Vitamin B12 Screening and Treatment in Patients Taking Metformin

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Doctoral Scholarly Project IV

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Abstract

Background: Long-term metformin therapy is linked with the potential side effect of vitamin B12 deficiency. Although screening is recommended, there is no standardized screening guideline. Vitamin B12 deficiency is frequently unrecognized. An electronic medical record-based alert may lead to more identification and better patient outcomes.

Purpose: The purpose of this project was to determine the impact of focused education on clinician perceptions about the importance of using an electronic medical record-based alert to ensure routine vitamin B12 monitoring in type II diabetic patients prescribed metformin.

Methodology: The organization site for this doctoral project was a single, stand-alone, primary care clinic located in a large metropolitan area in the Midwest of the United States. Clinicians were surveyed before and after participating in a live in-person educational PowerPoint presentation. Participants were given a pre- and post-survey to assess the clinicians own perceived levels of knowledge regarding metformin-induced vitamin B12 deficiency, current ADA recommendations, their current vitamin B12 monitoring practices and their willingness to utilize an EMR-based alert to ensure routine vitamin B12 monitoring.

Implications/Conclusion: Two-tailed t-tests were used to analyze the results. There was a statistical significance in the difference of pre-intervention scores (M = 35.7, SD = 9.3) and post-intervention scores (M = 55.7, SD = 2.9); t = -5.60, p = .001. The effect size, as measured by Cohen's d, was d = 2.90, indicating the intervention had a large effect. Results suggest that the intervention was overall effective. Survey results for this study are indicative of the need to educate clinicians about metformin-induced vitamin B12 deficiency and utilizing the EMR to improve vitamin B12 monitoring procedures.

Keywords: metformin, vitamin B12 deficiency, type II diabetes mellitus, clinical support tool

Vitamin B12 Screening and Treatment in Patients Taking Metformin

Metformin is among the first-line pharmaceutical treatments for type II diabetes (Infante et al., 2021). However, studies have reported a significant association between long-term metformin therapy and an increased prevalence of vitamin B12 deficiency (Infante et al., 2021). Vitamin B12 deficiency is a condition exhibited by an array of clinical manifestations allowing for it to be frequently omitted or misdiagnosed in its early stages (Infante et al., 2021; Langan & Goodbred, 2017; Wolffenbuttel et al., 2019). The American Diabetes Association (ADA) has established a consensus statement recommending periodic screening of vitamin B12 in patients taking metformin (2022). Given these relations, recognizing vitamin B12 deficiency could lead to better patient outcomes through implementation of a protocol for screening and treatment of vitamin B12 deficiency (Infante et al., 2021; Langan & Goodbred, 2017). This project examined whether focused education impacted clinician perceptions about the importance of using an electronic medical record (EMR)-based alert to ensure routine vitamin B12 monitoring in type II diabetic patients prescribed metformin.

Overview

Problem Description

Diabetes is an epidemic in the United States. According to the Centers for Disease Control and Prevention (CDC), over 37 million Americans have diabetes and face its devastating consequences (2022). Metformin is considered the gold standard in oral glucose-lowering pharmaceuticals to treat type II diabetes (Infante et al., 2021). While there is a current consensus on the medication's potential to lower vitamin B12 levels, there still remains no standardized algorithm to screen or treat B12 deficiency in patients taking it (Infante et al., 2021). Vitamin

B12 deficiency remains frequently unrecognized in type II diabetic patients taking metformin. Due to the reported association between metformin use and B12 deficiency, and the high risk for morbidity development, the present study aims to identify a method for prompting proactive vitamin B12 screening in type II diabetic patients prescribed metformin.

Potential barriers to routine vitamin B12 monitoring in diabetic patients include poorly defined or non-existent objectives and operating procedures. Notable constraints to screening for vitamin B12 deficiency in diabetic patients on long-term metformin therapy include lack of a standardized screening and treatment protocol, indefinable clinical manifestations of vitamin B12 deficiency, poor consensus among providers on when to screen, and low prioritization of vitamin B12 monitoring compared to other diabetes recommendations (Chappell et al., 2020; Longo et al., 2019; Wolffenbuttel et al., 2019).

Patients with untreated vitamin B12 deficiency are at an increased risk for significant neurologic complications due to demyelination and cell death (Saji & De Jesus, 2022). Peripheral neuropathy is a clinical manifestation seen in vitamin B12 deficiency and is a serious complication of diabetes mellitus. Peripheral neuropathy accounts for significant morbidity by predisposing the foot to ulceration characterized by full-thickness wounds, accompanied by skin necrosis, leading to lower extremity amputation (Badedi et al., 2019; Gordois et al., 2003). It is beneficial to evaluate and treat vitamin B12 deficiency in diabetic patients because it lowers the risk for development of further comorbidity. Therefore, the research question driving this project was, “Does focused education impact clinician perceptions about the importance of using an EMR-based alert to ensure routine vitamin B12 monitoring for patients prescribed metformin?”

Clinician education on vitamin B12 screening in diabetic patients taking metformin was proposed with the intended outcome of decreasing complications associated with peripheral

neuropathy by promoting early recognition of vitamin B12 deficiency. To evaluate the success of the clinician focused education, primary care clinicians rated their own perceived levels of knowledge regarding metformin-induced vitamin B12 deficiency, current ADA recommendations, their current vitamin B12 monitoring practices and their willingness to utilize an EMR-based alert to ensure routine vitamin B12 monitoring.

Available Knowledge

Vitamin B12 Absorption

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is derived naturally from animal products, fortified foods and dietary supplements. Vitamin B12 is only synthesized by microorganisms (Boachie et al., 2020). In humans, vitamin B12 manifests insufficient bioavailability. Consequently, vitamin B12 must be derived from food products that contain the essential vitamin. Once ingested, vitamin B12 must undergo a series of intricate absorption mechanisms before it can be rendered available to the body's peripheral tissues and the liver (Obeid et al., 2019; Shipton & Thachil, 2015). Considering the various phases of absorption, there are many opportunities in which vitamin B12 deficiency can develop.

Metformin reduces serum vitamin B12 levels through a process that has not been well elucidated. However, it is thought that metformin-induced vitamin B12 deficiency occurs through altered vitamin B12 absorption and metabolism (Infante et al., 2021). It has become recognized in several studies that metformin interferes with calcium-dependent membrane action responsible for vitamin B12 intrinsic factor absorption in the terminal ileum (Bell, 2022; Infante et al., 2021; Kim et al., 2019).

Despite the 2021 ADA Standards of Medical Care in Diabetes recommendation to consider a periodic assessment of vitamin B12 levels in patients with long-term metformin use,

including those with pre-diabetes, peripheral neuropathy or anemia, no definitive vitamin B12 screening guidelines exist (Infante et al., 2021). The ADA recommendation is based on a grade B level of evidence derived from many well-conducted studies and a report from the Diabetes Prevention Program Outcomes Study (DPPOS) (Infante et al., 2021). The DPPOS represents the largest and longest study of metformin treatment. An assessment of vitamin B12 status occurred for over 10 years and found that five years of metformin use was associated with increased risk of vitamin B12 deficiency (Aroda et al., 2016). There is sufficient evidence demonstrating a need for quality improvement regarding implementation of a tool that ensures optimal monitoring and treatment of vitamin B12 deficiency in patients taking metformin. Identifying measures to increase adherence to screening and treatment guidelines will ensure optimal monitoring in this high-risk population.

Metformin and Vitamin B12 Practices

Although metformin is the preferred medication used for stabilizing glucose for type II diabetics, it is linked with the potential side effect of Vitamin B12 deficiency (Miller, 2018). Many studies have demonstrated a significant association between long-term metformin treatment and increased risk for vitamin B12 deficiency (Infante et al., 2021). In an aim to assess the occurrence of monitoring vitamin B12 levels, Longo et al. (2019) found many patients in ambulatory care settings did not have vitamin B12 levels monitored. Likewise, Wolffenbuttel et al. (2019) found that vitamin B12 deficiency is frequently overlooked due to provider misconceptions regarding factors that predispose a patient to vitamin B12 deficiency.

The ADA (2022) has recognized guidelines encouraging periodic screening of vitamin B12 in patients prescribed long-term metformin. Despite ADA recommendations, many

providers do not observe routine vitamin B12 screening within their practice. Alshammari et al. (2019) found that many clinicians are unaware of the current ADA recommendations.

The dose and duration of metformin therapy can directly impact serum vitamin B12 levels. Aroda et al. (2016) assessed the risk for B12 deficiency with metformin use in the Diabetes Prevention Program which enrolled 3,234 participants with impaired glucose tolerance. This study found long-term use of metformin associated with a significant risk for vitamin B12 deficiency, which is correlated with peripheral neuropathy. Similarly, Alhaji (2022) found that vitamin B12 deficiency was negatively associated with the dose and duration of metformin therapy and Alharbi et al. (2018) discovered chronic metformin therapy frequently exhibited peripheral neuropathy in combination with existing vitamin B12 deficiency.

Peripheral Neuropathy

Peripheral neuropathy is a clinical manifestation seen in vitamin B12 deficiency. Early recognition is key to preventing further comorbidity development. Gordois et al. (2003) reports an estimated $4.3 billion to $12.7 billion annually for type II diabetes care, and Peacock (2019) identified 27% of such costs being directly attributed to peripheral neuropathy care. It is estimated that 85% of the annual cost of illness is attributable to the management of long-term complications and foot ulceration (Gordois et al., 2003). The cost of complications was estimated to be $47,240 per patient over 30 years (Caro et al., 2002).

Successful Interventions in Literature

Many studies have investigated strategies to increase vitamin B12 screening and improve interventions that will increase adherence to recommended monitoring guidelines. Mays (2021) implemented a quality improvement project focusing on increasing screening B12 levels in patients taking metformin. The project used baseline data from the EMR to manually alert

providers about patients' needs during morning meetings and before each patient was seen. The facility later switched to a new EMR system which could send notes or alert reminders to providers when the patient chart was accessed. Mays found that the rate of vitamin B12 screening steadily increased when compared to data prior to the intervention.

Peripheral neuropathy may be eluded or improved when consistently screening and treating vitamin B12 deficiency. Julian et al. (2020) completed a systemic review and discovered that there is evidence that vitamin B12 had a therapeutic effect in the treatment of peripheral neuropathy. Screening vitamin B12 levels and incorporating oral or parenteral supplementation into treatment plans can improve the patient's quality of life. Integrating a simple screening and treatment tool increases the patient's overall safety in the setting of peripheral neuropathy, reduces office visits secondary to neuropathic exacerbations, and provides the patient relief from symptoms (Peacock, 2019).

Significant improvement in patient outcomes may result from optimal monitoring and early treatment of B12 deficiency. This may consequently decrease the annual healthcare spending related to complications from neuropathic foot ulcers with deep infection, cellulitis or osteomyelitis at a given point in time and/or toe, foot or leg amputations during a year (Gordois et al., 2003). Proactively addressing the risk of developing low vitamin B12 levels in type II diabetics reduces potential for physical harm and lessens the financial burden of disease (Peacock, 2019).

Rationale

The precede-proceed model is a framework category that provides a structure for evaluating implementation endeavors (Nilsen, 2015). The precede model was developed by Lawrence Green and his colleagues in 1974 with the intention of providing a structure for

applying theories and concepts systematically to plan, evaluate and design health programs efficiently (Green & Figá-Talamanca, 1974). The precede model can be used to construct and appraise a health-related quality improvement intervention (Green & Figá-Talamanca, 1974). The proceed feature was added to the model in 1991 by Marshall Kreuter. Adding proceed to the model incorporated policy aspects and recognizing environmental factors as an important determinant of health (Lawrence & Kreuter, 1991)

The precede-proceed model has four phases. The first phase involves the audience and their active participation in determining the health-related issue, defining goals and establishing strategies to reach the expressed goals (Lawrence & Kreuter, 1991). In this instance, the identified need was inconsistent vitamin B12 monitoring, and the desired outcome was improved consistency in monitoring vitamin B12 levels which may lead to decreased co-morbidity of peripheral neuropathy. The phase two epidemiological assessment (Montano et al., 2008) resulted in knowledge that long-term metformin therapy is associated with vitamin B12 deficiency (Infante et al., 2021). The third phase involves identifying antecedent and reinforcing factors that should be in place to initiate and sustain the change process (Montano et al., 2008). The individual-level theory is most applicable to this stage because it addresses factors that influence behavior and current practice, such as knowledge. Studies have found that some primary care practices are unaware of ADA recommendations to monitor vitamin B12 levels in patients taking metformin (Alharbi et al., 2018; Longo et al., 2019). Likewise, inconsistent clinician knowledge regarding metformin's potential to interfere with vitamin B12 absorption, leads to decreased vitamin B12 monitoring in this patient population. Lastly, the fourth phase identifies resources, organizational barriers and facilitators, and policies that are needed for program implementation and sustainability (Montano et al., 2008).

This model aligns with vitamin B12 screening and treatment in requiring input from stakeholders. The framework targets an issue within a specific population that is changeable, similar to my intervention in reviewing clinician knowledge and willingness to utilize EMR optimization to adhere to vitamin B12 screening guidelines. This framework was expected to be successful because it has a demonstrated history of success in other areas of medicine and quality improvement initiatives. Overall, results of this study can be used to support, monitor, assess and improve vitamin B12 monitoring in primary care settings. It is well documented that screening and treating vitamin B12 deficiency leads to better patient outcomes by avoiding complications of peripheral neuropathy.

Purpose

The aim of this study was to provide clinician staff within a primary care clinic education regarding metformin-induced vitamin B12 deficiency and education on a method to increase adherence to screening guidelines. The main objective was to assess if focused education impacted clinician perceptions regarding utilization of an EMR-based alert to ensure routine vitamin B12 monitoring in patients prescribed metformin.

Methods

Context

The organization site for the doctoral scholarly project was a single, stand-alone, primary care clinic located in a large metropolitan area in the Midwest of the United States. The clinic serves a community of mostly middle-class families, where the median household income is $62,213 (United States Census Bureau, 2021). The community demographics are diverse with 75.9% Caucasian, 14% Hispanic or Latino and 12% Black or African American. Clinician staffing within the clinic included three doctors, three nurse practitioners specializing in

women's health and family medicine, four nurses and three certified medication aides. The clinic's mission is to provide preventative care and proactively manage diseases by helping patients achieve optimal health in accordance with the teachings of the Catholic Church. The majority of patients seen within the clinic are between the ages of 18 and 75 years old. Many patients treated within the clinic have the diagnosis of type II diabetes.

Intervention

The researcher provided a live educational PowerPoint presentation regarding metformin-induced vitamin B12 deficiency and a method to increase adherence to vitamin B12 screening guidelines. The participating staff were oriented to their role in the study. The researcher introduced the problem and discussed pertinent research, including findings in the DPPOS study, which serves as a grade B level of evidence, for ADA's recommendation to screen for vitamin B12 deficiency in diabetic patients taking metformin.

The education was designed to emphasize that although there is consensus on metformin's potential to cause vitamin B12 deficiency, there remains poorly defined objectives and operating procedures in patients prescribed metformin and screening for vitamin B12 deficiency remains low in clinical practice. The repercussions of undiagnosed vitamin B12 deficiency and a method to increase screenings by implementing an alert in the EMR were described. Findings in previous research regarding electronic based alerts and clinical support tools were explored. The education took place at the clinic's weekly staff meeting, in a classroom-like setting with a projector available. The intervention was approximately 30 minutes in length.

Study of the Intervention

To determine the success of the intervention, a pre-survey and post-survey was administered to the participants to evaluate the effectiveness of the education. The pre- and post-survey was designed to take approximately 5 minutes to complete. Data collection utilized Google Forms, an online survey development software. The identical surveys were distributed via a QR code immediately prior to the intervention and immediately following the intervention. Each participant was assigned a numerical identification code to properly compare the participants' pre- and post-survey.

Measures

The survey was designed to measure the participants' current knowledge and perceptions regarding metformin induced vitamin B12 deficiency, ADA recommendations, current vitamin B12 monitoring procedures and perception of medical record alerts. The survey was uniquely designed for the purposes of this study. All survey questions were designed so that the information was clear and easy to comprehend.

The survey consisted of 6 Likert scored questions. Question 1 examined the clinician's knowledge about metformin-induced vitamin B12 deficiency. Question 2 assessed the clinician's awareness of ADA's recommendations regarding vitamin B12 monitoring in patients prescribed metformin therapy. Question 3 and 4 assessed the clinician's current vitamin B12 monitoring procedures by asking if the clinician thought routine vitamin B12 monitoring, at least once annually, is important in patients prescribed metformin and if the clinician thought obtaining a baseline vitamin B12 level is important when initiating metformin therapy. Questions 5 and 6 assessed the clinician's feelings regarding whether EMR alerts would be beneficial to following vitamin B12 monitoring procedures and if the clinician would be willing to optimize the EMR to increase vitamin B12 monitoring procedures.

Analysis

An Excel spreadsheet was utilized to enter the data and keep it orderly. The data was double-checked for accuracy by creating and comparing two separate Excel spreadsheets to identify mistakes. Descriptive statistics and a paired t-test were conducted to analyze the results of this study. Descriptive statistics were performed on the data collection from the pre- and post-surveys. Aggregate averages were found for each outcome statement pre- and post-intervention, as well as for the total survey scores. The scores from each question were totaled from the pre- and post-survey data and reported as means and standard deviation. A paired t-test was conducted on Excel using the add-on Analysis ToolPak to analyze the results.

Ethical Considerations

The clinic manager gave permission to complete the study within their clinic. The researcher obtained Institutional Review Board (IRB) approval prior to initiating the doctoral scholarly project. The primary and secondary investigator completed Collaborative Institutional Training (CITI) modules. All documents and results of the project were kept confidential by the investigator. Participants consented to the study by scanning the QR code to access the surveys. Participant identifiers were not collected, and the information was only shared with project partners. Data was stored on the researcher's password protected computer and only they had access to it. The study involved little to no risk to the participants and the intervention provided in this project only served as a potential benefit. No potential conflicts of interest were identified.

Results

Nine individuals completed the pre-intervention survey and post-intervention survey after receiving education on metformin associated vitamin B12 deficiency and a method to increase adherence to screening guidelines. Two participants failed to report their identification code on

their post-survey. These responses were removed from the study because there was no way to pair them to the appropriate post-survey data. Therefore, seven participant pre- and post-survey responses were analyzed. A paired samples t-test was used to compare pre- and post-intervention surveys and an alpha of 0.05 was used to determine the efficiency of the intervention. Survey responses were coded in the form of a Likert scale 1 through 10, with 1 being Strongly disagree and 10 being Strongly agree. There was a statistical significance in the difference of pre-intervention scores (M = 35.7, SD = 9.3) and post-intervention scores (M = 55.7, SD = 2.9); t = -5.60, p = .001. The effect size, as measured by Cohen's d, was d = 2.90, indicating the intervention had a large effect. Results suggest that the intervention was overall effective. Table 1 demonstrates the comparison of pre-intervention to post-intervention results for each question. Each outcome had a mean increase in scores from the pre-intervention to the post-intervention mean. The largest increase in mean scores was demonstrated on question two in which the mean response pre-intervention was a 2 and then increased to a 9.143 post-intervention. The intervention appeared to have corrected this, creating consistency with knowledge and practice scores, along with an increase from initial means for the clinician's current vitamin B12 monitoring practice and willingness to utilize EMR optimization. The overall outcomes were met for this sample with an average of 3.3 increase in outcome scores.

Table 1

Outcome Results

Question	Pre-Intervention Mean	Post-Intervention Mean	t-stat	p-value
Q1: I have sufficient knowledge about metformin-induced vitamin B12 deficiency.	2.857	6.857	-3.144	0.020

Q2: I am aware of what the American Diabetes Association's recommendations are regarding vitamin B12 monitoring in patients prescribed metformin therapy.	2	9.143	-14.049	8.116
Q3: I think routine vitamin B12 monitoring, at least once annually, is important in patients prescribed metformin.	6.857	9.857	-2.930	0.025
Q4: I think it is important to obtain a baseline vitamin B12 level when starting a patient on metformin therapy.	6.429	9.857	-3.361	0.014
Q5: I feel that an electronic medical record alert would be beneficial in following vitamin B12 monitoring procedures.	9	10	-1.871	0.111
Q6: I would be willing to optimize the electronic medical record to increase vitamin B12 monitoring procedures.	8.571	10	-2.704	0.034

Discussion

Summary

This project examined the effect of focused education on clinician knowledge, awareness, thoughts and feelings regarding metformin-induced vitamin B12 deficiency and EMR optimization to increase vitamin B12 screening. Two-tailed p-values were reported and a p-value of < 0.05 was used to determine significance. Cohen's d was used to determine the magnitude of effect on the sample size, with a $d = > 0.8$ indicating a large effect. The pre-intervention survey demonstrated lack of knowledge regarding metformin-induced vitamin B12 deficiency and

current ADA recommendations. Each survey question had a mean increase in scores as shown in Table 1. This study revealed that focused education improved clinician knowledge regarding metformin-induced vitamin B12 deficiency, ADA recommendations, and improved clinician willingness to increase their current vitamin B12 monitoring practice and utilize the EMR to adhere to screening guidelines.

Interpretation

The association between the intervention and outcomes demonstrated the focused education intervention resulted in increased clinician knowledge and increased willingness to incorporate the use of clinical support tools, such as an EMR-based alert, to increase vitamin B12 monitoring procedures. This study aligns with the findings from Longo et al. (2019) in that many clinicians do not observe routine vitamin B12 monitoring in their practice. Based on this study's results, it can be hypothesized that lack of clinician knowledge regarding metformin's potential to instigate vitamin B12 deficiency is one potential reason for the lack of monitoring. In this study, the questions with the lowest initial mean were questions one and two which asked about the clinician's knowledge about metformin-induced vitamin B12 deficiency and current ADA recommendations. These outcomes had an average increase of 5.57 post-intervention demonstrating that the intervention was impactful and highlights the need for clinician education regarding vitamin B12 monitoring procedures. Focused education could help clinicians incorporate current recommendations into practice and aid in identifying patients at high risk for vitamin B12 deficiency. Survey results were also indicative of the need to educate clinicians about utilizing the EMR to improve vitamin B12 monitoring procedures. The results of this study can be used to support data-guided initiatives that focus on increasing the rate of vitamin B12 monitoring in primary care settings.

Limitations

This study had several limitations, including a small sample size with limited demographic diversity. The sample was a convenience sample, with a total of 7 participants, from one primary care clinic. It would be difficult to generalize these results to other clinicians in primary care settings. Second, the findings of this project relied on self-reported data from participants. Since results were limited to self-report, there was a chance for over or under-reporting and potential for response bias. Third, this study did not isolate responses dependent on the clinician role, therefore, the researcher was unable to determine if the impact was different for various roles (i.e., medical doctor vs. advanced practice provider vs. registered nurse). Future research could prepare for these limitations by having a larger sample size from several primary care settings. Isolating participant responses to only comprise primary care providers would help distinguish the need for provider education and change to current patient care processes.

Conclusions

The revised standards for quality improvement reporting excellence (SQUIRE 2.0) were used as a framework for reporting this project. The purpose of this project was to address poorly defined objectives and operating procedures regarding vitamin B12 screening and treatment in type II diabetic patients prescribed metformin. Clinician staff within a primary care clinic were given focused education regarding metformin-induced vitamin B12 deficiency, current ADA recommendations and a method to increase screenings. This study measured the clinician's perceptions surrounding vitamin B12 screening practices via a pre- and post-survey intervention. The intent of the education was to promote a greater understanding of metformin's potential to provoke vitamin B12 deficiency and measure clinician perceptions about the importance of using an EMR-based alert to ensure routine monitoring in diabetic patients prescribed metformin. The

findings of this study may support performance improvement efforts surrounding vitamin B12 monitoring in primary care settings. Future research that assesses a longitudinal survey of vitamin B12 monitoring would be valuable in describing the preferred interval for monitoring and allow for the development of a standardized vitamin B12 screening and treatment algorithm.

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