Vitamin D Supplementation and Glycemic Control in Patients with Type 2 Diabetes

Janice, Lazear, MN, CRNP, CDE

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Committee Membership:
Dr. Jane Kapustin, PhD, CRNP, ADM-BC, Chair
Dr. Lyn Stankiewicz Murphy, PhD, MBA, RN
Dr. Marisa Wilson, DNSc, MHSc, RN

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Abstract

Purpose: Treatment guidelines for the management of patients with type 2 diabetes (T2DM) and vitamin D deficiency do not exist. The primary purpose of this project was to describe repletion rates, prescribing patterns and monitoring patterns for patients with T2DM and vitamin D deficiency. This is a first step in the development of management guidelines. A secondary purpose was to examine glycemic control before and after correction of vitamin D hypovitaminosis. This was done in order to determine if future interventional studies examining the efficacy of treating vitamin D deficiency for patients with T2DM are warranted.

Significance: In the United States 25.8 million (8.3%) individuals have diabetes; 90 to 95% have T2DM. The disease is responsible for increased morbidity and mortality as well as annual costs in the billions. Vitamin D deficiency in the United States is estimated to affect 70% of Caucasians and 95% of African Americans. A link between T2DM and vitamin D deficiency has been described. However, guidelines for vitamin D repletion of individuals with T2DM are not available, and the effect of vitamin D repletion on glycemic control has not been well studied.

Methods: This project was a non-experimental retrospective audit of electronic medical records used in the outpatient diabetes department of a University Medical Center. Data were collected from the Epic documentation system. Descriptive statistics were used to describe care processes, and a paired samples Student t-test was used to examine A1C levels before and five to eight months after vitamin D repletion for subjects successfully repleted.

Results: A total of 366 subjects qualified for inclusion in the study. Follow-up testing ranged from one to twelve tests per subject with a mean of 2.6 (SD = 1.5) and a range from 0 to 12 tests. Successful repletion rates per follow-up period ranged from 4.7 to 23.6%. Five to eight months after initiation of vitamin D, only 97 subjects (26.5%) were successfully repleted. Within this

group results demonstrated a significant decrease from an initial to a follow-up mean A1C value (8.33 ± 0.69 vs 7.9 ± 1.3), indicating improved glycemic control (t = 3.58, p = .001).

Conclusions: Treatment guidelines and standardization of care for patients with T2DM and vitamin D deficiency are needed. Further investigation is needed to investigate why the majority of patients were not successfully repleted. The findings of improved glycemic control for subjects with repletion also indicate a need for interventional studies with randomized controlled trials to investigate the effect of treating vitamin D deficiency on glycemic control.

Section I: Background and Significance

Diabetes is currently a worldwide epidemic. The global prevalence is projected to be 7.7 percent in 2030, affecting 439 million adults. It is projected that a 69 percent increase in diabetes will occur from 2010 to 2030 in developing countries and a 20 percent increase in developed countries (Shaw, Sicree, & Zimmett, 2010). Currently 25.8 million individuals in the United States (8.3 percent of the population) have diabetes. Type 2 diabetes mellitus (T2DM) is much more common than type 1 diabetes mellitus, accounting for 90 to 95 percent of all cases of diabetes diagnosed. In Maryland in 2008 an estimated 8.7 percent of adults had been diagnosed with T2DM (Maryland Department of Health and Mental Hygiene (MD DHMH), 2009). The diabetes prevalence in Baltimore City was 10.5 percent between 2003 and 2007 (MD DHMH, 2010). The annual cost of diabetes in the U.S. was approximately $174 billion in 2007. Direct medical care accounted for $116 billion and $58 billion was attributed to indirect costs, including disability, lost wages and productivity, and early death (National Institute of Diabetes and Digestive and Kidney Disorders (NIDDKD), 2008). In 2006 the total cost of diabetes in Maryland was estimated to be $3.7 billion (Maryland, Diabetes Prevention and Control Program Fact Sheet, 2009).

Diabetes is a topic of much concern due to the increasing prevalence as well as the significant impact the disease has on morbidity and mortality. Cardiovascular disease is increased in this population with a mortality rate of 68 percent from heart disease or stroke. Diabetes is the leading cause of kidney failure, new cases of adult blindness and nontraumatic amputation of the lower limbs. Additionally 60 percent to 70 percent of diabetics have nervous system damage (NIDDKD, 2008).

Modifiable risk factors that can be eliminated or decreased to achieve improved glycemic control are needed to manage the epidemic and reduce the impact on morbidity and mortality. Modifiable risk factors include being overweight and obese, having a sedentary lifestyle, dietary factors, and intrauterine environmental factors such as low birth weight and exposure to diabetes in utero (Alberti, Zimmet, & Shaw, 2007). Weight loss has been found to be successful in the management of T2DM. However, a high rate of regained weight limits the usefulness of weight loss as a successful strategy (Nathan et al., 2006). Interventions that are easy to adhere to, inexpensive, readily accessible and can be sustained long term are needed.

Mounting evidence suggests a link between vitamin D deficiency and T2DM (Ozfirat & Chowdhury, 2010). Vitamin D has become a focus of health care research, as benefits beyond bone health and mineral homeostasis are being explored, including attenuation of cardiometabolic risk. Low vitamin D levels have been associated with abdominal obesity, hypertension, and dyslipidemia, all components of the metabolic syndrome (Baz-Hecht & Goldfine, 2010). Vitamin D deficiency is highly prevalent with 30 percent to 50 percent of adults at risk. (Parker et al, 2010). If vitamin D supplementation is found to be effective in improving glycemic control it is an intervention that can be used by many patients to help achieve euglycemia and avoid the long term complications of diabetes. Pittas, Lau, Hu and Dawson-Hughes (2007) performed a systematic review and meta-analysis examining the relationship between vitamin D status, glucose intolerance and T2DM. The majority of the studies, but not all, reported an inverse relationship between the two variables indicating an association between low vitamin D and less than optimal glycemic control.

Statement of the Problem and Research Question

There is limited and contradictory evidence to support correcting vitamin D deficiency as a strategy to improve glycemic control. Although resources are being used to treat and monitor vitamin D deficiency for patients with T2DM, there is also a lack of guidelines regarding the type of vitamin D used for repletion, the dose and length of time used for repletion and follow-up vitamin D monitoring. Therefore, there may be great variability in prescribing patterns and a lack of consistent results. The accessibility, relative inexpensive, and ease of use associated with vitamin D makes this intervention worth investigating. For the intervention to be recommended as a routine strategy in the management of T2DM, further investigation of effectiveness is needed.

The purpose of this study was twofold. First the process of care associated with treating T2DM patients with vitamin D hypovitaminosis was described. In addition, A1C levels before and after successful treatment of vitamin D deficiency in a sample of patients with T2DM was examined.

Because monitoring and repletion of vitamin D in patients with T2DM is a new trend and because there are no guidelines or standardization for these practices, the investigator described the type of vitamin D used for repletion and monitoring strategies utilized at the diabetes center that was the site in which subjects received care. Provider prescribing practices, including type and dose of vitamin D and number of follow-up tests were examined. Another important measure, the rates of repletion were included in order to assess if treatment goals are being reached.

In addition, the investigator examined glycemic control in adults with T2DM before and after correction of vitamin D deficiency. The investigator compared the individual participant's

baseline A1C levels measured prior to the initiation of vitamin D supplementation and five to eight months after supplementation was initiated. The outcome of interest is any significant change or lack of change in the mean A1C values before and after successful treatment of vitamin D deficiency.

Theoretical Framework

An important component of the role of the doctor of nursing practice (DNP) prepared nurse is advancing evidence-based practice by promoting the translation, implementation and dissemination of research findings. The Diffusion of Innovation Theory (DIT) was first developed by Everett Rogers (2003) in the early 1960s and provides a framework for facilitating the adoption and dissemination of evidence-based research findings. At the conclusion of this study, the findings will be disseminated to providers who care for diabetic patients. DIT was first applied to agricultural innovation. Since that time it has been applied to technology innovations, advancements in communication and health care. This widely used theory gives the DNP leader a framework to guide the implementation of evidence-based practice changes. Confusion regarding approaches for correcting suboptimal vitamin D and monitoring exists. The findings of this study will be disseminated to providers of diabetic patients and DIT will be used as a framework to encourage the adoption of standardized approaches and the development of guidelines.

Potential Significance of the Study and Potential Findings

Prescribing patterns including type of vitamin D prescribed and follow-up monitoring will be described. This is a first step to establishing a standardized approach. Based on the findings of a study by Sabherwal, Bravis and Devendra (2010) in which a sample of individuals with vitamin D deficiency and T2DM were found to have significantly decreased A1C levels after vitamin D replacement therapy, it is expected that similar results will be found in this study. If vitamin D is found to be associated with improved glycemic control it will give providers and patients an easy to adhere to, accessible and inexpensive option for the management of T2DM. Given the consequences of the diabetes epidemic in terms of morbidity, mortality and financial costs, this would be a positive contribution to management of individual patients and the diabetes epidemic.

Section II: Literature Review

Introduction

This review of the literature includes an overview of Vitamin D and treatment of Vitamin D deficiency. Studies that focus on the relationship between vitamin D and glycemic status and the development of T2DM will be reviewed. Research that examines the use of vitamin D supplementation to improve glycemic control for individuals with T2DM will also be reviewed.

Search Strategy

A literature search of MEDLINE, CINAHL and PubMed was done to indentify evidence regarding vitamin D and management of T2DM. The key words used for the search included; vitamin D, vitamin D deficiency, A1C and T2DM. Articles were retrieved for review if the subject was vitamin D and glycemia, insulin resistance, or T2DM. Reference lists from retrieved articles were reviewed to identify additional pertinent articles.

Vitamin D Overview

Vitamin D deficiency is increased in populations with increased requirements such as infants, adolescents and women who are breastfeeding (Ozfirat & Chowdhury, 2010). Decreased exposure to the sun experienced by people living in high latitudes as well as populations that wear clothing that covers most of the body, such as residents of parts of the Middle East, have traditionally been at greater risk for Vitamin D deficiency. Populations with dark skin such as Blacks and South Asians also have higher rates of vitamin D deficiency than Caucasians. This is due to the higher levels of skin pigmentation that absorb UV-B light, limiting vitamin D production (Ozfirat & Chowdhury, 2010). Osei (2010) points out that vitamin D deficiency rates

are rising in those not traditionally at risk. High rates of vitamin D deficiency are being seen in seemingly healthy populations in Western industrialized countries. The author postulates that although the reason for the increased prevalence of vitamin D in well-nourished populations in the United States is not certain, it is likely due to the overweight and obesity epidemic. Body fat is a repository for 25-OH vitamin D which is a fat soluble vitamin (Osei, 2010). Vitamin D that is deposited in adipose tissue is biologically inactive: thus individuals with an increased body mass index are often Vitamin D deficient (Ozfirat & Chowdhury, 2010).

There is not a universal definition of vitamin D adequacy or deficiency. Osei (2010) states that optimal 25-OH vitamin D levels may differ for prevention or treatment of various diseases. Obese patients may need greater doses of vitamin D than those who are not obese. Binkley, Ramamurthy and Krueger (2010) state that there is an increasing consensus that 25(OH)D levels should not be less than 30 to 32 ng/mL. Kauffman (2009) points out that vitamin D toxicity is not observed until serum levels are > 150 ng/mL and that a lack of toxicity has been demonstrated. The author states that recommendations for supplementation levels are increasing due to the relative safety of vitamin D supplementation. Kauffman (2009) also reports that the best results in trials have been achieved with vitamin D levels $\geq$ 30/ng/mL and that recommendations for a target of $\geq$ 50 ng/mL exist.

Vitamin D is a fat soluble vitamin comprised of two molecules; ergocalciferol (D2) which is dependent on sunlight exposure, and cholecalciferol (D3) that is consumed in foods. Foods rich in vitamin D are limited and include fatty fish, eggs from hens fed vitamin D and fortified milk and cereal (Penckofer, Kouba, Wallis & Emanuele, 2008). Vitamin D is produced in the skin from exposure to the sun or from the intake of food or supplements. It then is converted in the liver to 25-hydroxyvitamin D (also referred to as calcidiol or 25(OH) D). This is

the form in which most of the vitamin D circulates and is measured to determine vitamin D adequacy. Concentrations of 25(OH) D include vitamin D from exposure to the sun, food intake and supplementation (Yetley, 2008). The 25-hydroxyvitamin D is hydroxylated in the kidney and becomes the most active form of vitamin D, 1,25-dihydroxyvitamin D (Holick, 2008).

It has been postulated that vitamin D has an influence on glycemic control in a number of ways (Pittas, Lau, Hu & Dawson-Hughes, 2007). Pancreatic beta cell function may be affected by the existence of specific vitamin D receptors in the beta cells and by the role of vitamin D in the regulation of calcium as insulin secretion is dependent upon calcium. It is thought that vitamin D may have a role in stimulating glucose transport and in preventing systemic inflammation which is associated with insulin resistance and secretion (Pittas, Lau, Hu & Dawson-Hughes, 2007).

Grinde, Liu, & Camargo (2009) compared data from the National Health and Nutrition Examination Survey (NHANES) III collected in 1988-1994 and in 2001-2004. The mean serum 25(OH) D level found in the 1988 to 1994 survey was 30 ng/mL. In the data collected from 2001 to 2004 the mean level was 24 ng/mL. For some individuals barriers to an adequate intake of vitamin D may exist due to lactose intolerance or restricted dietary intake that is common in the management of T2DM (Penckofer, Kouba,Wallis & Emanuele, 2010).

Treatment of Vitamin D Deficiency

In addition to the intake of foods with vitamin D content and exposure to the sun, supplementation for the treatment of vitamin D is often recommended. Holick (2007) recommends a weekly vitamin D_2 dose of 50,000 IU for 8 weeks with a repeat of the regimen if 25 (OH) D levels are not greater than 30 ng/mL after initial supplementation. The author states

that this initial treatment should be followed by the intake of 50,000 IU of vitamin D_2 every 2 to 4 weeks. Other strategies include a daily vitamin D_3 intake of 1000 IU to 3000 IU or 100,000 IU of vitamin D_2 every three months (Penckofer, Kouba, Wallis & Emanuele, 2010).

Recommendations for specific doses of vitamin D supplementation in patients with T2DM and adequate vitamin D or vitamin D deficiency have not been determined (Penckofer, Kouba, Wallis & Emanuele, 2008). The only established guidelines for vitamin D repletion are for patients with chronic kidney disease (Carlton, Clopton & Cappuzzo, 2010). The Institute of Medicine (IOM) made new recommendations for Vitamin D reference ranges in a report that was released on November 30, 2010 (IOM, 2010). The recommendations made by the IOM only address vitamin D requirements for adequate bone health. After reviewing over one thousand studies and hearing testimony from scientists and stakeholders the IOM committee preparing the report recommended no greater than 600 IU of vitamin D a day, except for people $\geq$ 71 and who may need 800 IUs. The IOM committee states that studies reviewed regarding extraskeletal health benefits of vitamin D were mixed and inconclusive; therefore, the recommendation for daily intake of vitamin D are based on bone health. The IOM report did not address repletion strategies for those with inadequate vitamin D levels. Broder, Tobin and Putterman (2010) state that disease specific definitions of vitamin D deficiency may need to be established in order to determine vitamin D treatment therapy for specific conditions.

Peiris, Bailey, Manning and Adebonojo (2010) state that there is little information regarding serial monitoring of vitamin D levels after treatment in the vitamin D literature. The authors point out that vitamin D has a half life of approximately one month with a steady state achieved in about 4 half-lives; therefore, deficiency or vitamin D excess can develop in a matter of months. In a retrospective study the investigators examined vitamin D monitoring of 278

veterans with suboptimal vitamin D levels for the first year after supplementation was initiated. In those who did have follow-up 25(OH) D testing, 90 percent achieved a level of $\geq$ 30 ng/mL. However, only 31 percent of the subjects had follow-up monitoring. Peiris, Bailey, Manning and Adebonojo (2010) state that assumptions by providers that an adequate vitamin D level is achieved and a lack of formal guidelines may explain the lack of follow-up monitoring.

Vitamin D studies and the Development of Diabetes

Kositsawat, Freeman, Gerber and Geraci (2010) performed a secondary data analysis on data from the NHANES study. The study is a cross sectional national survey. The investigators looked at subjects over the age of 18 both with and without diabetes. Of the 9,773 participants, 899 are diabetic. The patients are classified as diabetic if they stated they had been told by a doctor that they have diabetes or reported current use of insulin or oral agents used in the treatment of T2DM. Using multivariate linear regression the relationship between A1C and 25(OH) D levels was examined. It was found that lower 25(OH) D levels have a significant inverse relationship with A1C levels in subjects from age 35 to 74 for those who did not report a history of diabetes. This relationship was not found for any other age group or for participants who reported a history of diabetes. A strength of the study is the large sample size. It is possible that a diagnosis of diabetes that was based on self-report could be inaccurate. In addition the investigators did not collect specific data regarding diabetes medication and doses that may have impacted the study results.

The Women's Health Study, a randomized controlled trial was conducted to ascertain if supplementation with 1000 mg of calcium and 400 IU of vitamin D_3 per day reduced the risk of development of drug-treated diabetes. The sample is comprised of 33,951 postmenopausal

women. After a mean follow-up time of seven years, 2,291 women were diagnosed with diabetes. It was found that the supplementation with calcium and vitamin D did not reduce the incidence of diabetes. Limitations of the study include the small dose of vitamin D and possible "cross contamination" as the participants were not prevented from taking vitamin D supplements outside of the study protocol (Pittas & Dawson-Hughes, 2010).

In order to investigate the association between vitamin D and insulin sensitivity, Chiu, Chu, Liang, Go and Saad (2004) recruited 126 residents of California who did not have diabetes for a correlational study. The researchers assessed insulin sensitivity and first and second phase insulin response by using a hyperglycemic clamp. A positive correlation was found between vitamin D levels and insulin sensitivity ($p < .0001$) and a negative association was found with first phase insulin response ($p = .0045$) as well as second phase insulin response ($p = <.0001$). The use of the hyperglycemic clamp is a strength of the study. The authors concluded that hypovitaminosis increases the risk of insulin resistance. The study was conducted with subjects who are glucose-tolerant and results cannot be generalized to individuals with T2DM. However, it does demonstrate an association between vitamin D and insulin sensitivity.

Pittas, Lau, Hu & Dawson-Hughes (2007) conducted a systematic review and meta-analysis to determine the role of vitamin D with T2DM. The authors report that an inverse relationship exists in numerous studies between vitamin D, measures of glycemic control and having T2DM. However, the relationship is not consistent with other studies that did find this relationship. The meta-analysis from all studies that examined the relationship between vitamin D and the prevalence of T2DM did not find a significant relationship, however, when non-Hispanic blacks were excluded from the analysis an inverse relationship between low vitamin D and T2 DM was found to be significant Pittas, Lau, Huh and Dawson-Hughes (2007)

hypothesize that vitamin D and calcium homeostasis for blacks may be different than for Caucasians. The authors also reviewed the data from case-control studies and found that the majority, but not all of the studies found that patients with T2DM or pre-diabetes were found to have lower vitamin D levels than controls.

Vitamin D Supplementation and Type 2 Diabetes

Although a relationship between vitamin D deficiency and T2DM has been demonstrated, few studies have been conducted to examine the effect of vitamin D supplementation on glycemic control, particularly for patients who are vitamin D deficient. Of the studies reviewed by Pittas, Lau, Hu and Dawson-Hughes (2007) none are longitudinal (with the numbers of days of supplementation ranging from four days to three weeks) or focused on the effect of vitamin D supplementation for patients with T2DM who are vitamin D deficient. Most of the studies have a small sample size. Pittas, Lau, Hu and Dawson-Hughes (2007) reviewed six studies that investigated the effect of vitamin D supplementation on glycemia. The only study that has greater than 20 subjects is a randomized controlled trial that randomized 65 middle-aged men with pre-diabetes or mild diabetes for vitamin D supplementation for three months; however the subjects were not vitamin D deficient which is a limitation of the study. No effect was found on A1C, fasting glucose values or stimulated glucose tolerance (Ljunghall et al., 1987). Jorde and Figenshau (2009) conducted a randomized controlled trial to determine if study participants with T2DM who received 40,000 IU of cholecalciferol per week would have improved glycemic control with vitamin D supplementation. The researchers randomized 36 subjects to a treatment group that received vitamin D and a control group that was given a placebo for six months. Fasting glucose, C-peptide, fructosamine and A1C levels were not found to be significantly

different from baseline levels. The subjects, however, were not vitamin D deficient; and, the sample size was small, both are limitations of the study.

Suzuki et al (2006) conducted a descriptive study of 581 Japanese patients with T2DM. The aim of the study was to ascertain the prevalence of vitamin D deficiency in patients with T2DM and to determine if an association exits between serum vitamin D levels and microvascular complications. Patients who were receiving supplementation with vitamin D or calcium were excluded from the study. The investigators found that 70 percent of the sample had vitamin D deficiency. The relationship between vitamin D levels and A1C was significant ($r = -.512$, $p = .013$) as was the number of complications ($r = -.669$, $p = .027$). This study had a large sample size and demonstrated that vitamin D hypovitaminosis is negatively correlated with A1C levels and microvascular complications. This study does not examine the efficacy of supplementation.

A study that focuses on vitamin D deficient or insufficient South Asians living in the United Kingdom with T2DM was conducted by Sabherwal, Bravis and Devendra (2010). The study which is a retrospective review of patient records was done to determine the effect of vitamin D and calcium replacement on glycemic control. Patients who had vitamin D supplementation of 400 IU of vitamin D_3 were included in the study. The investigators collected data from the records of subjects before initiation of vitamin D therapy and 16 to 24 weeks after the initiation of vitamin D supplementation. Of the 52 subjects in the study, 29 were vitamin D deficient, defined as a 25(OH)D level of < 12.5 (equivalent to 5 ng/mL) and 23 were found to have vitamin D insufficiency, defined as values $\geq$ 12.5 nmol/l and < 50 nmol/l (equivalent to 20 ng/mL) . The mean total A1C before supplementation was 8.94 percent with a decrease to 8.46percent after treatment. This was a significant finding ($p < 0.001$). This study focuses on

patients with T2DM as well as hypovitaminosis. In addition the design allowed for a longer period of time from initiation of supplementation to determination of the impact on A1C. The subject size of 52 is larger than most of the other studies that examined the influence of vitamin D supplementation on A1C. The length of time between initiation of vitamin D treatment and assessment of A1C is a strength of the study. The dose of vitamin D is relatively low, however the findings are significant.

Summary

It has been demonstrated that a relationship exists between vitamin D deficiency, insulin resistance and glycemic control. Most studies focusing on vitamin D as a strategy to manage T2 DM are limited in number and the results are not consistent. In addition, sample sizes of these studies are small and most do not focus on using vitamin D supplementation in patients who are vitamin D deficient. Further investigation of the impact on A1C of correcting vitamin D hypovitaminosis in patients with T2DM is needed, as well as guidelines regarding prescribing patterns. If it is found that vitamin D is an effective strategy, it will have important public health implications as it is a safe, accessible and inexpensive intervention.

Section III: Methodology

Vitamin D deficiency is highly prevalent, particularly among select populations including those with obesity and T2DM. Many providers caring for patients with T2DM are screening patients for vitamin D deficiency and treating patients who are deficient. Although an association between vitamin D status and glycemia has been discussed, little is known about the association between correcting vitamin D deficiency and improved glycemic control. In addition vitamin D repletion guidelines are needed to inform providers treating individuals with T2DM and vitamin D deficiency. Describing prescribing patterns and monitoring of vitamin D is a first step toward developing recommendations.

Strategies for managing the T2DM epidemic are needed to prevent the morbidity, mortality and financial burden that are consequences of the burgeoning prevalence of the disease. If vitamin D is found to be effective in improving glycemic control the intervention would be a major addition to the strategies used to address the epidemic. Vitamin D is inexpensive, accessible and a treatment option that is easy to adhere to on a long term basis. In the following section the design, setting, sample measurement methods, data collection and analysis plan, limitations, protection of human rights and plan for dissemination will be addressed.

Project Design

This project is a non-experimental retrospective audit designed to assess management patterns utilized for vitamin D repletion, repletion rates, and follow-up monitoring in patients with T2DM. The A1C values of patients with T2DM and vitamin D deficiency who have been placed on vitamin D supplementation and successfully repleted were reviewed at baseline (initiation of supplementation) and again approximately five to eight months after initiation of

treatment. Appointments for diabetes management are scheduled at approximately three month intervals. However, patients may schedule appointments at intervals greater than three months. The A1C level from a visit close to six months after initiation of supplementation (five to eight months) was collected. The type and doses of vitamin D prescribed, the number of follow-up vitamin D tests and the 25(OH) D levels were collected to determine the monitoring patterns and efficacy of treatment.

Setting and Population

Data for the study were obtained from electronic patient records at a mid-Atlantic University-based medical center outpatient diabetes center. Patient records for all patients with T2DM seen between June 18, 2008 (date of initiation of the EMR) and September 1, 2010 who received vitamin D supplementation were screened for admission to the study. The inclusion criteria for the study include: a c) age $\geq$ 18 years d) a diagnosis of T2 DM as determined by ICD-9 codes, 250.0 (T2 DM not stated as controlled) and 250.2 (T2 DM stated as uncontrolled) e) vitamin D deficiency, defined as 25(OH)D levels $\leq$ 30 ng/mL at entry in the study f) prescribed vitamin D therapy after the 25(OH)D level of $\leq$ 30 ng/mL was recognized. g) 25 (OH) D h) A1C levels between 7.5 and 10 percent. Those subjects with a 25 (OH) D level of > 30 ng/ml after five to eight months of enrollment in the study were included in the analysis of the A1C value before and after treatment.

Exclusion criteria include a) age < 18, b) diabetes not classified by ICD-9 codes 250.0 or 250.2, c) an initial vitamin D level of $\geq$ 30 ng/mL, d) hypovitaminosis with vitamin D therapy not prescribed e) an initial A1C level ,< 7.5 percent or > 10 percent. Subjects who do not have a 25(OH)D level > 30 ng/mL five to eight months after initiation of vitamin D therapy were not included in the analysis of A1C values before and after treatment.

Procedures

Following IRB approval, a retrospective electronic medical record audit was conducted to describe the process of vitamin D repletion and follow-up testing and examine A1C levels before and after repletion. The following variables were collected: a) age at initiation of the study b) gender c) ethnicity d) the lowest and highest weight and BMI during the study period e) the number of follow-up 25(OH) D tests and results f) the type of vitamin D prescribed g) A1C values five to eight months after supplementation was initiated for subjects with a 25(OH) D level of > 30. The A1C values were measured rather than fasting or postprandial glucose values as it is a measure that gives an estimate of glucose levels over time

Operational Definitions

1. T2 DM – ICD-9 codes of 250.0 or 250.2 extracted from the Epic System
2. Vitamin D deficiency – 25(OH)D levels $\leq$ 30 ng/mL
3. Vitamin D supplementation – any regimen used to replete vitamin D levels to > 30 ng/mL, supplementation may be continued or discontinued after > 30 ng/mL levels are reached as long as the 25(OH)D levels do not fall below 30 ng/mL
4. A1C – glycosylated hemoglobin expressed as a percentage. The A1C is based on a weighted mean; 50 percent of the result reflects the most recent month, and 25 percent the previous month and the other 25 percent of the value is based on the glycemic control in months three and four (Peragallo-Dittko, 2003).

Data Analysis

Data were analyzed using PASW version 19 for Windows® . Descriptive statistics were used to describe the sample, and an inferential statistic (a paired sample t-test) was conducted to compare A1C levels at time of initiation of vitamin D supplementation and after correction of vitamin D deficiency five to eight months later.

Human Subjects

After initial approval from the University of Maryland, School of Nursing Research Review Committee an application for an exemption was approved by the Institutional Review Board (IRB) of the University of Maryland Medical Systems. The study is a retrospective audit of the electronic medical record. Members of the study team had no access to any identifier that would provide a link to individual subjects. Therefore, the audit posed a minimal risk to patients.

Section IV: Results

Demographics

A query of the Epic database identified 374 subjects who met the criteria for inclusion in the study. One record was eliminated due to missing data. Another record was eliminated due to an A1C value that was obviously an error as it was too high to be biologically possible. After screening and data cleaning, the final sample size was 366 subjects.

The mean age of the sample was 54.9 years of age (SD 12.3), Fifty-six (56) percent (n=205) were female, 44 percent were male (n=161). Almost seventy percent (69.7 percent) were African American (n=255), 25.1percent (n=92) were Caucasian, there were small numbers of subjects in other racial/ethnic categories. The mean minimum weight was 213.5 (SD 59.1), and the mean maximum weight was 226.4 (SD 61.4). The mean minimum BMI was 33.6 (SD 8.5), and the mean maximum BMI was 35.7 (SD 8.8) (See Table 1).

Type and Dose of Vitamin D Prescribed

During the study period a total of 986 prescriptions were written for the subjects. The greatest number, 747 (75.8 percent) were for ergocalciferol (vitamin D2) 50,000 units taken orally with a range of frequency from three times a week to monthly. The rest of the prescriptions for vitamin D were as follows: 74(7.5 percent) 2000 IUs daily, 52 (5.3 percent) 1000 IUs daily, 35 (3.5) were various different prescriptions that included vitamin D with calcium, 10 (1 percent) 400 IUs daily and 57 (5.89 percent) were for other prescriptions, including a variety of vitamin D doses and multivitamins that included vitamin D.

All of the prescriptions for 50,000 IUs of vitamin D did not specify that they were for ergocalciferol (vitamin D2) versus cholecalciferol (vitamin D3). However, it can be assumed that

all of the prescriptions were ergocalciferol as it is the only form available in high doses in the United States (Binkley et al., 2010). The prescriptions for the other most commonly prescribed doses, 2000, 1000 and 400 IUs did not indicate a type of vitamin D.

Vitamin D Testing and Vitamin D Repletion

On average, the subjects received 2.6 (SD 1.5) vitamin D follow-up tests (range 1 to 12 tests). The majority received an initial (99.2 percent) and second (73.8 percent) 25(OH)D follow-up test. However, after the second follow-up test, the rate of testing decreased. The percentage of subjects who received third, forth, and fifth tests was 42.5percent, 21.1percent, and 9.3 percent consecutively. Furthermore, the percentages of subjects who received six to twelve follow-up tests ranged from 4.4 percent to 0.3 percent. It is important to note that the number of tests per subject was influenced by when they entered the study period. Subjects who began care later in the study period would be expected to have fewer 25 (OH) D tests (see Table 2).

For those subjects receiving the first follow-up 25(OH) D, only 4.7 percent were successfully repleted at > 30 ng/mL (see Figure 1). Of the 73.7 percent of the subjects who received a second test, 23.6 percent were successfully repleted. From the third to the fifth testing period the rates of repletion ranged from 7.1 to 15.9 percent. Subsequent tests had very small numbers of subjects in each group making repletion rates less meaningful (see Figure 1).

Inferential Statistics

In addition to describing 25 (OH) D monitoring and repletion rates, a comparison was made between A1C levels before and after successful treatment of vitamin D deficiency. Only 26.5 percent (n=97) of the participants had been successfully repleted five to six months after initiation of treatment and were included in the analysis. Results of a paired-samples Student *t*-test demonstrated a significant decrease in the A1C (indicating improved glycemic control) between the initial A1C values, M = 8.33, SD .69 and the follow-up A1C value, M = 7.9, SD 1.3, t (96) = 3.58, p = .001 (two tailed).

Section V: Discussion

Type and Dose of Vitamin D Prescribed

The type of vitamin D, dose, frequency and duration of treatment should be based on the goal of correcting vitamin D deficiency for individual patients. Heaney, Davies, Chen, Holick and Barger-Lux (2003) found that for healthy individuals every 100 IUs of oral vitamin D taken daily resulted in an increase of 1 ng/mL. Gallagher and Sai (2010) state that a daily dose of approximately 4000 IUs of vitamin is needed to replete individuals with vitamin D deficiency to a 25 (OH) D level of 30 ng/mL.

Cronin (2010) points out that the response to standard doses of vitamin D has considerable variation and patients with chronic diseases may require doses that are substantially higher than those for healthy patients. Randomized controlled trials (RCT) are needed to determine the best regimens for repletion of patients with T2DM and vitamin D hypovitaminosis. These RCTs would need to examine stategies for patients with a number of characteristics that influence vitamin D status such as BMIs, ethnicity and age.

In the meantime, standardizing treatment approaches at a given clinical setting would improve care processes as long as a "one size fits all" approach is not employed. The patient's vitamin D level before treatment would be a logical starting point on which to base a regimen. In this audit there were many different approaches to repletion. Due to the variability in patient characteristics a variety of approaches is appropriate. However, examining the efficacy of various approaches in an interventional study for various groups of patients is an important next step in the development of guidelines.

Medicaid does not cover the cost of vitamin D prescriptions. The majority of vitamin D prescriptions were for 50,000 IUs of vitamin D2 which cannot be obtained over the counter.

Commonly 50,000 IUs vitamin D2 is prescribed weekly for six to eight weeks. The cost of eight doses of 50,000 IUs vitamin D2 is approximately $20.00. One hundred doses of Vitamin D3 5000 IUs can be purchased for less than $6.00 from retailers. By following common prescribing practices providers may have inadvertently created a barrier to improved repletion rates.

The hospital pharmacy adjacent to the project site is able to obtain medications for patients at sharp discounts, the $6:00 cost of the 100 doses of vitamin D3 could be further reduced. Discussing the change from giving patients a prescription for vitamin D to recommending over the counter forms should be addressed with providers. In addition, an arrangement could be made with the pharmacy to provide the vitamin inexpensively. A form about Vitamin D (with the types of vitamin D and prices) could be given to patients at the Diabetes Center. This would encourage patients to obtain it from the pharmacy.

Follow-up Monitoring

Vitamin D hypovitaminosis can develop in as little as three weeks making serial monitoring of 25(OH) D important, particularly after treatment of vitamin D deficiency (Peiris et al., 2010). Peiris, Bailey, Manning and Adebonojo (2010) found that only a third of veterans with vitamin D deficiency had follow-up testing in the year after diagnosis. In addition it was found that the likelihood of follow-up testing was not related to the initial vitamin D level. In the current study the majority of subjects did receive at least one to two follow-up tests with a mean of 2.6 tests per subject. However, a minority of patients received subsequent tests with the rate decreasing with each follow-up period.

Repletion of Vitamin D

The number of follow-up tests should be considered in the context of the subjects' repletion rates. In this investigation, the repletion rate for the first follow-up test was very low at 4.7 percent. A second follow-up test was done for 73.7 percent of the participants with a repletion rate of 23.6 percent; this is improved over the initial set of follow-up tests. However, the majority, 76.4 percent, had inadequate vitamin D levels. After the second set of tests, repletion rates continued to decline, with the majority of subjects never achieving a 25 (OH) D value > 30 ng/mL. The number of follow-up tests declined as well in spite of the fact that the clinical goal of correcting vitamin D deficiency was not reached. The failure to replete greater that two thirds of the subjects is the most important finding from this project. In planning next steps the primary goal should be developing an approach to treatment that will result in successful repletion of vitamin D.

The United States Department of Health and Human Services created the Health Information Technology (HIT) for Economic and Clinical Health Act (HITECH) Act in 2009 in order to incentivize healthcare organization and providers for the meaningful use of EMRs. The aim of the HITECH act is to encourage adoption of health information technology in order to improve health outcomes and control costs (Blumenthal, 2010). Classen and Bates (2011) point out that the adoption of HIT has not always led to improved health outcomes. The use of the Epic System made data mining possible. The data obtained demonstrated that efforts to correct vitamin D deficiency have not been highly successful. To achieve meaningful use the process of care must be modified and outcomes improved.

The cost of a 25 (OH) D test at the clinical site used for the project is approximately $39.91. The mean number of tests was 2.6 with a maximum number of 12 tests. The many

follow-up tests did not result in high repletion rates. If follow-up action is not taken when less than adequate rates are found the costs and time spent monitoring vitamin D levels is not justified. Follow-up tests should be ordered judiciously in order to control costs. Reducing the testing schedule to every six months to yearly would greatly reduce the costs of monitoring. However, the frequency of follow-up tests may be influenced by the severity of vitamin D deficiency.

In addition to assuring that vitamin D is accessible and affordable patient education is needed regarding vitamin D deficiency, online patient education resources that may be printed out and given to patients are readily available and should be utilized. The focus of the clinical site is diabetes care. However, since screening, treatment and follow-up monitoring of vitamin D are also part of the process of care, education about vitamin D should be included in routine patient education.

Peiris, Bailey, Manning and Adebonojo (2010) point out that a successful repletion strategy will vary according to factors such as age and body size and that some patients will need much higher doses than others. In this study the mean of the minimum BMIs during the study period was 33.6 and the mean of the highest BMIs was 35.7. It is known that vitamin D deficiency is increased in obese patients and those with T2DM (Ozfirat & Chowdhury, 2010, Pittas et al., 2007). Additionally, the subjects were approximately 70 percent African American, a group with increased risk for and incidence of vitamin D deficiency (Ozfirat & Chowdhury, 2010). Treating this group of patients would likely require higher doses of vitamin D and longer times for repletion as well as serial monitoring.

The failure to successfully correct vitamin D deficiency in the majority of the subjects is a finding that has important implications for practice. The time and expense involved in

screening, management and follow-up testing should be considered in the context of the results of this audit. The reason for this is not evident from the findings. Further investigation is needed to determine if the issue is adherence to the regimen or other factors such as inadequate dosing or duration of treatment.

An important next step is to ascertain adherence rates for various regimens, as well as the reasons for adherence or nonadherence. Weekly dosing may seem to be easier to adhere to. However, it may also be easier to forget to take a weekly dose rather than a daily dose. Patients may not perceive vitamin D as a "real medication" as they would an oral hypoglycemic agent. The expense of screening, treatment and follow-up are hardly justified if this issue is not addressed. Patients could be surveyed anonymously about their attitudes and behavior regarding supplementation. The results of this survey would determine if interventions are needed to address adherence to prescribed regimens.

A1C testing

It was found that the 97 subjects successfully repleted had significantly lower A1C values after successful treatment of vitamin D hypovitaminosis. This is consistent with the findings of significantly lower A1C levels after supplementation in the study of T2DM patients with vitamin D deficiency conducted by Sabherwal, Bravis and Devendra (2010). This result should not be generalized to other populations as many factors that were not controlled for impact glycemic control such as medication regimens, comorbidities and activity levels. However, the finding of significantly improved glycemic control justifies further study regarding the efficacy of correcting vitamin D deficiency for T2DM patients in order to improve glycemic control.

The Development of Practice Guidelines

Although RCTs directing the ideal approach to correcting vitamin D deficiency for patients with T2DM do not currently exist, guidelines to standardize and improve practice could be and should be developed. Specific dosing, frequency and duration of supplementation are based on individual patient characteristics. However, guidelines could suggest practice approaches based on baseline vitamin D levels. A schedule for follow-up testing and approaches for patients not successfully repleted would be included.

A flow chart in the EMR tracking vitamin D prescriptions, follow-up tests and results would facilitate the use of guidelines. Additionally, patients could be questioned about adherence and perceived barriers to adherence. This information could be included in the flow chart. Patients often see a number of different providers. If providers are able to access information and see patterns easily, guideline adherence would be more likely and individual patient issues could be addressed.

Meaningful Use Issues

In examining the data for this project it was evident that standard terms have not been employed. There were multiple terms used to describe 25 (OH) D tests and vitamin D prescriptions that were synonymous. This resulted a in time consuming review of terms for the purposes of this project. In order to efficiently and accurately mine data for quality improvement and research standardization is essential. Additionally, a lack of consistent terminology can be a source of medical error. In order to realize the goal of meaningful use standardized terminology is needed.

Section Six: Plans for Translation

The findings from this audit will be presented to providers and nursing staff of the site in which the subjects received care. Recommendations will include an investigation regarding the reasons for poor repletion rates, including a patient survey, the development of guidelines and a screen for tracking vitamin D screening, treatment, monitoring and results in the Epic System.

The framework chosen to guide translation of the findings from this audit in the practice setting is Evert Roger's DIT. The theory provides guidance to the process of adoption and diffusion of innovations and has been used extensively in healthcare settings. Specific principles of the DIT will guide the translation plan.

Rogers (2003) states that innovations that are perceived as having a greater degree of relative advantage, compatibility, trialability, observability and low complexity will adopt at a faster rate. When an innovation is presented, relative advantage is perceived in terms of economic factors, social prestige factors, satisfaction and convenience (Rogers, 2003). Costs and benefits of the innovation are weighed by the provider. Relative advantage has been found to be a strong predictor of the rate of adoption. The cost benefit ratio of the translation plan will be discussed with providers and relative advantage addressed. Costs are time and dollars spent on the management of screening, treatment and follow-up for patients with vitamin D deficiency. These costs are already being occurred. However, the repletion rates do not point to a satisfactory return on the costs of current practice.

Compatibility refers to the degree to which an innovation is consistent with values, needs and past experiences of adopters. Correction of vitamin D is already being addressed by providers. Therefore, providers will not need to accept the costs of adopting a new clinical

practice. The focus will be to implement new approaches to improve the management of vitamin D inadequacy, a practice already recognized as important enough to be a component of current care.

Complexity is the degree to which an innovation is perceived as difficult. Innovations that are easily understood are more rapidly adopted (Rogers, 2003). Guidelines once established would make decisions about the management of vitamin D deficiency less complex. The tracking of vitamin D treatment and results would be facilitated by the EMR that is already being used by providers and nurses at the clinical site. If lab results and prescriptions placed in the EMR populated the screen used to track vitamin D management the relative perceived difficulty of the process would be decreased.

In addition to addressing the complexity of an innovation the ability to trial an innovation facilitates adoption. Rogers (2003) states that new ideas that can be trialed adopt more rapidly, he refers to this as trialability. Before implementing the interventions with all of the providers a pilot with a smaller number of receptive providers will be initiated. The approach is linked to observability, defined by Rogers (2003) as the degree to which innovations are visible to others. If the use of guidelines and the EMR in a pilot program improve both the process of care and repletion rates it will be observable to the entire group of providers and more likely to be adopted.

Communication channels are defined by Rogers (2003) as the means in which messages are transmitted between individuals. Communication channels may be formal such as a grand rounds presentation or informal such as discussion among providers in the clinical setting. A number of communication mechanisms could be used to facilitate the adoption of the innovation, including face-to-face interaction and the use of electronic media.

Initial face-to-fact communication could occur at a scheduled presentation for providers and nursing staff at the clinical site. This would allow for discussion regarding the findings of the audit. The reactions of providers and nursing staff (the key stakeholders) would be used to guide plans for the development and adoption of guidelines. Strategies suggested by providers and perceived barriers to adoption would be ascertained.

Rogers (2003) states that the Internet is an additional channel of communication, that may be used in the diffusion of innovations. The e-mail system and intranet could be used to communicate as guidelines are developed and implemented. This is a tool that will be utilized to communicate about the practice change and receive feedback in an expedient manner.

Rogers (1995) describes the steps in the innovation-decision process as; knowledge of an innovation, formation of an attitude about the innovation, the decision to adopt or reject the innovation, implementation of the innovation and confirmation of the innovation decision.

The knowledge stage is the first in the innovation-decision process. Innovation messages are accepted if the innovation is perceived as consistent with an individual's belief system, Rogers (2003) states that when individuals receive new information selective perception occurs based on past experiences, beliefs and attitudes. As discussed, a presentation of the audit findings is planned. Discussions will be encouraged so that concerns regarding findings and next steps are addressed.

Persuasion is defined by Rogers (2003) as the stage in which a favorable or unfavorable attitude is formed regarding an innovation. Sharing the findings obtained from this project is a first step in persuading providers that guidelines are needed. Further persuasion could be accomplished as key stakeholders who agree that guidelines are needed informally influence others.

The translation of research is a primary focus of the DNP role. Facilitating the establishment of guidelines would require that the DNP collaborate with providers .The guidelines would need to fit well with the workflow of the clinical site and be acceptable to the providers and nursing staff in order to be adopted. After collaborating with providers to develop guidelines the next role for the DNP would be to facilitate the adoption of the guidelines.

During the decision stage an innovation is either adopted or rejected. This stage is linked to trialability; if potential adopters have the opportunity to pilot test an innovation, adoption may be more likely. Shirey (2008) advocates the use of opinion leaders and interpersonal communication channels during the decision stage and states that support and service excellence by a change agent is critical for success. A change agent committed to the innovation should be identified. That individual would develop support from opinion leaders who will be consulted as the innovation is adopted and diffused.

Rogers (1995) states that prior to the implementation stage activities are limited to mental exercises. During implementation new behaviors are required as the innovation is first adopted. Shirey (2008) discusses the need for a change agent to provide technical assistance during implementation as well as building infrastructures necessary for successful adoption of an innovation. The DNP is ideally suited to the role of change agent due the focus on the translation of evidence. The DNP as the identified change agent would educate staff and assist in initial guideline implementation and computerized tracking.

Rogers (1995) states that empirical evidence indicates that the final decision to adopt or reject an innovation does not occur during the decision stage, it occurs during the final stage, confirmation. During the confirmation stage the individual will attempt to avoid internal dissonance by rejecting the innovation if it is not perceived as favorable or to accept it if it is.

Shirey (2008) states that confirmation should be supported by external sources. Monitoring of the progress of the innovation via audits of the electronic medical record with feedback and reinforcement for providers involved in the innovation would help sustain the intervention. Communication through interpersonal channels and the organization's e-mail system would be utilized. Keeping open communication channels with opinion leaders will be important in sustaining the adoption of guidelines.

Wider dissemination will be accomplished by presenting findings at national professional organization meetings such as the American Association of Diabetes Educators annual conference and the American Academy of Nurse Practitioners annual conference. A manuscript for publication in a journal such as the *Journal of the American Academy of Nurse Practitioners* will be submitted in order to reach a broader audience.

Summary

Little guidance is available for providers treating patients with T2DM and vitamin D hypovitaminosis. The description of prescribing patterns, monitoring and repletion rates generated by this audit of the EMR is a first step in developing guidelines that can be used in clinical practice. The less than ideal repletion rate indicates a need for further investigation regarding the current process of care and guidelines to facilitate best practices.

A significantly improved A1C in patients with successful treatment of vitamin D deficiency was found in this audit. Although this was not an RCT and the results may not be generalized to the population of T2DM patients with inadequate vitamin D, it validates the continued screening and management of vitamin D deficiency at the clinical site in which the subjects were treated. The finding also indicates a need for prospective interventional research

to investigate the efficacy of this easily obtained and relatively inexpensive treatment modality. When vitamin D management activities and outcomes are captured by the EMR further investigation of treatment outcomes will be facilitated.

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Table 1

Demographic Characteristics of the Sample (N = 366)

Characteristic	n	%
Gender:		
Female	205	56.0
Male	161	44.0
Race:		
American Indian-Eskimo	5	1.4
Asian	3	0.8
Black or African American	255	69.7
Hispanic	3	0.8
Other	7	1.9
Unknown	1	0.3
White or Caucasian	92	25.1

Table 2

Demographic Characteristics of the Sample (N = 366)

Characteristic	M	SD
Age:	54.9	12.3
Min Weight (lb)	213.5 (59.1)	52.9 – 421.4
Max Weight (lb)	226.4 (61.3)	68.3 – 443.6
Max BMI (kg/m^2)	35.7 (8.8)	19.2 – 78.6
Min BMI (kg/m^2)	33.7 (8.5)	14.9 – 74.6

Table 3

Vitamin D Prescriptions (N = 986)

Prescription	n	%
50,000 IUs	747	75.8
2000 IUs	74	7.5
1000 IUs	52	5.3
400 IUs	10	1.0
Calcium with Vitamin D	35	3.5
Multivitamins/Other	57	5.89

Table 4

A1C Levels Before and After Vitamin D Repletion (N = 97)

	M	SD	*t (p)*
Before Repletion	8.3	.69	3.58(.001)
After Repletion	7.9	1.3	

Figure 1

Follow-up 25 (OH) D Tests and Repletion

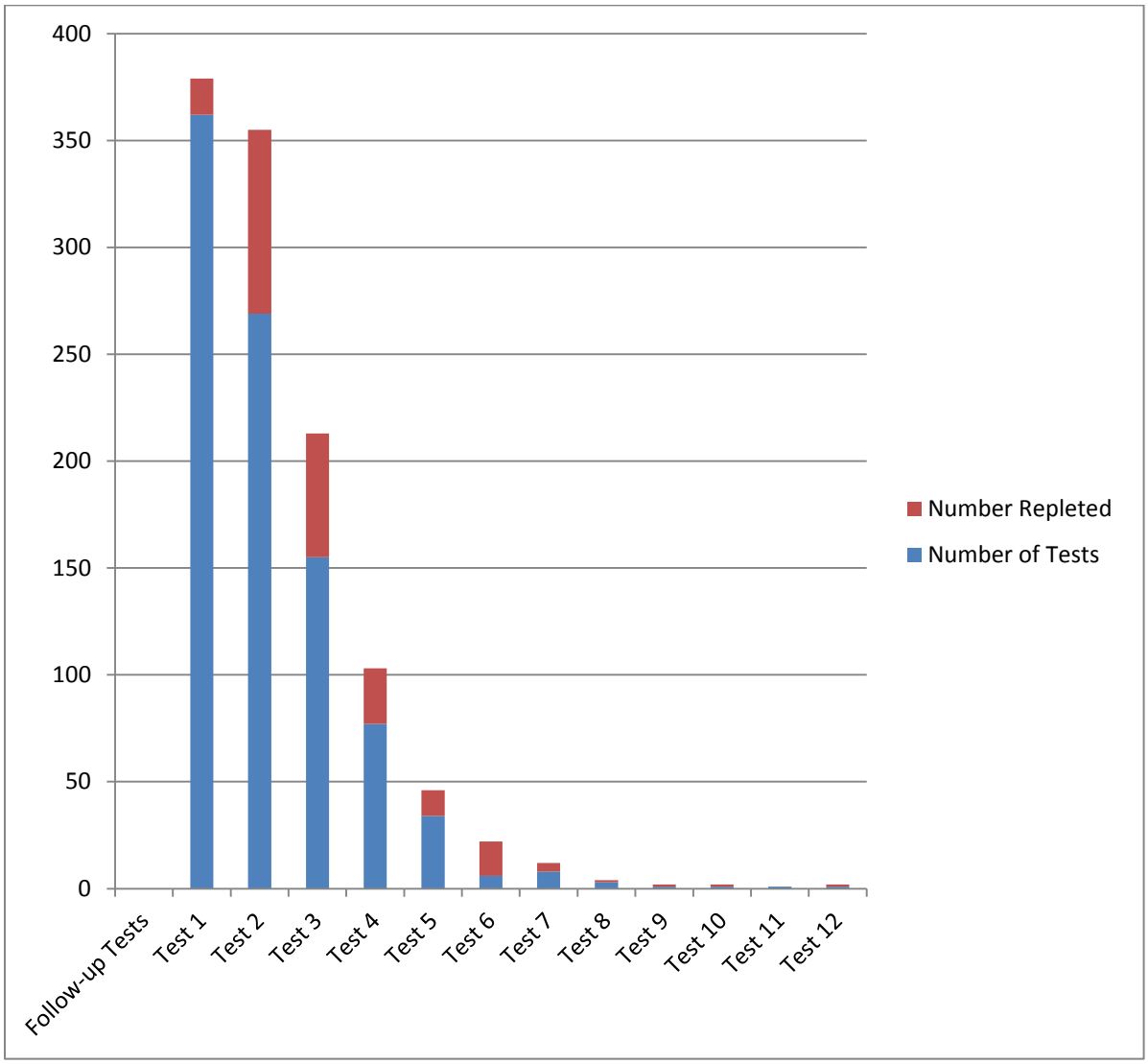

Figure 2

Applying DOI Theory to Practice Change