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METFORMIN-INDUCED VITAMIN B12 DEFICIENCY IN CRITICALLY ILL PATIENTS: A RETROSPECTIVE ANALYSIS AT QUEEN ALIA HEART INSTITUTE

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ABSTRACT

1. Introduction: Metformin is a widely prescribed medication for type 2 diabetes mellitus, known for its efficacy in glucose control and relatively low side effect profile. However, long-term Metformin therapy has been associated with vitamin B12 deficiency, posing concerns for patient's neurological and hematological health. Understanding the impact of Metformin on vitamin B12 levels is crucial, especially in intensive care unit (ICU) patients who are already at higher risk for complications related to nutritional deficiencies. This study aims to investigate the relationship between Metformin use and vitamin B12 levels in ICU patients at the Queen Alia Heart Institute, Jordanian Royal Medical Services (JRMS), from 2019 to 2021.

2. Objective: The primary objective of this study is to evaluate the average vitamin B12 levels in ICU patients treated with Metformin during the specified three-year period. Secondary objectives include analyzing differences in vitamin B12 levels between male and female patients and different age groups and discussing the clinical implications of vitamin B12 deficiency in ICU patients.

3. Methodology: This retrospective study will utilize patient data from the ICU at the Queen Alia Heart Institute/JRMS. A sample of 80 patients, comprising an equal distribution of 40 males and 40 females, will be analyzed. Extracted data will include patient demographics (age, gender) and vitamin B12 levels measured in picograms per milliliter (pg/mL). Statistical analysis, including descriptive statistics and comparative analyses, will be used to evaluate trends and correlations in vitamin B12 levels among ICU patients receiving Metformin therapy.

KEYWORDS: Metformin, Vitamin B12, Critical Care, ICU Patients, Retrospective Analysis, Queen Alia Heart Institute, Gender Disparities, Age Factors, Nutritional Management.

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1. INTRODUCTION

Background: Owing to its effectiveness in reducing blood glucose levels and its very low adverse effect profile, Metformin is a key component in the treatment of type 2 diabetes mellitus and is frequently recommended. Metformin, which was first identified in the 1920s and put into clinical use in the 1950s, largely reduces the amount of glucose produced in the liver by blocking hepatic gluconeogenesis. It also improves peripheral tissue insulin sensitivity, which makes it a useful tool for managing hyperglycemia[1].

Long-term Metformin therapy has a number of negative effects despite its benefits, however vitamin B12 insufficiency is among those that should be especially concerned. Cobalamin, often known as vitamin B12, is a water-soluble vitamin that is vital for brain health as well as the synthesis of DNA and red blood cells. Fish, meat, poultry, eggs, milk, and milk products are among the animal products that naturally contain it. The synthesis of DNA and RNA, the body's genetic material, as well as the maintenance of healthy nerve cells depend on vitamin B12[2].

Mechanism of Metformin-Induced Vitamin B12 Deficiency: The specific processes behind the widely recognized association between vitamin B12 deficiency and Metformin use remain unclear. Several hypotheses have been proposed[1,3]:

1. Modified Small Bowel motility: Metformin may cause gastrointestinal motility to change, which could result in an overabundance of bacteria in the small intestine. This overgrowth may reduce the availability of vitamin B12 by competing with the host for it.
2. Interference with Absorption: The calcium-dependent membrane activity of the vitamin B12-intrinsic factor complex in the terminal ileum may be disrupted by Metformin, which could result in malabsorption.
3. Effect on Intrinsic Factor: Research indicates that Metformin may have an impact on how well vitamin B12 binds to intrinsic factor, a stomach-secreted protein necessary for the small intestine to absorb vitamin B12.

Clinical Consequences of Vitamin B12 Deficiency: A lack of vitamin B12 can cause a variety of neurological and hematological conditions. Megaloblastic anemia, a condition marked by the presence of huge, irregular red blood cells, is one of the hematological symptoms. More mild and diverse neurological symptoms include tingling and numbness in the hands and feet, balance issues, depression, disorientation, dementia, memory loss, and discomfort in the mouth or tongue. Since diabetic neuropathy and these symptoms might coexist, it's critical to distinguish between the two in order to administer the proper care[4,5].

Importance of Vitamin B12 in ICU Patients: Critical illness, elevated metabolic needs, and restricted nutritional intake are among the many factors that put patients confined to intensive care units (ICUs) at risk for nutritional deficiencies. ICU patients frequently get a wide range of medical treatments, including prescription drugs that may have an impact on their nutritional status. Furthermore, the stress of a serious illness can cause catabolic states, which raise the body's need for vital minerals and vitamins like vitamin B12[6].

Rationale for the Study: Since patients in the intensive care unit (ICU) are already more likely to have difficulties from nutritional deficiencies, it is especially crucial to comprehend how Metformin affects vitamin B12 levels in these patients. The Queen Alia Heart Institute, which is part of the Jordanian Royal Medical Services (JRMS), offers a distinctive environment for researching this link because it treats critically ill patients comprehensively and uses Metformin extensively to manage diabetes.

Study Objectives: This study aims to:

1. Evaluate the average vitamin B12 levels in ICU patients treated with Metformin at Queen Alia Heart Institute from 2019 to 2021.
2. Analyze the differences in vitamin B12 levels between male and female patients.
3. Discuss the clinical implications of vitamin B12 deficiency in ICU patients and provide recommendations for monitoring and management.

Research Questions: The primary research questions this study seeks to address are:

1. What are the average vitamin B12 levels in ICU patients treated with Metformin?
2. Are there significant differences in vitamin B12 levels between male and female patients?
3. What are the potential clinical implications of these findings for the

management of ICU patients on Metformin therapy?

Significance of the Study: The importance of this study lies in its emphasis on the necessity of closely monitoring vitamin B12 levels in patients receiving Metformin in the intensive care unit. By identifying and treating vitamin B12 insufficiency early on, major neurological and hematological consequences can be avoided, leading to better patient outcomes. Additionally, the study can add insightful information to the body of knowledge, assisting medical professionals in improving the care of diabetes patients in critical care environments. The study intends to improve clinical procedures and guarantee improved nutritional management for ICU patients receiving Metformin medication by identifying trends and correlations.

2. METHOD

Study Design: This retrospective observational study was conducted using patient data from the ICU at Queen Alia Heart Institute, JRMS. The study focused on vitamin B12 levels in patients treated with Metformin over three years (2019-2021).

Data Collection: Data were extracted from electronic medical records, including patient age, gender, year of admission, and measured vitamin B12 levels (pg/mL). The sample comprised 40 male and 40 female patients.

Statistical Analysis: Descriptive statistics, including mean, and median of vitamin B12 levels, were calculated. Comparative analyses between genders and across different years were performed. Data were analyzed using statistical software to identify trends and correlations.

3. RESULTS

Vitamin B12 Levels: The vitamin B12 levels of the patients were recorded over three years, from 2019 to 2021. The data was analyzed to understand the trends and variations in vitamin B12 levels among ICU patients on Metformin therapy (Table 1 and Table 2).

Table 1: The levels of vitamin B12 among female patients

Female Patients				
Year	**Number of Patients**	**Levels Range**	**Mean**	**Median**
2019	17	64-144	104.7	109
2020	7	149-179	165.5	164
2021	16	184-259	218.6	224

Table 2: The levels of vitamin B12 among male patients

Male Patients				
Year	**Number of Patients**	**Levels Range**	**Mean**	**Median**
2019	15	59-309	172.2	74
2020	7	234-557	276.3	259
2021	18	209-284	240.1	244

Demographic Analysis

Eighty ICU patients from the Queen Alia Heart Institute were involved in the study; 40 of them were female and 40 of them were male. The patients ranged in age from 68 to 87 years for the male patients and from 43 to 89 years for the female patients. This wide age range offers a thorough grasp of how Metformin affects vitamin B12 levels in various age groups in a critical care environment (Table 3).

Table 3: frequency and distribution of patients by gender and age

	Age Range	Average Age
Female Patients	43-89 years	69.1 years
Male Patients	68-87 years	76.3 years

Gender Analysis: Throughout the study period, male patients generally had greater B12 levels than female patients, with this difference being most evident in 2020, according to the data (Table 4).

Table 4: The levels of vitamin D among patients by gender and year

	Mean B12 Level (pg/mL)	
Year	Female Patients	Male Patients
2019	93.41	214.29
2020	164	293
2021	230.19	239.06

As shown in the following figure, it's evident that male patients generally have higher mean B12 levels compared to female patients across all three years (Figure 1).

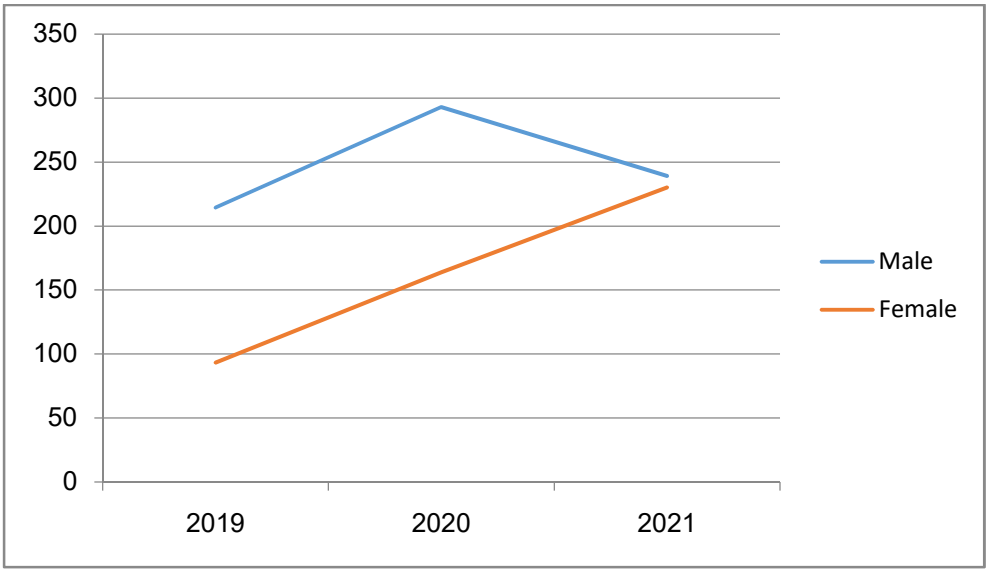

Figure 1: The vitamin B12 levels among patients by gender over study years

Age Analysis: Male patients have an average age of 76.3 years compared to female patients' 69.1 years, although this difference is not directly related to the B12 levels. Given that elderly people may have differing vitamin B12 requirements or absorption rates, this age difference may have an impact on B12 levels (Table 5).

Table 5: The distribution of age of patients per gender

	Age Range	Average Age
Female Patients	43-89 years	69.1 years
Male Patients	68-87 years	76.3 years

Interpretation:

1. Gender Differences: There may be gender-based differences in B12 metabolism or absorption, as seen by the higher mean B12 levels in male patients as compared to female patients.
2. Age Influence: Given that age-related factors may affect B12 absorption or utilization, the average age difference between male and female patients may account for some of the variations in B12 levels. Extensive investigation of the correlation among age, gender, and B12 levels in intensive care unit (ICU) patients may yield significant knowledge for improving patient care and nutritional strategies.

In summary, research is necessary to clarify the precise processes underlying these connections and to create individualized therapies for optimizing B12 status in critically ill populations, even though gender and age may have an impact on vitamin B12 levels in ICU patients.

4. DISCUSSION

Interpretation of Results

Gender Disparities in B12 Levels: The results show significant variations in vitamin B12 levels between ICU patients who are male and female. Male patients had mean B12 levels that were repeatedly higher than those of female patients during the course of the trial. This finding is consistent with the body of research pointing to possible gender-based variations in the metabolism or absorption efficiency of vitamin B12[7,8].

Age Influence on B12 Levels: Although it was not evaluated specifically in this study, B12 levels may be impacted by the average age difference between male and female patients. Age-related alterations in gastrointestinal physiology, such as reduced stomach acid secretion and altered intrinsic factor production, are common in the elderly and may have an impact on the absorption of B12[9,10]. To get further insight into the intricate details of B12 metabolism in intensive care unit patients, future studies should investigate the relationship between age, gender, and B12 levels.

Clinical Implications

Importance of Nutritional Monitoring: The gender differences in B12 levels that have been seen highlight the significance of routine nutritional monitoring in intensive care unit patients, especially those who are on long-term Metformin medication. In order to quickly diagnose and treat B12 deficiency, healthcare providers should be cautious while evaluating the status of B12, particularly in sensitive populations like older adults and females. Standardized B12 screening procedures and customized supplementation plans might be necessary to improve patient outcomes and avoid harmful neurological and hematological consequences[11].

Tailored Intervention Strategies: The variability observed in B12 levels among male patients underscores the necessity for customized intervention approaches aimed at reducing the likelihood of insufficiency. Thorough nutritional evaluations, including food records and prescription analyses, might assist in pinpointing modifiable elements impacting the absorption and utilization of vitamin B12. Furthermore, multidisciplinary partnerships between pharmacists and dietitians are critical to optimizing nutrient delivery in intensive care units and creating individualized supplementation regimens.

Limitations and Future Directions

Limitations of the Study: The small sample size and retrospective nature of this study may limit how broadly the results may be applied. The insufficiency of comprehensive data regarding the dosage of Metformin, length of therapy, and vitamin B12 intake through diet further restricts the ability to evaluate outcomes. Furthermore, a thorough knowledge of the determinants impacting B12 levels in ICU patients is hindered by the lack of data on other potential confounding variables, such as co morbidities and concurrent medications.

Future Research Directions: Subsequent investigations ought to concentrate on lessening the constraints of our study and augmenting our understanding of the correlation among Metformin usage, gender, age, and B12 levels in intensive care unit patients. Gender differences in B12 metabolism and absorption need to be further clarified by prospective longitudinal studies using larger sample sizes and thorough data collection techniques. In addition, to improve clinical outcomes and patient care in critical care settings, interventional trials evaluating the effectiveness of specific nutritional interventions such as B12 supplementation strategies are necessary.

In conclusion, The complicated interactions between vitamin B12 levels, age, gender, and Metformin use in ICU patients are highlighted by this study's result. Although B12 levels are

generally greater in male patients than in female patients, the variation in B12 levels highlights the necessity of customized nutritional management plans. Healthcare professionals might enhance B12 status and improve outcomes for ICU patients using Metformin medication by addressing the limitations of this study and adopting a multidisciplinary approach to patient care.

5. CONCLUSIONS

This study clarifies the complex interactions among vitamin B12 levels, age, gender, and Metformin use in intensive care unit patients. The results offer important insights into the dietary dynamics of critically ill patients, despite the limitations associated with its retrospective methodology and small sample size.

Key Findings

Gender Disparities: Gender-specific characteristics should be taken into account when developing nutritional management strategies, as evidenced by the gender differences in vitamin B12 levels that have been reported. Male patients have consistently shown higher mean B12 levels than female patients.

Age-Related Considerations: The average age difference between patients who are male and female emphasizes how age affects the metabolism and absorption of B12. Targeted nutritional treatments may be necessary to prevent B12 shortage in elderly individuals, as they frequently encounter age-related physiological changes that limit the absorption of vitamins.

Clinical Implications

Individualized Nutritional Monitoring: The results highlight the need of customized nutritional monitoring for patients in intensive care units, especially those on long-term Metformin medication. Prioritizing routine B12 screening and taking age and gender specific characteristics into account when determining nutritional status and supplementation regimens are important recommendations for healthcare practitioners to make[12].

Multidisciplinary Approach: To optimize B12 status and improve clinical outcomes in critical care settings, healthcare practitioners from multiple disciplines must collaborate in a multidisciplinary approach to patient care. Personalized nutritional therapies that are suited to the individual needs of every patient are developed in collaboration with dietitians, pharmacists, and other members of the healthcare team.

Future Directions

Addressing Limitations: The retrospective design and limited sample size, of this study are two of its shortcomings that should be addressed in future research projects. Prospective longitudinal studies that employ more extensive data collection techniques and larger cohorts are necessary to confirm the observed trends and clarify the underlying mechanisms causing age- and gender-related differences in B12 levels.

Interventional Trials: To improve clinical results and patient care in intensive care units, interventional trials evaluating the effectiveness of specific nutritional procedures, such as B12 supplementation , are necessary. The most beneficial supplementation regimens should be found and their effects on B12 status and patient prognosis should be assessed in these trials[6].

This study's findings emphasize the significance of proactive nutritional management for intensive care unit (ICU) patients and the demand for customized strategies that take age and gender specific factors into account. Healthcare practitioners can enhance patient outcomes and quality of treatment in critical care settings by addressing the complicated processes of B12 metabolism and absorption in critically ill patients. In order to improve patient care practices in intensive care units and expand our knowledge of nutritional dynamics, cooperation between medical professionals and ongoing research projects are crucial.

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