Prevalence of vitamin B12 deficiency in type 2 diabetes patient treated with metformin

Mohammad B. Jajah (1)
Amjad A. Althagafi (2)
Norah M. Alamri (2)
Reham M. Altowairqi (2)
Sarah S. Binbaz (2)
Hadeel S. Ashour (2)

(1) Consultant Endocrinologist, Al- Hada Armed Forces Hospital, Taif city, Saudi Arabia
(2) Medical Intern, Taif city, Saudi Arabia

Corresponding author:
Amjad A. Althagafi
Medical Intern, Taif city,
Saudi Arabia
Tel.: 0507277519
Email: amjad.th@outlook.com

Received: November 2019; Accepted: December 2019; Published: January 1, 2020.
Citation: Mohammad B. Jajah, Amjad A. Althagafi, Norah M. Alamri, Reham M. Altowairqi, Sarah S. Binbaz, Hadeel S. Ashour. Prevalence of vitamin B12 deficiency in type 2 diabetes patient treated with metformin. World Family Medicine. 2020; 18(1): 54-59. DOI: 10.5742MEWFM.2020.93730

Abstract

Background: Metformin-induced vitamin B12 deficiency was shown by several studies with a prevalence estimate ranging from 5.8% to 52%.

Objectives: This study aimed to assess the prevalence of vitamin B12 deficiency in patients with Type 2 diabetes mellitus (T2DM) on metformin.

Methods: A cross-sectional observational study was done on 347 type 2 diabetic patients who were using the drug 'metformin' for at least six months and who attended a specialty diabetic clinic at Taif city of Saudi Arabia. Information on patients age, gender, type of metformin, assay results for Vitamin B12, and medical history were obtained. Vitamin B12 levels in serum were tested.

Results: The mean age of the patients was found to be 58.10 ± 14.31, and the mean Vitamin B12 level was found to be (464.99 ± 419). The prevalence of vitamin B12 deficiency among participants was 10.4%. Patients with borderline levels were approximately 20.2% and the remaining 69.5% had normal vitamin B12 levels. No statistically significant difference was found between different age groups according to the mean level of Vitamin B12. Those who were on Metformin 1 mg and Metformin 750 mg had a statistically significant higher percentage of those who had deficient Vitamin B12 (<200) than those on Metformin 500 mg.

Conclusions: Vitamin B12 supplementation should be prescribed for diabetic patients to prevent the occurrence of vitamin B12 deficiency complications.

Key words: Prevalence, vitamin, B12, deficiency, diabetes, metformin

Introduction

Diabetes mellitus is a metabolic disorder in which there is a higher blood glucose level than normal, which produces symptoms like polyuria, polydipsia and polyphagia and may produce complications like kidney problems, heart attack, blindness, nerve problems, loss of limbs, and sexual dysfunction (1). Metformin (a biguanide derivative), is the most commonly prescribed anti-diabetic drug and is associated with certain adverse effects, mainly lactic acidosis (2). Metformin reduces these complications by controlling blood glucose levels and restores the body's response to insulin (3).

Vitamin B12 plays a fundamental role in biological activities including DNA synthesis, haemopoesis and neurological functions. Hence its deficiency may cause haematological and neuro-cognitive dysfunctions (4). Many research studies have suggested an association between Metformin use and vitamin B12 deficiency (5,6,7).

The first evidence of vitamin B12 malabsorption in patients who were under Metformin was reported by Berchtold et al in 1969 (8). Although the association between long-term metformin use and low vitamin B12 levels has been shown, studies show that there are considerable variations in the prevalence estimates of metformin-induced vitamin B12 deficiency which ranges from 5.8% to 52% (9-13). These wide variations could be due to the differences in the associated factors such as patient's age, study settings, metformin dosage and duration of use etc. The exact mechanism of how metformin induces vitamin B12 deficiency is not clear, but currently the accepted explanation is interference of calcium dependent membrane at the terminal ileum, which is responsible for Vitamin B12 –intrinsic factor absorption. (14-15). This effect could be reversed with calcium supplementation (16).

In the Kingdom of Saudi Arabia, the effect of metformin in Vitamin B12 metabolism is poorly studied and there is lack of data regarding its deficiency. Hence this study aimed to assess the prevalence of vitamin B12 deficiency in patients with Type 2 diabetes mellitus (T2DM) on metformin and if the presence of vitamin B12 deficiency has a relationship with dose of metformin consumed.

Subjects and Methods

Study design and time frame: This study was a cross-sectional observational study done between March and May 2019.

Study setting: The study was done on patients attending a specialty diabetic clinic in Taif city of Saudi Arabia.

Sampling methodology: The study participants included Type 2 diabetic patients who were using the drug 'metformin' for at least six months. All ages and both genders were included. Patients who have or had previous history of pernicious anemia, alcoholism, gastrectomy, gastric bypass surgery, pancreatic insufficiency, malabsorption syndromes, and surgery involving small intestine or HIV infection were not included in our study. Patients who were on Vitamin B12 supplementation in any form for the last 6 weeks were also excluded from our analysis.

Study instrument: Information on patient's age, gender, type of metformin, assay results for Vitamin B12, medical history were obtained. Vitamin B12 levels in serum were tested after explaining the nature of the study and those who agreed to have the assay was performed in the laboratory of the study setting (clinics) after the concerned doctors requesting the same. Vitamin B12 levels were categorized into normal (>300 mg/dl), borderline (200-300 mg/dl) and deficient (<200 mg/dl) as suggested by Berg RL and Shaw GR (17).

Ethical considerations: Ethical clearance for the study was obtained from the Research Ethics Committee of Medical Services Department for Armed Forces Scientific Research Center and from Taif University. Patients were informed about the nature of study and consent was taken from all participants.

Statistical analysis: Data were analyzed using the SPSS statistical program version 23. (IBM Corp. USA). Categorical variables were expressed as number and frequencies and Chi-square test was used to assess the relationship between variables. Quantitative variables were presented as mean and standard deviation, and independent sample t- test and ANOVA test were used to assess the relationship between variables. A p-value of less than 0.05 was considered significant.

Results

Our cross-sectional study included a total of 347 patients who were on metformin for Type 2 diabetes mellitus (T2DM). We had 211 females and 136 male patients spread across different age groups (Figure 1, Figure 2). The mean age of the patients was found to be 58.10 ± 14.31, where females had a mean age of 56.27 ±13.9 and males mean age was 60.9 ± 14.4 (Table 1). The mean Vitamin B12 level was found to be 464.99 ± 419.00 where females had a mean level of 473.2 ±502.45 and males had a mean level of 452.13 ±238.70 (Table 2).

When the mean level of Vitamin B12 across different age groups was compared we didn't find any statistically significant differences (p>0.05). The mean level was found to be more in the age group of 61-89 years followed by 41-60 years (Table 3).

The vitamin levels were categorized into 'Normal (>300), Borderline (200-300) and Deficient (<200). When we assessed the relationship of the levels of Vitamin B12 with type of the dosage of Metformin used, we found that the 'Deficient levels (<200) were more in Metformin 1 mg and Metformin 750 mg than Metformin 500 mg and this had a statistically significant association (p<0.05) (Table 4).

When we compared levels of Vitamin B12 across different types of metformin consumed, it was found that the type metformin 1 gm had comparatively low levels of Vitamin B12 than other types and this was statistically significant ($p<0.05$). The mean level of Vitamin B12 in patients who are on Metformin 750 mg was about 430.6 ± 250.9 and in those who were on Metformin 500 mg was 520.8 ± 538.27.

Figure 1: Gender distribution of the participants

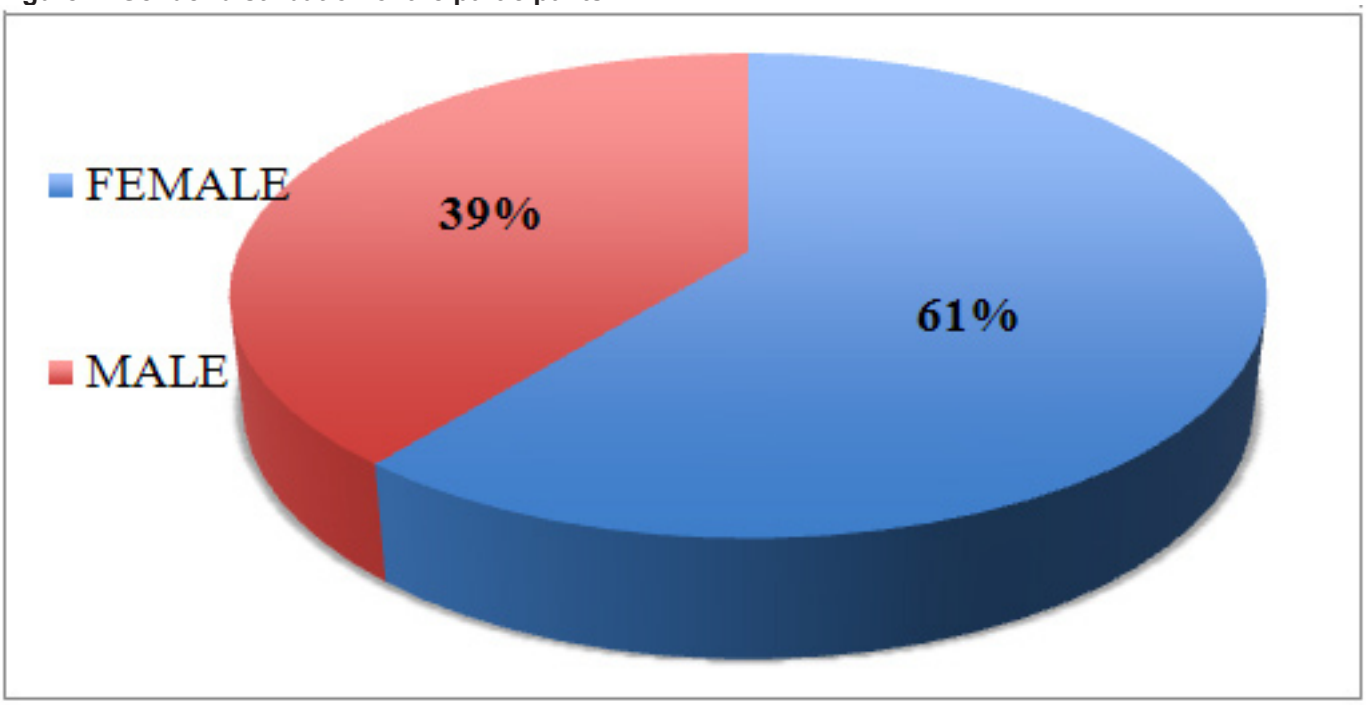

Figure 2: Age distribution of the participants

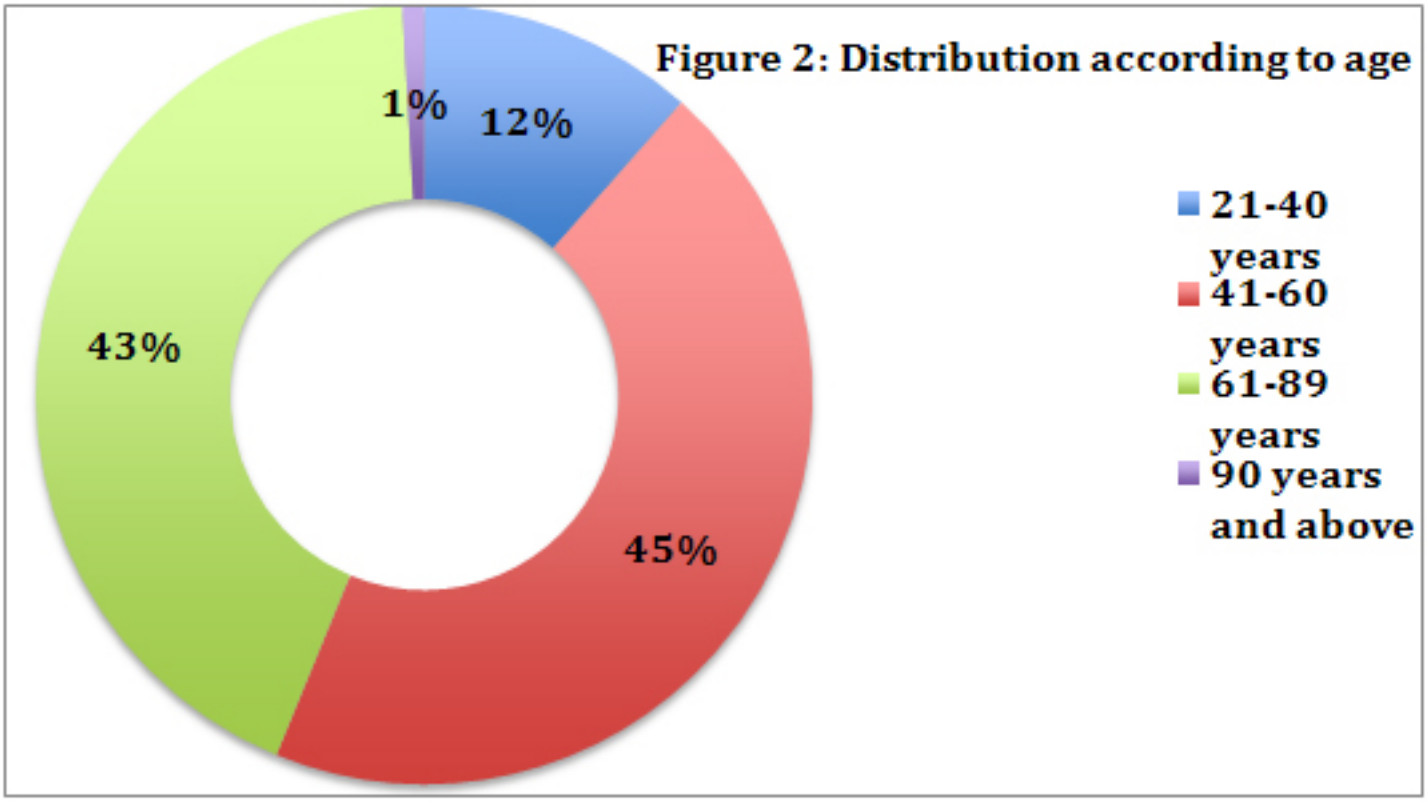

Table 1: Mean age of the participants

Gender	N	Mean	Std. Deviation	Minimum	Maximum
Female	211	56.27	13.929	21	103
Male	136	60.96	14.493	29	96
Total	347	58.10	14.317	21	103

Table 2: Mean vitamin B12 levels based on gender

Gender	N	Mean	Std. Deviation	Minimum	Maximum	Independent 't' test	
						t	p-value
Female	211	473.28	502.45	105	6001	0.459	0.647
Male	136	452.13	238.70	157	1683		
Total	347	464.99	419.00	105	6001		

Table 3: Comparison of vitamin B12 levels in different age groups

Age	N	Mean	Std. Deviation	Minimum	Maximum	ANOVA test	p-value
21-40	40	374.6	128.9	117.00	835.0	0.735	0.532
41-60	155	474.5	512.9	158.00	6001.0		
61-89	149	480.5	356.8	105.00	2778.0		
≥90	3	403.0	418.2	135.00	885.0		

Table 4: Relationship of drug used and vitamin B12 levels

Variable		Drug type			Total	Chi-square test	p value
		Metformin 500 MG Tablets	Metformin 750 MG XR Tablets	Metformin 1 GM Tablets			
Vitamin B12 Levels	Normal >300	130 (73.9%)	79(67.5%)	32(59.3%)	241 (69.5%)	11.7	0.019
	Borderline 200-300	35(19.9%)	25(21.4%)	10(18.5%)	70 (20.2%)		
	Deficient <200	11(6.3%)	13(11.1%)	12(22.2%)	36(10.4%)		
Total		176 (100%)	117(100%)	54 (100%)	347 (100%)		

Discussion

Studies have already shown that metformin use has an impact on the serum Vitamin B12 levels in type 2 DM patients (18,19). Our study evaluated whether there were any differences in the Vitamin B12 levels between three dosages of metformin oral drugs such as Metformin 500 mg, 750 mg and 1000 mg (1 gm).

The mean Vitamin B12 level in the study participants was found to be 473.28 ±502.45. A study done by Aroda VR et al. reported mean Vitamin B12 levels of 546 ± 337.2 in those who are at one-year follow up of metformin therapy and 615.9 ± 503.8 in those who were on 13-year metformin follow up (20). Another study done in South Africa reported a mean Vitamin B12 level of 260.6 ±163.7 those who are metformin therapy (21).

In our study, it was not surprising to note that the mean Vitamin B12 levels are more than the expected deficient or borderline levels as there are previous studies, which have also demonstrated similar findings (20,22). A study done in Saudi Arabia, which compared the Vitamin B12 levels between Metformin users and non-metformin users found that mean level in metformin users was 313.68 ±141.84 and in non-users, it was 365.37±189.88 (23). Even though the selected study patients did not consume any Vitamin B12 supplements; the diet of these people has not been recorded.

There could be a possibility that the usual diet of the patients may be the reason for comparatively high levels of serum vitamin B12 levels than the expected deficient levels. Food items like meat, fish, chicken; fortified cereals and dairy products are major sources of vitamin B12 (24,25) and most of the Saudi population follow a non-vegetarian diet which includes the above-mentioned food items which are rich in Vitamin B12 levels (26). When compared to non-vegetarians, the prevalence of vitamin B12 deficiency is high among vegetarians (27).

Our findings didn't find any gender-based differences in the vitamin B12 levels for those who are on metformin therapy. A Study done in one of the Middle Eastern countries has shown a mean deficiency level of 312.36 pmol/ in women and 284.31 pmol/L in men (28). The difference in deficiency levels between the two genders has been attributed to certain biological factors. In women, estrogen may play a helping role against vitamin B12 deficiency by reducing the homocysteine levels (29).

Another factor is albumin, which is comparatively more in men than women. The levels of albumin increase as the muscle mass increases and hence it has an inverse relationship with vitamin B12 levels (30,31). The gender differences in vitamin B12 levels could also be explained based on genetic variations. Studies show that single nucleotide polymorphism in the gene 'fucosyl-transferase 2' has been associated with vitamin B12 malabsorption in men (32,33).

It is well postulated that the risk of vitamin B12 deficiency and type 2 diabetes mellitus increases as age increases (34,35). The prevalence of vitamin B12 deficiency (<148pmol/L) above the age of 65 ranges from 6-25%(36.37). Surprisingly in our study, we observed that the mean levels of vitamin B12 above 60 years were more than those below 40 years of age in patients on metformin therapy. This finding in the Saudi population contrasts with the claim that metformin therapy decreases the vitamin B12 levels. Even though the mean levels of vitamin B12 in the age group >60 years is more than <40 years, the mean levels remain below the defined high serum vitamin B12 level (950 pg/ml (701 pmol/l) (38).

The reason for these normal levels of vitamin B12 in some of the patients on metformin therapy could be again explained on the basis of the diet, which is very rich in vitamin B12 (26). A study reported that presence of immune complexes of IgG, IgM, and vitamin B12, contributing to the increased vitamin B12 concentrations in patients without any diseases like disseminated neoplasia, hepatic disease, myeloproliferative disorders, and hypereosinophilic syndromes etc. that usually have high serum vitamin B12 levels.

One of the unique aspects of this study was the comparison of vitamin B12 deficiency levels in patients with three different doses of metformin (500 mg, 750 mg and 1000 mg). To our knowledge, there are no previous studies done in the Kingdom, which used these doses of metformin to compare the levels of vitamin B12 deficiency. There are studies done in Saudi Arabia which compared the levels of vitamin B12 in patients who are consuming metformin 1000 mg, 1000-2000 mg, <2000 mg (23). Our results showed that only 6.3% of the patients who used metformin 500 mg had vitamin B12 levels in the deficient category compared to 750 mg and 1000 mg groups. Also, we noticed (73.9%) were in the normal range. These findings show that low doses of metformin (500 mg) might not cause severe vitamin deficiency. Studies show that low doses (250 mg X 3 times/day, 500 mg X 2 times/day) of metformin can be prescribed for patients who are pre-diabetic for the prevention of diabetes (40,41).

Limitations

Several limitations of the study should be addressed before generalizing the findings. The duration and frequency of metformin use were not studied as both could influence the levels of vitamin B12 (20,22). The dietary pattern of the patients was not studied and most of the people of Saudi Arabia consume a non-vegetarian diet, that has high cobalamin content which could also compensate for the deficiency of vitamin B12 from metformin use. Another drawback could arise from the reporting bias of metformin use by the patients. The self–reported frequency of metformin usage might be different from the actual usage since the doses used in our study are comparatively lower doses (<=1500 mg) and there is a tendency in patients to miss or ignore the timely intake of prescribed drugs either due to carelessness or forgetfulness. We also didn't assess the Body mass index as obesity could have an effect on vitamin B12 levels (42). The smoking status of patients was not assessed as smoking could have vitamin B12 deficiency (43). All these factors must be considered when planning a more evaluative study in the future.

Conclusion

The overall prevalence of vitamin B12 deficiency in metformin users in our study was found to be 10.4%. Patients with borderline levels were about 20.2% and the remaining 69.5% had normal vitamin B12 levels. There was a statistically significant relationship seen between the dosage of metformin and vitamin B12 deficiency. Patients who consumed Metformin 1000 mg showed more vitamin B12 deficiency than 500 mg. Low doses of metformin <=500 mg might not have a profound effect on vitamin B12 metabolism which suggests that these doses could be used in pre-diabetic conditions. Vitamin B12 supplementation should be prescribed for diabetic patients to prevent the occurrence of vitamin B12 deficiency complications.

Competing interests: no competing interests.
Funding: none
Acknowledgments
The authors express our gratitude to all patients who participated in this research. The authors gratefully acknowledge the cooperation of Mohammed A. Alabdalli, Dr Jihad F.Kheir for participation and facilitating the data collection.

References

1. Scheen AJ, Paquot N. Metformin revisited: A critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. Diabetes Metab 2013;39:179–90.
2. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci 2014;19(7):658–664.
3. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med 2002;137:25–33.
4. Oh R, Brown D. Vitamin B12 Deficiency. Am Fam Physician 2003;67:979–86.
5. Tung ML, Tan LK. Long term use of metformin leading to vitamin B 12 deficiency. Diabetes Res Clin Pract 2014;104: e75–e76
6. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. Age Ageing 2006;35:200–201.
7. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med 2015; 10:93–102.
8. Berchtold P, Bolli P, Arbenz U, Keiser G. Disturbance of intestinal absorption following metformin therapy (observations on the mode of action of biguanides) [in German]. Diabetologia 1969; 5:405–412.
9. de Jager J, Kooy A, Lehert P, Wulffele MG, van der Kolk J, Bets D, et al. Long-term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ 2010;340:c2181.
10. Singh AK, Kumar A, Karmakar D, Jha RK. Association of B12 deficiency and clinical neuropathy with metformin use in type2diabetespatients.JPostgradMed2013;59(4):253–257.
11. Calvo Romero JM, Ramiro Lozano JM. Vitamin B (12) in type 2 diabetic patients treated with metformin. Endocrinol Nutr 2012;59(8):487–490.

12. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling ST, Bilo HJ, Kleefstra N. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. Neth J Med 2013;71(7):386–390.
13. Beulens JW, Hart HE, Kuijs R, Kooijman-Buiting AM, Rutten GE. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. Acta Diabetol 2014;52(1):47–53.
14. Carmel R, Rosenberg AH, Lau KS, Streiff RR, Herbert V. Vitamin B12 uptake by human small bowel homogenate and its enhancement by intrinsic factor. Gastroenterology. 1969;1;56(3):548-55.
15. Schäfer G. Some new aspects on the interaction of hypoglycemia-producing biguanides with biological membranes. Biochem Pharmacol 1976;25(18):2015-24
16. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes care 2000;23(9):1227-31.
17. Berg RL, Shaw GR. Laboratory evaluation for vitamin B12 deficiency: the case for cascade testing. Clin Med Res 2013;11(1):7–15.
18. Raheel I, Sultan MK, Adnan Q, et al. Prevalence of Vitamin B12 deficiency in patients of type 2 diabetes mellitus on metformin: a case control study from Pakistan. The Pan African Medical Journal 2013; 16:67
19. Adams JF, Clark JS, Ireland JT, et al. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. Diabetologia 1983; 24:16–8.
20. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101(4):1754–61.
21. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. BMC Pharmacol Toxicol 2016;17(1):44-54.
22. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2012;35(2):327–33.
23. Alharbi TJ, Tourkmani AM, Abdelhay O, Alkhashan HI, Al-Asmari AK, Rsheed AM, Abuhaimed SN, Mohammed N, AlRasheed AN, AlHarbi NG. The association of metformin use with vitamin B12 deficiency and peripheral neuropathy in Saudi individuals with type 2 diabetes mellitus. PloS one 2018;13(10):e0204420.
24. Watanabe F. Vitamin B12 sources and bioavailability. Exp. Biol. Med 2007; 232: 1266–74.
25. Tucker KL, Rich S, Rosenberg I,Jacques P, Dallal G, Wilson PW, Selhub J. Plasma vitamin B-12 concentrations relate to intake source in the framingham offspring study. Am J Clin Nutr 2000; 71, 514–22
26. Moradi-Lakeh M, El Bcheraoui C, Afshin A, Daoud F, AlMazroa MA, Al Saeedi M, et al. Diet in Saudi Arabia: findings from a nationally representative survey. Public Health Nutr 2017;20(6):1075–81
27. Herrmann W, Schorr H, Obeid R, Geisel J. Vitamin B-12 status, particularly holotrans¬cobalamin II and methylmalonic acid con¬centrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr 2003; 78: 131–6.
28. Margalit I, Cohen E, Goldberg E, Krause I. Vitamin B12 deficiency and the role of gender: a cross-sectional study of a large cohort. Ann Nutr Metab 2018;72(4):65-271.
29. Morris MS, Jacques PF, Selhub J, Rosenberg IH. Total homocysteine and estrogen status indicators in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2000; 152: 140–8.
30. Bulut EA, Soysal P, Aydin AE, Dokuzlar O, Kocyigit SE, Isik AT: Vitamin B12 deficiency might be related to sarcopenia in older adults. Exp Gerontol 2017; 95: 136–40.
31. Mühlberg W, Sieber C: Sarcopenia and frailty in geriatric patients: implications for training and prevention. Z Gerontol Geriatr 2004; 37: 2–8.
32. Tanaka T, Scheet P, Giusti B, et al: Genomewide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. Am J Hum Genet 2009; 84:477–82.
33. Mohrenweiser HW, Tsujimoto S, Gordon L, Olsen AS: Regions of sex-specific hypo- and hyper-recombination Identified through Integration of 180 genetic markers into the metric physical map of human chromosome 19. Genomics 1998; 47: 153–162.
34. American Diabetes Association. Standards of medical care in diabetesd2010. Diabetes Care 2010;33(Suppl. 1): S11–S61
35. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC, National Academy Press, 1998
36. Sanchez H, Albala C, Herlramp F, Verdugo RE, Lavados MA, Castillo JL, Lera L, Uauy R. Prevalence of vitamin B-12 deficiency in older adults. Rev Med Chil 2010 Jan;138(1):44-52
37. Evatt ML, Terry PD, Ziegler TR, Oakley GP. Association between vitamin B12- containing supplement consumption and prevalence of biochemically defined B12 deficiency in adults in NHANES III (third national health and nutrition examination survey). Public Health Nutr 2010; 13:25–31
38. Chiche L, Jean R, Romain F, Roux F, Thomas G, Canavese S, Branger S, Harlé JR, Durand JM. Clinical implications of high cobalamin blood levels for internal medicine. Rev Med Intern 2008;29(3):187-94.
39. Bowen RA, Drake SK, Vanjani R, Huey ED, Grafman J, Horne MK. Markedly increased vitamin B12 concentrations attributable to IgG–IgM–vitamin B12 immune complexes. Clin Chem 2006;52(11):2107-14.
40. Lily M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis [published correction appears in Can Fam Physician. 2010 Jan;56(1):18. Lilly, Muriel [corrected to Lily, Muriel]. Can Fam Physician 2009;55(4):363–9
41. Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. Drugs 2015;75(10):1071-94.
42. Baltaci D, Kutlucan A, Turker Y, Yilmaz A, Karacam S, Deler H, Ucgun T, Kara IH. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Med Glas (Zenica) 2013;10(2):203-10.
43. Khan A, Shafiq I, Shah MH. Prevalence of vitamin B12 deficiency in patients with type II diabetes mellitus on metformin: a study from Khyber Pakhtunkhwa. Cureus 2017; 9(8): e1577.