm$9.84. We are conducting this pilot study based on patients seen during the summer months and are screening to include those with low

vitamin D levels <20. Recruitment will increase during the fall and winter months when lower vitamin D levels are anticipated (reduces the risk for false "normal" values).

Collected DEXA baseline data are described in Table 3. It is too early to statistically analyze all the data as very few participants have completed 6-month follow-up DEXA and labs. Multi-variate analysis will include sports activity (weight-bearing versus non-weight bearing) in different seasons, amount of active time per week, and any differences in DEXA data between sedentary and active children. Multi-variate analysis will also include fracture severity, mechanism of injury, amount of sun exposure, sunscreen use, and dietary preferences (calcium intake, caffeine intake, etc.). We will report initial and follow-up strength analysis with grip-strength testing with multi-variate analysis and change over time will be reported. Pilot study DEXA data is reported below (Table 4). Table 4 disaggregates the baseline DEXA data by race to show differences by skin tone-based absorption. African American patients report higher BMD and BMC levels in the L/S and TBLH regions. Neither racial category has consistently lower z-scores. Femoral neck DEXA data is not available for all patients, so the data were not reported.

Table 3: Patient characteristics N=14 (data from: Stephanie Chu, AHS Statistician)

Age	mean±SD	11.929±3.407
	median (min-max)	11 (7-18)
Gender	Female	4 (28.57%)
	Male	10 (71.43%)
Ethnicity	NOT Hispanic or Latino	9 (64.29%)
	Hispanic or Latino	5 (35.71%)
Race	White	9 (64.29%)
	Black or African American	4 (28.57%)
	Asian	1 (7.14%)
Vitamin D Level	mean±SD	19.88±9.84
	median (min-max)	18.25 (8.2-46.2)

Table 4: Patient DEXA Diagnostics (Black or African American Patients Separated) (Data from Stephanie Chu, AHS Statistician) *TBLH Z score is not available for African American patients because there is not a reference population for African American children in the software for the GE Lunar Prodigy DEXA machine at the AHS facility.

	Not African American	**African American**
	n=10; mean (SD), min-max	n=4; mean (SD), min-max
L/S BMD	0.8013 (0.2027), 0.548-1.141	1.0707 (0.0498), 1.028-1.142
L/S Z Score	-0.09 (1.161), -1.5-1.8	-0.2 (1.152), -1.4-1.1
L/S BMC	29.4 (14.52), 14.56-59.41	51.17 (10.95), 43.2-66.86
TBLH BMD	0.8143 (0.1482), 0.588-1.088	1.0288 (0.0943), 0.918-1.113
TBLH Z Score	0.12 (1.223), -1.8-1.9	*
TBLH BMC	1127 (624), 427-2440	2100 (249), 1793-2403

Follow up DEXA data is available for 6 of the 14 patients from the pilot study. The current demographics of the follow-up data are not representative of the total population. All 6 patients are male (Table 5), which likely has to do with the order in which the patients were recruited (random chance). All follow-up patients were compliant to the vitamin D and calcium supplementation six months after the initial

fracture and DEXA scan. Fifty percent of the follow-up patients showed statistically significant increases in BMD after six months of supplementation and healing (Table 5), but all six patients showed general increases in BMD in the L1-L4 and TBLH regions (Table 6). Data were not available for the DEXA measurements on the left and right femoral heads because there was not complete data on all the follow-up patients for analysis.

Eighty-three percent of the follow-up patients were within a normal range of BMD for their age, weight, height, and sex (Table 6). Patients 1 and 2 had z-scores for the L1-L4 and TBLH regions that were within a 0.2 difference, while patients 3,4, and 5 had z-scores for the L1-L4 and TBLH regions that were greater than or equal to a 0.5 difference. Table 7 shows the percent change in BMD relative to the percent change in BMC, which is relevant for growing populations (all patients were in an age range where normal body growth would be expected). With the exception of patient 4 (L1-L4 region) and patient 6 (TBLH region), all of the patients' BMCs increased at a greater rate than their BMDs for both the L1-L4 and the TBLH regions.

Table 5: Follow-up DEXA data patient characteristics

	Race	Sex	Age	Height (inches)	Weight (lbs.)	Compliant (calcium and vitamin D)	Significant increase at 6-month follow up?
Patient 1	White	Male	8	50	148	Yes	no
Patient 2	White	Male	10	57	67	Yes	no
Patient 3	White	Male	14	70	185	Yes	yes
Patient 4	Hispanic	Male	11	57	105	Yes	yes

Patient 5	Hispanic	Male	11	58.5	146.5	Yes	no
Patient 6	Black	Male	14	70	252	Yes	yes

Table 6: Follow-up DEXA data BMD and BMC results after 6 months of supplementation

	(L1-L4) BMD (gm/cm^2)	(L1-L4) BMD Increase (gm/cm$^{2)}$	(L1-L4) Z-score	(L1-L4) BMC (g)	TBLH BMD (gm/cm^2)	TBLH BMD increase (gm/cm^2)	TBLH Z-score	TBLH BMC (g)	BMD impre-ssion
Patient 1	0.564	0.016 2.9%	-1.4	16.01	0.611	0.023 3.9%	-1.6	493.4	low
Patient 2	0.682	0.001 0.1%	-0.6	23.42	0.705	0.008 1.1%	-0.8	812.3	normal
Patient 3	1.192	0.051 4.5%	1.3	67.19	1.191	0.103 9.5%	2.6	2689.2	normal
Patient 4	0.739	0.079 12%	-0.4	21.11	0.833	0.02 2.5%	0.4	1131.1	normal
Patient 5	0.966	0.016 1.7%	1.7	37.70	0.954	0.008 0.8%	2.3	1843.2	normal
Patient 6	1.050	0.002 0.2%	0.1	45.79	1.177	0.064 5.8%	n/a	2497.9	normal

Table 7: BMC change relative to BMD change

	Original L1-L4 BMC (g)	Follow up L1-L4 BMC (g)	% BMC Change	% BMD Change	Original TBLH BMC (g)	Follow up BMC (g)	% BMC Change	% BMD Change
Patient 1	14.56	16.01	1.45 9.6%	0.016 2.9%	426.5	493.4	66.9 15.7%	0.023 3.9%
Patient 2	23.0	23.42	0.42 1.8%	0.001 0.1%	719.0	812.3	93.3 13.0%	0.008 1.1%
Patient 3	59.41	67.19	7.78 13.1%	0.051 4.5%	2440.0	2689.2	249.2 10.2%	0.103 9.5%
Patient 4	19.13	21.11	1.98 10.4%	0.079 12%	934.2	1131.1	196.9 21.1%	0.02 2.5%
Patient 5	35.85	37.70	1.85 5.2%	0.016 1.7%	1751.5	1843.2	91.7 5.2%	0.008 0.8%
Patient 6	44.13	45.79	1.66 3.8%	0.002 0.2%	2403.2	2497.9	94.7 3.9%	0.064 5.8%

Figures 8 and 9 contain DEXA imaging data from patient 3's follow-up scan. Figure 8 details the BMD report for the L1-L4 region. The L1-L4 vertebrae are enlarged to provide details of the areal BMD measure. Patient 3 has a 1.092 gm/cm^2 BMD measurement for the L1-L4 region, which is broken down into the four vertebrae, and then compared to the original BMD measurement from 6 months prior. Figure 11 details the BMD report for the TBLH region. The whole body is shown to provide details of the

areal BMD measure. Patient 3 has a 0.103 gm/cm^2 BMD measurement for the TBLH region, which is compared to the original BMD measurement from 6 months prior.

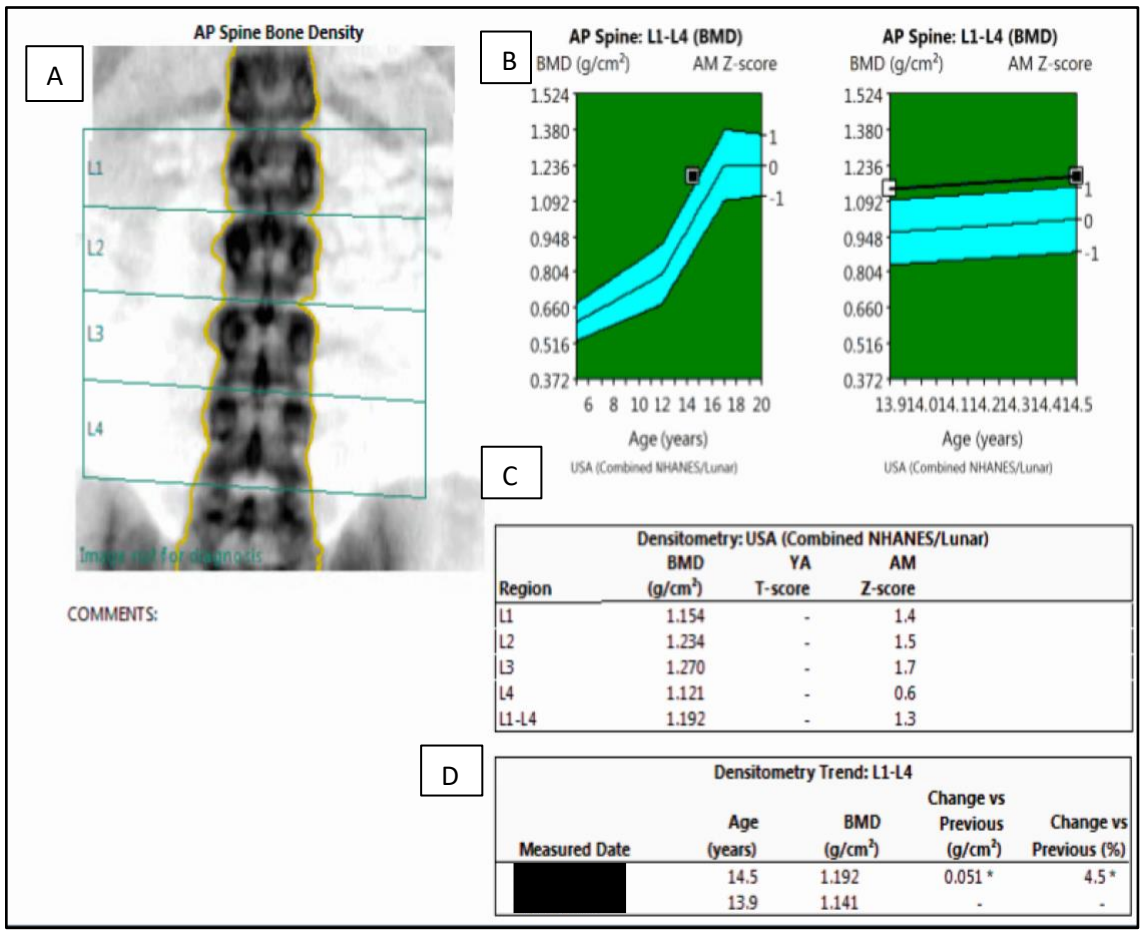


Figure 10: DEXA L1-L4 Follow-up scan patient 3 image obtained from EPIC Hyperspace (Epic Systems Corporation) close-up density scan of the L1-L4 vertebrae (a), BMD Z-score charts for patient 3's demographic (b), the BMD break down for each of the four vertebral BMD score that make up the composite L1-L4 score (c), and the progress made in BMD over a 6-month period (d).

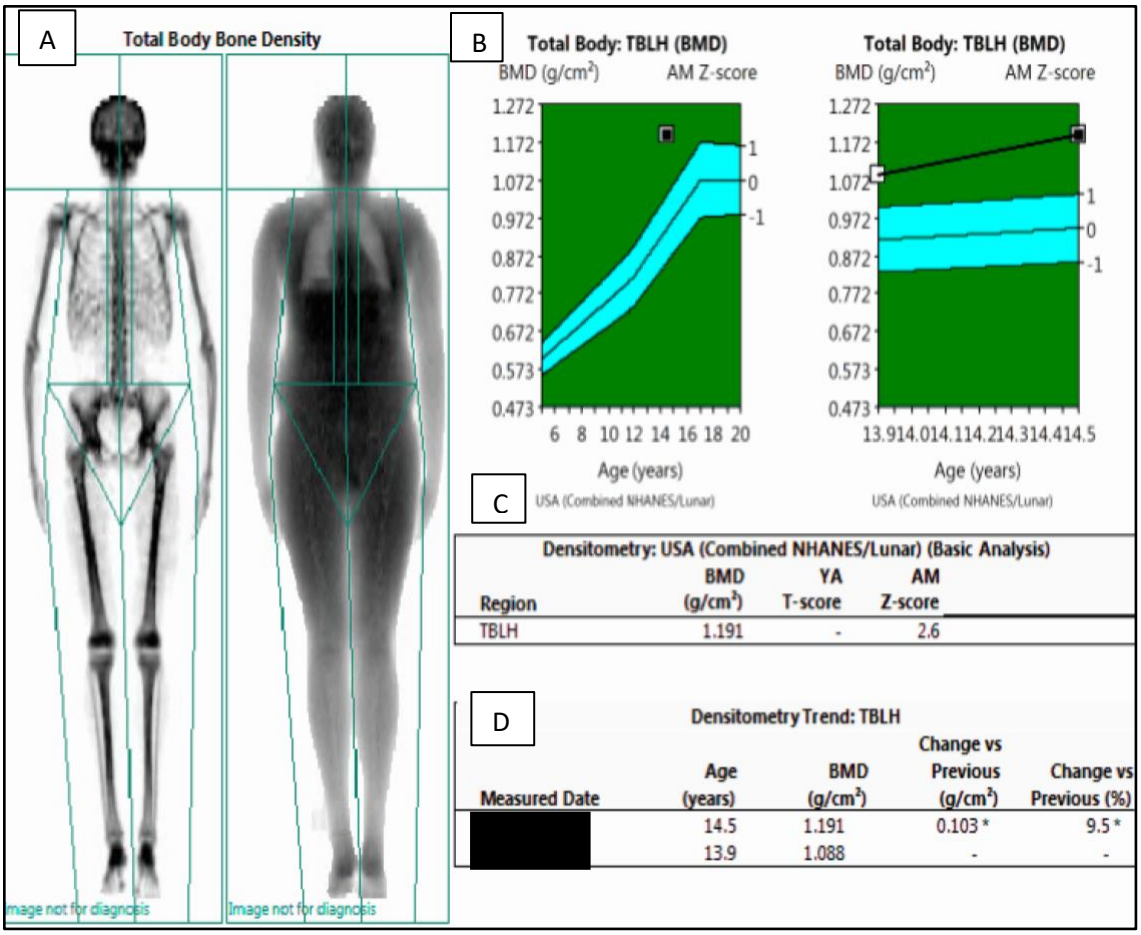


Figure 11: TBLH DEXA Follow-up scan patient 3 image obtained from EPIC Hyperspace (Epic Systems Corporations) density scan of the total body less head (TBLH) region (a), BMD Z-score charts for patient 3's demographic (b), the BMD break down for TBLH region (c), and the progress made in BMD over a 6-month period (d).

Discussion:

We can draw observations from the first 14 patients in the pilot DEXA study. Although there is not an even split between male and female participants, there is diversity amongst race and ethnicity (Table 3). The complete study is likely to yield a more even split between participant sex and even greater ethnic/racial diversity. The mean baseline vitamin D level of 19.88±9.84 ng/ml with a range of 8.2-46.2 ng/ml

indicates that a majority of the patients are presenting with a vitamin D deficiency at the time of fracture. The preliminary data indicates that there may be a heightened association between fracture risk and vitamin D deficiency.

The preliminary DEXA data indicates racial differences in BMC, BMD, and z-scores in the L/S and TBLH regions (Table 4). Within the lumbar spine region, African American or Black participants present with higher BMC and BMD on average with a lower median z-score -0.2 (-1.4-1.1) compared to -0.09 (-1.5-1.8) for the White or Asian participants. The results are mirrored with the TBLH region, since the BMC and BMD are higher for the African American or Black participants.

The observation that the White or Asian demographic is presenting with poorer BMD and BMC outcomes at the baseline indicates evidence contrary to what is currently known about the relationship between skin pigmentation and vitamin D absorption. The data in Table 4 show how the African American and Black participants are presenting with higher baseline BMC, BMD, and z-scores in the regions studied. If individuals with darker skin pigmentation are expected to present lower vitamin D levels but have higher quantitative measures of bone density, then there may be a gap in the literature regarding the relationship between vitamin D levels and bone strength. The follow-up data from 6 months of supplementation may yield stronger associations between these variables.

A longitudinal study of 135 non-fractured Caucasian children tracked BMD changes in the L1-L4 region with respect to age and found that the BMD increased significantly with age [39]. More specifically, within the time range of the patients enrolled in the study (8-14), “the accumulation of total bone mineral [comparable to

TBLH] is about 146 g/year, or 6% of the total body mineral each year" [40]. The current follow-up DEXA data reports approximately 6 months' worth of growth. Assuming that the amount of growth in 6 months is half of that accrued in a year (146/2= 73 g/6months or 3%), we can estimate whether the percentage increase in BMC is can be attributed to the vitamin D supplementation or to general growth patterns evident in BMC. Five of the six patients exhibited changes in BMC greater than 73 g/6months, but the one patient who only showed a 66.9 g increase had a 15.7% increase overall (Table 7). The data are still preliminary, but there is a basic trend showing that patients are showing a higher than average increase in BMD and BMC relative to their expected increase in BMC.

The limitations of the current study are a result of the small sample size and the inability to perfect measurements of patient compliance. The full version of the study will include a significantly larger sample size, so the sample size issue will be corrected. Since patients are also reminded to comply by their physician, compliance cannot be completely contributed to the salience of the DEXA scans. Future studies should address questions pertaining to the relationships between skin tone, age, and BMD/BMC. Additionally, longer longitudinal studies may provide more validity for the role of vitamin D supplementation to a level that may be taken more seriously by the AAP.

Policy Conclusion

Part I concluded that health insurance is not a patient compliance incentive and that patients are more likely to respond to more salient conditions. From there, part II addressed the preference for the saliency observation in an actual pediatric population and concluded that patients with lower levels of vitamin D were more likely to comply with a supplementation protocol. Part III addressed how to improve compliance with a vitamin D supplementation protocol, concluding from the preliminary follow up data that DEXA scans promote compliance to vitamin D supplementation and that the supplementation regimen promotes increased bone mineral density, thus decreasing fracture risk.

The full extent of the invisibility of bone integrity and fracture risk is both in the problem itself and in the treatment; patients cannot see bone strength without DEXA scans and cannot visualize impact of treatment without DEXA scans. The three-part analysis of improving vitamin D compliance in the pediatric fracture population addresses both issues regarding the invisibility of this disease. Ordering patients to get a vitamin D blood test that can be visualized and monitored provides an estimate of risk, thus making the condition more salient. Part II concluded that patients with lower vitamin D levels were more likely to comply to the vitamin D supplementation regimen. Patients with deficient levels of vitamin D (below 20 ng/ml) were able to visualize the elevated risk of future fracture, refracture, and unsatisfactory healing and therefore, concluded that complying with the supplementation regimen was worth the effort and cost. Patients with insufficient and sufficient vitamin D levels (above 40 ng/ml) were less able to visualize

their risk and likely did not register that the risk was worth the time, effort, or cost of medical compliance.

Part III also addressed the invisibility of both the condition and the treatment. Patients in this part of the study got baseline DEXA scans in addition to the vitamin D blood draw. Instead of simply quantifying the risk of poor bone mineralization (a potential consequence of a vitamin D deficiency at the time of fracture), the DEXA scan provides the actual level of bone mineralization. The DEXA scan provides a risk indicator of future fracture, refracture, and unsatisfactory healing. The treatment and compliance data will be provided in the full version of the observational DEXA study. Patients will collect data on vitamin D level, DEXA measures (BMD and BMC of the four regions), and compliance at two other stages of treatment: six months after fracture and one year after fracture. The preliminary data indicate that vitamin D supplementation improves the bone mineralization in all patients following the protocol. Although the data pool is small, the compliance rate is 100%, a rate unseen in any of the literature previously mentioned in this study.

Evidence from this three-part analysis shows that patients are more likely to act upon conditions that are more salient; so, to improve medical compliance for an "invisible" condition, physicians and health practitioners must make the condition more salient. All three studies dealt with pediatric populations as to model a preventive strategy for addressing bone fragility and fracture risk. Long-term financial and health consequences were evident in part I, with the clear difference in present and future value of expected labor income. Follow up results from part III may yield information

pertaining to decreased future fracture risk as a consequence of increased bone mineralization. Studies like these validate the role of supplementation in healing and prevention, making the long term economic and health impacts more salient.

Just like with the hypertension solution (constant blood pressure monitoring), children should be able to see their vitamin D levels on a more regular basis. Annual pediatric appointments for at risk populations or sports physicals would be appropriate times to encourage blood draws. Currently, the American Academy of Pediatrics (AAP) takes no formal stance on the value of vitamin D supplementation in pediatric bone strength. Preliminary data from the retrospective analysis and the observational DEXA study show that the majority of fracture patients are presenting a baseline vitamin D level below acceptable threshold (40 ng/ml).

Preliminary evidence from follow-up DEXA and Vitamin D results after six months of supplementation supports the Minkowitz Protocol. There is a positive trend between indicators of bone mineralization (BMD and BMC) and vitamin D. Furthermore, it would be wise for the AAP to not only show their support for the supplementation protocol, but to recommend regular vitamin D monitoring in pediatric patients at risk for poor bone mineralization that could lead to a lifetime of fractures and increased osteoporosis risk.

One of the unaddressed observations from this study was the patients' (in addition to the parents') desires to return back to sports and activities. Premature return to sports can hinder proper healing of fractures and can easily lead to subsequent refractures. The significance of this desire was never explored. By including vitamin D levels in annual

athletic evaluations, physicians and coaches may be able to include vitamin D and bone strength in the conversation of sports injuries. Consequences of legitimizing the importance of vitamin D in health may include less impatience to prematurely return to sports and less disregard for the importance of vitamin D supplementation post fracture or even to prevent a fracture from occurring in the first place.

Future experiments should address limitations from this analysis. Studies could incorporate broader racial, ethnic, and geographic diversity in the study sample. Upbringing, diet, and environment likely play significant roles in vitamin D deficiency risk, fracture risk, and the likelihood to comply with treatment regimens. These studies could also be replicated in different age demographics, examining compliance incentives while still addressing the preventive role of vitamin D in fracture risk. Although it is not viable to track patients over their entire lifetimes, as was modeled in the economic portion of the analysis, a retrospective study could plot history of fractures in recently diagnosed osteopenia and osteoporosis patients. Researchers could conduct epidemiological studies that looks at histories of fractures, refractures, and vitamin D levels in both osteoporotic patients and patients presenting with healthy bones (in the same demographic group). Studies like these could yield more evidence about the relationship between fractures in early life and future osteoporosis risk. Researchers could also track whether the DEXA scan that provided a osteopenia or osteoporosis diagnosis is effective in promoting compliance with osteoporosis treatment and prevention of further degradation.

The analysis presented above placed the issue of patient medical compliance in the context of osteoporosis risk prevention in a pediatric population. The general conversation surrounding patient medical compliance is one that should be amplified in the medical, public health, and economic communities. Proper compliance with treatments strengthens the power to treat diseases or to prevent them from occurring overall. Increasing the saliency of invisible conditions may be the key to curbing the incidence of debilitating conditions that plague aging populations and the young alike.

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