AlQalam
Alq J Med App Sci
https://journal.utripoli.edu.ly/index.php/Alqalam/indexeISSN 2707-7179

Original article

Prevalence of Vitamin B_{12} Deficiency in Libyan Type 2 Diabetic Patients Treated with Metformin

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ARTICLE INFO

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Received: *26-08-2024*
Accepted: *22-10-2024*
Published: *08-10-2024*

Keywords. *Diabetes Mellitus, Metformin, Vitamin B12.*

ABSTRACT

Metformin is the most-used drug in type 2 diabetes mellitus management and its long-term use may consequent to vitamin B_{12} deficiency. The lack of studies from Libya investigating the risk of association between these two presents a gap in our understanding of this issue. Our study aimed to estimate the prevalence of vitamin B_{12} deficiency in metformin treated diabetic patients and non-metformin treated patients and its correlation with diabetic duration and gender. Specifically, we tested the hypothesis that T2DM patients treated with metformin exhibit a decrease in vitamin B_{12} levels and are considered at risk for developing B_{12} deficiency depending on the diabetic duration and metformin use. A total of 81 samples of metformin treated diabetic patients (N=58) and non-metformin diabetic treated patients (N=23) were collected and underwent assessment of F.B.S, HbA1c and B12 level. The total mean age was 46.4± 8.27 (47.25± 9.22 for males and 45.55± 7.32 for males respectively). Total mean and standard deviation of blood glucose level was 173.93± 29.87 mg/dl (158.25± 27.35 and 184.18± 27.06 for males and females, respectively). Total mean and standard deviation HbA1c level was 6.81± 1.98% (5.94± 1.31 and 7.37± 2.14 for males and females, respectively). Total mean and standard deviation of vitamin B12 level was 435.53 ± 251.31 (575.62 ± 250.21 and 342.76± 205.91 for males and females, respectively). Our study indicated that the shortage of vitamin B12 was generally found in our population, insufficient vitamin B12 level was frequently reported in metformin administration to patients with T2DM and could progress into deficiency. Further larger studies are required to assess vitamin B12 level in those patients.

Cite this article. *Gamag E, Alsalmi W. Prevalence of Vitamin B12 Deficiency in Libyan Type 2 Diabetic Patients Treated with Metformin. Alq J Med App Sci. 2024;7(4):1072-1076. https://doi.org/10.54361/ajmas.247422*

INTRODUCTION

Diabetes mellitus is a primary public health concern with increasing prevalence and long-lasting complications. Despite the great advances in medical and diabetes sciences, it is still an incurable life-long disease leading to a major public panic, and swiftly growing among different age groups of both men and women [1]. The global prevalence of diabetes is expected at 7.5% (374 million) in 2019 and is projected to reach 8.0% (454 million) by 2030, and the number of people with diabetes is expected to reach to 693 million by 2045 [2]. More importantly, it is reported that Libya has the highest prevalence in North Africa and among Arabic nations, in a study included 4000 individuals, 73% of the

individuals are diabetic or at high risk to have diabetes [3]. Diabetes has been classified into two fundamental categories: insulin-dependent diabetes mellitus (T1DM), and non- insulin-dependent diabetes mellitus (T2DM)[2].

Metformin is the most commonly prescribed oral anti-diabetic drug in patients with T2DM[4]. Metformin, which belongs to biguanide group of drugs has been the treatment of choice of non- insulin-dependent diabetes mellitus [1]. However, long-term usage of metformin is a known pharmacological cause of Vitamin B_{12} deficiency[4]. The mechanism by which metformin causes vitamin B_{12} deficiency has not been clearly understood; however, changes in small bowel motility as a result of hypocalcemia that leads to enhancement of bacterial overgrowth with substantial vitamin B_{12} deficiency and suppression of vitamin B_{12} absorption are proposed mechanisms [5].

Increasing evidences shown a strong correlation between prolonged usage of metformin and vitamin B_{12} deficiency. It may affect the calcium dependent absorption of vitamin B_{12}, the serum vitamin B_{12} values was showed to be inversely related to the dose and duration of metformin usage [1]. The diagnostic criteria for vitamin B12 deficiency are based on a decreased serum concentration of vitamin B12 combined with hematological and/or clinical signs of vitamin B12 deficiency [6]. Furthermore, measurements of metabolites such as methylmalonic acid and homocysteine have been shown to be more sensitive in the diagnosis of vitamin B_{12} deficiency than measurement of serum B_{12} levels alone [7].

The association of metformin with vitamin B_{12} deficiency has been widely studied, its duration of use and dose of metformin have also been shown to influence vitamin B_{12} levels. While some clinical studies showed that metformin is a leading cause of decreased vitamin B_{12} levels, other studies did not find this to be significant. A meta-analysis of six randomized controlled trials showed a crucial decrease in vitamin B_{12} levels stimulated by metformin and recommended that this may be dose dependent [8]. Another published study reported that Korean patients on higher doses (metformin >1g daily) and with longer treatment duration (>4 years) were more likely to exhibit a reduction in vitamin B12 levels[9]. However, no crucial correlation between serum B_{12} level among patients treated with metformin in different doses was recently reported [10].

The high incidence of DM and elevated morbidity rate of vitamin B_{12} deficiency with metformin use, which has been reported in several studies worldwide, in addition to the lack of studies from Libya investigating the association between these two presents a gap in our understanding of this issue. Therefore, we aimed to estimate the prevalence of vitamin B_{12} deficiency in metformin-treated T2DM patients and non-metformin treated patients and its association with diabetic duration and gender. Specifically, we tested the hypothesis that T2DM patients treated with metformin will exhibit a decrease in vitamin B_{12} levels and are considered at risk for developing B_{12} deficiency depending on the diabetic duration and metformin use.

METHODS

Study design

A cross sectional study was conducted in western Libya particularly in Sabrathra and Surrman provinces to estimate the prevalence of vitamin B_{12} deficiency in metformin-treated T2DM patients and non-metformin treated patients.

Data collection

Data were collected from private laboratories in the city of Sabratha and Surman-Libya. A total of 81 samples of T2DM patients who visited Alweqaia laboratory in Sabratha and Central laboratory in Surman between February and July were included in our study. Questionnaires were completed and participants with T2DM treated with metformin as well as those not on metformin treatment underwent assessment of FBS, HbA1c and B_{12} level.

Ethical consideration

This work was established according to medical research ethics, patients were informed about the study and agreed to participate.

Statistical analysis

The results were analyzed using SPSS software package version 20 to apply one way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

RESULTS

In the present study 81 type 2 diabetes mellitus patients were included for both sexes (32 males and 49 females) (Figure1).

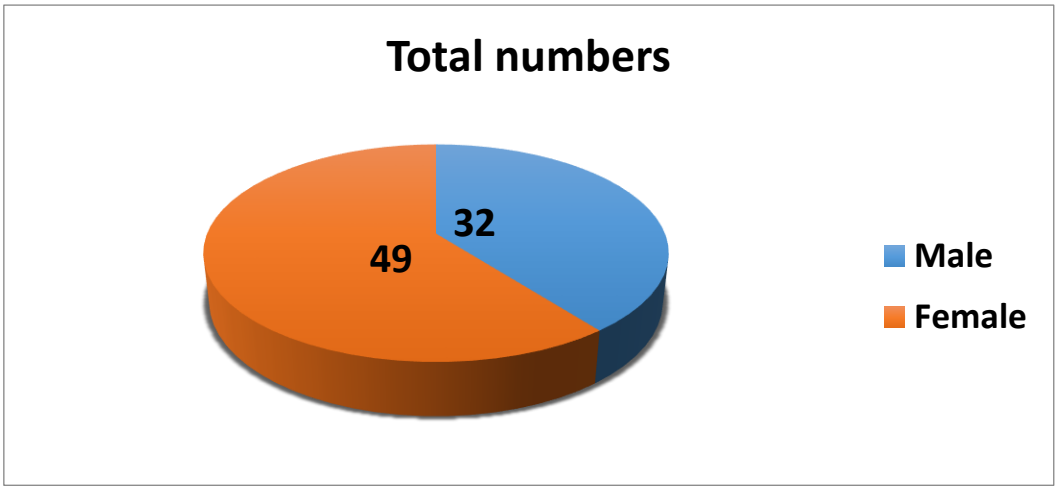

Figure 1. The total numbers of males and females

Out of 92 sample size 81 subjects were recruited of whom 23 were not on metformin supplementation and 58 were on metformin supplementation. The total mean age was 45.68 ± 7.80 for metformin taken patients and 47.56± 8.89 for patients not on metformin. Vitamin B_{12} in patients on metformin was 377.20 ±219.74 whereas those not on metformin vitamin B_{12} level was 582.60±270.12 (Table 1).

Table 1. Distribution of biochemical parameters (blood glucose, HbA1c and vitamin B12) in accordance to metformin intake.

Parameters	Metformin taken N= 58	Metformin non taken N= 23	P. Value
Age	45.68 ± 7.80	47.56± 8.89	0.3
Duration of diabetes	9.60 ±5.29	4.82 ± 2.60	< 0.01
Blood glucose levels mg/dl	181.10±30.46	155.86±19.07	< 0.01
HbA1c %	6.92±1.90	6.51±2.17	0.40
Vitamin B12	377.20 ±219.74	582.60±270.12	< 0.01

The present study shows total means and standard deviations of biochemical parameters of blood glucose, HbA1c and vitamin B_{12}. Total mean age was 46.4± 8.27 (47.25± 9.22 or males and 45.55± 7.32 for males and females, respectively). Total mean and standard deviation of blood glucose level was 173.93± 29.87 mg/dl (158.25± 27.35 and 184.18± 27.06 for males and females, respectively). Total mean and standard deviation HbA1c level was 6.81± 1.98% (5.94± 1.31 and 7.37± 2.14 for males and females, respectively). Total mean and standard deviation of vitamin B_{12} level was 435.53± 251.31 (575.62± 250.21 and 342.76± 205.91 for males and females, respectively) (Table 2).

Table 2. The means and standard deviations of biochemical parameters (blood glucose, HbA1c and vitamin B12) in males and females.

Parameters	Total mean and standard deviation	Male Mean± SD	Female Mean±SD	P. Value
Age (years)	46.4± 8.27	47.25± 9.22	45.55± 7.32	0.84
Blood glucose mg/dl	173.93± 29.87	158.25± 27.35	184.18± 27.06	< 0.01
HbA1c %	6.81± 1.98	5.94± 1.31	7.37± 2.14	< 0.01
Vitamin B12	435.53± 251.31	575.62± 250.21	342.76± 205.91	< 0.01

Our results also revealed to the distribution of blood glucose, HbA1c and vitamin B12 levels in accordance to the duration of diabetes (< 5 years, 5-10 years and > 10 years). Mean blood glucose levels were 147.18 ± 15.28, 177.25 ± 15.42 and 197.37 ± 30.80 (< 5 years, 5-10 years and > 10 years, respectively). Mean HbA1c levels was 5.25 ± 0.75, 7.43 ± 1.90 and 7.74 ± 2.02 (< 5 years, 5-10 years and > 10 years, respectively). Mean vitamin B12 levels was 711.85 ± 239.64, 371.85 ± 54.91 and 222.88 ± 58.53 (< 5 years, 5-10 years and > 10 years, respectively) (Table 3).

Table 3. Distribution of biochemical parameters (blood glucose, HbA1c and vitamin B12) in accordance to the duration of diabetes mellitus.

Parameters	Duration of diabetes mellitus			P value
	< 5 years N = 27 2.66 ± 1.07	**5-10 years N = 27 7.59 ± 1.47**	**> 10 years N = 27 14.48 ± 2.25**	
Blood glucose levels mg/dl	147.18 ±15.28	177.25 ±15.42	197.37 ±30.80	**< 0.01**
HbA1c %	5.25 ±0.75	7.43 ±1.90	7.74 ±2.02	**< 0.01**
Vitamin B12	711.85 ±239.64	371.85 ±54.91	222.88 ±58.53	**< 0.01**

DISCUSSION

In our study we observed a significant correlation between metformin administration and vitamin B_{12} insufficiency. Patients treated with metformin exhibit significantly lower B_{12} level (377.20) than non-metformin treated patients (582.60) with p value <0.01. These findings were consistent with a previously published data in which a remarkable decrease in vitamin B_{12} level with metformin treated patients was reported. One of these studies showed a crucially increased prevalence of vitamin B_{12} deficiency in patients with T2DM treated with metformin [8]. A recent study also reported a decreased vitamin B_{12} level and an increased risk of vitamin B_{12} deficiency with metformin intake to patients with T2DM [2]. Long term duration and accumulative dose of metformin significantly increases the risk of vitamin B_{12} deficiency [11]. On the other hand, no crucial correlation between serum B_{12} level among patients treated with metformin in different doses was recently reported [10].

In the present study, a normal vitamin B_{12} concentration (more than 220pg/ml) in both male and female was identified despite the remarkable difference in vitamin B_{12} concentration between genders. Females exhibit a decreases vitamin B_{12} level (342.76) compared to males B_{12} level (575.62) with P value <0.01. These results were concur with a recent study which showed a higher prevalence of vitamin B_{12} deficiency in woman [11]. In addition, a previous study conducted in the city of Benghazi showed a noticeably lower vitamin B_{12} level in females than males [12]. However, these findings were different to other study in which female patients found to have higher levels of vitamin B_{12} compared to male[13]. Most studies do not describe the differences between vitamin B_{12} levels according to gender and no physiological explanation was indicated for these results. Our study did not demonstrate any noticeable correlation between vitamin B_{12} levels and age.

Our study demonstrated that the risk of cobalamin deficiency is correlated with an increase in diabetic duration with P value <0.01. Patients with diabetes longer than ten years exhibit a significant lower B_{12} levels (222.88) in comparison to those less than 5 years diabetic patients (711.85). Moreover, patients with diabetes 5-10 years duration showed a decrease vitamin B_{12} level (371.85). Our findings clearly showed that a potential vitamin B_{12}deficiency increases with long term diabetic duration, these finding were consistent with a study which demonstrated that the risk of developing vitamin B_{12} deficiency is correlated with an increase in diabetic duration [10].

Several factors are contributed to vitamin B_{12} deficiency including insufficient nutrition and acquired or inherited defects which disrupt B_{12} absorption and processing pathway. It has been widely explained that the interference by metformin on calcium dependent membrane action responsible for vitamin B_{12}intrinsic factor absorption in the terminal ileum[8]. Additionally, vitamin B_{12} malabsorption alterations, alterations of the motility of small intestinal with consequent bacterial overgrowth, or effects on inhibition of vitamin B_{12} intrinsic factor secretion are participates in metformin induced B_{12} deficiency [13].

CONCLUSION

This study indicated that the shortage of vitamin B_{12} was generally found in our population, insufficient vitamin B_{12} level was frequently reported in metformin administration to patients with T2DM and could progress into deficiency. vitamin B_{12} deficiency is influenced by the occurrence and duration of diabetes. Routine monitoring for vitamin B_{12} serum levels is needed to patients with T2DM, prolonged T2DM duration. Further studies are needed to assess the correlation between metformin duration and dose.

Conflict of interest. Nil

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مدى انتشار نقص فيتامين ب 12 لدى مرضى السكري من النوع الثاني الذين يعالجون بالميتفورمين

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المستخلص

يعتبرالميتفورمين من أكثرالادوية استخداما في علاج مرض السكري من النوع الثاني لكن استخدامه على المدى الطويل قد يؤدي إلى نقص فيتامين ب $_{12}$. إن عدم وجود دراسات من ليبيا تبحث في خطر الارتباط بين هذين الأمرين يمثل فجوة في فهمنا لهذه الموضوع. هدفت دراستنا إلى تقدير مدى انتشار نقص فيتامين ب $_{12}$ لدى مرضى السكري المعالجين بالميتفورمين والمرضى غير المعالجين بالميتفورمين وارتباطه بمدة الإصابة بالسكري والجنس. على وجه التحديد، قمنا باختبار الفرضية القائلة بأن مرضى السكري الذين عولجوا بالميتفورمين يظهرون انخفاضًا في مستويات فيتامين ب $_{12}$ ويعتبرون معرضين لخطر الإصابة بنقص ب $_{12}$ اعتمادًا على مدة الإصابة بالسكري واستخدام الميتفورمين. تم جمع 81 عينة من مرضى السكري منهم 58 يعالجون بالميتفورمين و23 عسنة لايعالجون بالميتفورمين. بلغ متوسط العمر الإجمالي 46.4±8.27 (47.25±9.22 للذكور و45.55±7.32 للاناث على التوالي). كان المتوسط الإجمالي والانحراف المعياري لمستوى الجلوكوز في الدم 173.93 ± 29.87 ملغم / ديسيلتر (158.25 ± 27.35 و 184.18 ± 27.06 للذكور والإناث على التوالي). كما أن المتوسط الاجمالي والانحراف المعياري لمستوى كان HbA1c 6.81 (5.94 ± 1.31) ٪1.98 ±و 7.37 ± 2.14 للذكور والإناث على التوالي. كماأن المتوسط الإجمالي والانحراف المعياري لمستوى فيتامين ب 12 435.53 ± 251.31 (575.62 ± 250.21 و 342.76 ± 205.91 للذكور والإناث على التوالي). أشارت دراستنا إلى أن النقص في فيتامين ب12 موجود بشكل عام في مجتمعنا، وقد تم الإبلاغ عن عدم كفاية مستوى فيتامين ب$_{12}$ بشكل متكرر عند تناول الميتفورمين للمرضى الذين يعانون من السكري ويمكن أن يتطور إلى نقص حاد.

الكلمات الدالة. مرض السكري، الميتفورمين، فيتامين ب$_{12}$.