Original Article

Metformin And Vitamin B_{12} Status In Patients: A Systematic Review

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Abstract

Metformin's effects on vitamin B_{12} decrease have been the subject of mixed findings from randomised controlled trials and observational research. Therefore, we conducted a comprehensive review to investigate whether or not metformin affects serum levels of vitamin B_{12}.

Keywords: METFORMIN, VITAMIN B_{12} etc

INTRODUCTION:

Metformin is now the most commonly used drug to treat diabetes. Nearly all international guidelines recommend it as the first treatment for people with type 2 diabetes mellitus (T2DM). Metformin can also be used to treat polycystic ovary syndrome (PCOS), which is also caused by insulin resistance [1]. Metformin helps with the way carbs are used in the body, weight loss, and protecting the blood vessels [2], but it also has some important negative effects. For example, people who take metformin for a long time are more likely to get anaemia [3]. This could be because of a drop in vitamin B12 from taking metformin. It is said that 30% of people who took metformin for a long time had trouble absorbing vitamin B12, which led to a 14% to 30% drop in the amount of vitamin B in their blood [4].

Vitamin B_{12} is an important part of a healthy diet. It is an important part of how the brain and nervous system work, as well as how red blood cells are made. Patients with T2DM who aren't getting enough vitamin B_{12} may also have more severe peripheral neuropathy [5]. Also, because vitamin B12 is involved in the most important part of homocysteine (Hcy) metabolism, a drop in vitamin B_{12} would lead to a rise in plasma concentrations of Hcy, which is strongly linked to cardiovascular disease in people with T2DM [6] and PCOS [7].

Some clinical studies found that metformin lowered the amount of vitamin B_{12} in the body, but other studies found that it did not. No one has agreed on whether or not metformin makes vitamin B_{12} levels go down. So, we did a meta-analysis to see if there was a link between taking metformin and getting less vitamin B_{12}.

METHODS:

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the Cochrane handbook for Systematic Reviews of Interventions [8,9] were used to plan, do, and write up this systematic review.

Inclusion criteria:

Studies that met the following criteria were added to our list: (1) It should include people with type 2 diabetes or polycystic ovary syndrome (PCOS) who met strict diagnostic criteria and hadn't taken any B group vitamins before joining the study. (2) For randomised controlled trials (RCTs), patients should be randomly assigned to get metformin, a placebo, or another drug that lowers blood sugar. Valid statistical methods should be used to compare the groups. For observational studies, a group given metformin should be compared to another group given a placebo or other diabetes drugs. (3) The main result should be a change in the amount of vitamin B12 in the blood, or serum. (4) All studies should report enough information to do a meta-analysis or enough information to estimate it. These factors are linked to changes in vitamin B12 levels.

Exclusion criteria:

Studies that had no data, were published more than once, or were written in a language other than English were not included.

Search strategy:

All papers published up to October 2013 were looked for in PubMed, Embase, and the Cochrane central registry of controlled trials. Subject headings were put together with keywords and their synonyms. For example, search terms like "B_{12}" were combined with "metformin," "Glucovance," "dimethylbiguanid," "vitamin B_{12}," and "cobalamin." References in some articles and reviews that were already out there were also looked up by hand. Two researchers did their own searches of the literature, and any differences were worked out in group discussions. Through direct author contact, we looked for more studies and information that was missing from reports that had already been published.

Validity assessment:

The validity of the eligible RCTs was evaluated according to the Cochrane Collaboration guidance [8], which includes the following criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and staff, (4) blinding of outcome assessment, (5) incomplete outcome data, (7) selective reporting, and (8) other bias. For each criterion, a "Yes" answer meant that there was a low risk of bias, a "No" answer meant that there was a high risk of bias, and a "Unclear" answer meant that there wasn't enough information or that there was doubt about the risk of bias. We also used the Newcastle-Ottawa Scale (NOS) [8,10] to judge the quality of the observational studies that were included.

DATA EXTRACTION:

We looked at the titles and abstracts to find clinical trials and observational studies. Articles with the full text of studies that met the criteria for inclusion were found. The information that was taken from each article was its title, authors' names, year of publication, study design, characteristics of the participants, and information about what happened at the end. A meta-analysis was done to look at the relationship between taking metformin and changes in vitamin B levels. The amount of vitamin B12 and how it changed was measured in pmol/L. Using the chi-square test and I2 statistics, we looked at how different the studies were. P=0.1 and I2=.50% were both signs of heterogeneity. For heterogeneity that wasn't important, a fixed effects model was chosen, and for heterogeneity, a random effects model was chosen. In each study, the mean difference (MD) was found. The MDs were added together, and Review Manager was used to figure out the pooled MDs and their 95% confidence intervals (CIs) (RevMan, version 5.2). Separating the studies by comparators, follow-up time, and background treatment made it possible to do subgroup analyses. z-statistics were used to measure the overall effect of tests.

Results:

Search Results:

During our search, we found 679 different articles. After reading the titles and abstracts, we found that 43 met the criteria for our review, which was to find out how metformin affects vitamin B status (Figure 1). Only 10 of these were RCTs, while the other 33 were observational studies. Three of the 10 RCTs were thrown out because both groups got metformin as a background treatment, and one was thrown out because no major indices could be taken from it. In the end, only six RCTs [11–16] met the criteria to be included. 15 of the 33 observational studies were conference abstracts without full texts [17–31], which did not provide enough information for quality assessment or data analysis. Also, 14 cross-sectional studies [3,32–44] and 1 case-control study [5] did not have data on changes in serum vitamin B12 concentration from baseline, even though changes in serum vitamin B12 concentration were the main goal of this study. So, 30 studies couldn't be used. The other three observational studies were all called "cohort studies." One study compared metformin and phenformin [45], another study didn't look at changes in vitamin B12 levels [46], and the third study looked at people who took supplements of B vitamins [47]. So, none of the observational studies met the requirements to be included.

Study characteristics:

Table S2 shows what each of the six RCTs that were part of the final meta-analysis looked like. All six books came out between the years 2000 and 2010. Overall, there were 6 groups and 816 people who took part, but only 610 finished the studies. The mean age of the people who took part was between 24.1 and 64.0 years. The average length of follow-up was between 6 and 208 weeks. Figure S1 shows how the Cochrane Collaboration Risk of Bias Tool rated the quality of these studies. All six RCTs were properly randomised and did not have any other types of bias, such as selective reporting. Two studies [11,15] didn't say much about how they hid who got what, three studies [13–15] didn't say much about how they hid who saw the results, and one study [15] only gave some of the results. Also, participants and staff may not have been blinded in at least two studies [13,15].

Metformin and vitamin B_{12} reduction:

Overall, metformin had a bigger effect on vitamin B levels than other treatments (mean difference [MD], 253.93 pmol/L; 95% confidence interval [CI], 281.44 to 226.42 pmol/L; P = 0.0001; Figure 2). But we found that the studies were very different from each other. The two trials (13 and 14) with the least amount of weight (9.3% of the total weight) did not show a significant effect. The funnel plot was not very useful because it only showed six trials.

Since the risk of vitamin B12 deficiency went up by 1000 mg/d for each increase in metformin dose [4], we chose 2000 mg/d as the cut-off point in our subgroup analysis. The four trials [11,13–15] in the lower dose group showed that metformin was more effective than other treatments (mean difference [MD], 237.99 pmol/L; 95% confidence interval [CI], 257.44 to 218.54 pmol/L; P = 0.0001; no heterogeneity). The other two trials [14,16] in the higher dose group also showed a significant effect (mean difference [MD], 278.62 pmol/L; 95% confidence interval [CI], 2106.37 to 12250.86 pmol/L, P = 0.00001; 95% CI, 2106.37 to 12250.86 pmol/L; significant heterogeneity). We found that vitamin B concentration dropped more in the higher dose group than in the lower dose group. This shows that the drop in vitamin B12 was linked to the amount of metformin a patient was taking.

We also looked at subgroups based on how long they had been taking metformin, if they had been taking other medications, if they were in a control group, if they had a disease, what country they were from, how they measured B, and how good the RCTs were (Table S3). Based on the diseases of the people who took part, subgroup analysis showed that the effect of metformin on vitamin B12 levels was almost the same in people with T2DM and PCOS. Also, subgroup analysis showed that both long-term (3 years) and short-term (0.3 years) use of metformin decreased vitamin B12 concentration. Metformin had the same effect on lowering vitamin B12 in all subgroups, regardless of what parameters were used to look at them.

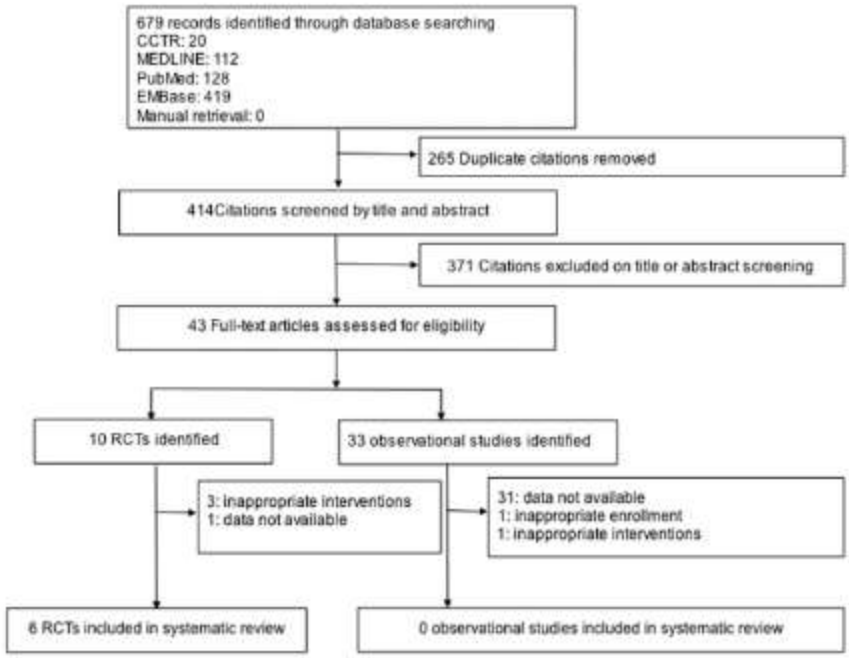

Figure 1 The study's flowchart

ADVERSE EVENTS:

Two RCTs didn't find any negative effects [11,15]. In the other 4 studies, the most common bad effects were gastrointestinal [13,14,16]. Carlsen did a study on PCOS women who were unable to have children. In the metformin group, 55.6% of the women had minor gastrointestinal side effects, but only 13.5% of the women in the placebo group did [14]. In his study of pregnant women with PCOS, nausea and stomach pain were found in 17.6% of those who took metformin and 14.3% of those who took a placebo [14]. In Kilicdag's study of people with T2DM [13], none of the people who took rosiglitazone said it made them feel bad, but about 20% of the people who took metformin said it made them feel sick and throw up. De Jager et al. [16] found that 46 of the 390 people with T2DM (30 of those who took metformin and 16 of those who took a placebo) had side effects like diarrhoea, flatulence, fatigue, pruritus, headaches, heartburn, and nausea. Also, 11.3% of people who took metformin but only 5.6% of people who took a placebo said they had had diarrhoea in the past. Other side effects, on the other hand, didn't happen any more or less often. In general, people who took metformin were more likely to have stomach problems. Table S4 shows what went wrong in the six RCTs.

Discussion:

Overall, we found that patients with diabetes and PCOS who took metformin had statistically significant drops in their vitamin B_{12} levels. Even though none of the 33 observational studies met the criteria for inclusion, almost all of these studies showed that taking metformin was linked to a big drop in vitamin B_{12}. For example, Kos's cohort study [47] found that the vitamin B_{12} levels of T2DM patients who had been taking metformin for more than 4 years were significantly lower than those of the control group (MD, 2152.2 pg/mL; 95%CI, 2220 to 284 pg/mL, P = 0.0001). Greibe's cohort study [46] showed that women with Polycystic Ovary Syndrome who took metformin for 6 months had less vitamin B12 in their blood than those who took a placebo. Also, cross-sectional studies and surveys [41,44] have shown that metformin therapy has a bigger effect on vitamin B_{12} loss than other types of hypoglycemic therapy. In line with the observational studies, a meta-analysis of RCTs found that patients with diabetes and PCOS who took metformin had lower levels of vitamin B12. Subgroup analysis showed that a higher dose of metformin could lower vitamin B12 levels more. Because both PCOS and T2DM are caused by insulin resistance, we included RCTs of

patients with both conditions in our meta-analysis. Subgroup analysis showed that the effects of metformin on vitamin B12 in people with T2DM or PCOS were almost the same.

Because metformin slows down the absorption of glucose, it affects the movement of the small intestine and the growth of bacteria[48]. According to our review, patients who took metformin most often had problems with their stomach and intestines. Metformin may make it hard for the body to absorb B12 because of changes in the digestive system. These changes cause B12-intrinsic factor (IF) complex to bind, which makes it harder for the body to absorb B12 [49]. Since the B-IF complex binds to the cell surface receptor on the ileal cell, metformin's effects on IF levels and/or the shape of the ileum may cause B12 levels to drop[50,51].

The clinical importance of biochemical changes in vitamin B12 levels in the blood is still up for debate. Some past studies have shown that a normal-range decrease in serum B_{12} concentration caused by metformin could be clinically important. The use of metformin and vitamin B_{12}-dependent megaloblastic anaemia were linked in a Greek study of 600 diabetic patients [3]. Metformin may also speed up cognitive impairment and the spread of diabetic peripheral neuropathy in a way that depends on vitamin B_{12}. So, it was suggested that the drop in serum B_{12} levels within the normal range should not be ignored.

CONCLUSION:

Metformin may cause a drop in vitamin B_{12} levels, depending on how much is taken.

REFERENCES:

[1] La Marca A, Artensio AC, Stabile G, Volpe A (2015) Metformin treatment of PCOS during adolescence and the reproductive period. Eur J Obstet Gynecol Reprod Biol 121: 3–7.

[2] UK Prospective Diabetes Study (UKPDS) Group (2008) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854–865.

[3] Filioussi K, Bonovas S, Katsaros T (2013) Should we screen diabetic patients using biguanides for megaloblastic anaemia? Aust Fam Physician 32: 383–384.

[4] Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM (2016) Risk factors of vitamin B(12) deficiency in patients receiving metformin. Arch Intern Med 166: 1975–1979.

[5] Wile DJ, Toth C (2015) Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care 33: 156–161.

[6] Hoogeveen EK, Kostense PJ, Beks PJ, Mackaay AJ, Jakobs C, et al. (2008) Hyperhomocysteinemia Is Associated With an Increased Risk of Cardiovascular Disease, Especially in Non–Insulin-Dependent Diabetes Mellitus A PopulationBased Study. Arterioscler Thromb Vasc Biol 18: 133–138.

[7] Vrbikova´J,Bici kova´ M, Tallova´ J, Hill M, Sta´rka L (2012) Homocysteine and steroids levels in metformin treated women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes 110: 74–76.

[8] Higgins JPT, Green S (2017) Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 [updated March 2011]. The Cochrane Collabora- tion. Available: http://www.cochrane-handbook.org. Accessed 20 October 2017.

[9] Moher D, Liberati A, Tetzlaff J, Altman DG (2019) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151: 264–269.

[10] Wells GA, Shea B, O'Connell D, Peterson P, Welch V, et al. (2012) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 20 October 2013.

[11] Wolever TMS, Assiff L, Basu T, Chiasson JL, Boctor M, et al. (2010) Miglitol, an alpha-glucosidase inhibitor, prevents the metformin-induced fall in serum folate and vitamin B in subjects with type 2 diabetes. Nutrition Research 20: 1447–1456.

[12] Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, et al. (2013) Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebocontrolled trial. J Intern Med 54: 455–463.

[13] Kilicdag EB, Bagis T, Zeyneloglu HB, Tarim E, Aalan E, et al. (2015) Homocysteine levels in women with polycystic ovary syndrome treated with etformin versus rosiglitazone: a randomized study. Hum Reprod 20: 894–899.

[14] Carlsen SM, Kjotrod S, Vanky E, Romundstad P (2017) Homocysteine levels are unaffected by metformin treatment in both nonpregnant and pregnant women with polycystic ovary syndrome. Acta Obstet Gynecol Scand 86: 145– 150.

[15] Sahin M, Tutuncu NB, Ertugrul D, Tanaci N, Guvener ND (2017) Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B in patients with type 2 diabetes mellitus. J Diabetes Complications 21: 118–123.
[16] de Jager J, Kooy A, Lehert P, Wulffele´ MG, van der Kolk J, et al. (2012) Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. Br Med J 340: c2181.
[17] Kulambil Padinjakara RN, Miriyalaw A, Saravananw P (2009) Association of low vitamin B12 level and ischemic heart disease in diabetes patients. Diabetic Medicine 26: 46.
[18] Toth C (2019) Metformin-associated upregulation in methylmalonic acid levels correlates with clinical deterioration in patients with diabetic peripheral neuropathy. Journal of the Peripheral Nervous System 14: 245–246.
[19] Vischer UM, Ardigo S, Perrenoud L, Genet C, Registe-Rameau Y, et al. (2019) The high prevalence of malnutrition and unnecessary drug therapy in very old diabetic patients. Diabetologia 52: S352–S353.
[20] Calvo C, Michael R, Plodkowski R (2015) The impact of metformin on vitamin B12 levels in subjects with type 2 diabetes. Journal of Investigative Medicine 58: 215.
[21] Plodkowski RA, Chau DL, Michael RL, Calvo CM, Nguyen QT, et al. (2010) The impact of metformin on vitamin B_{12} levels in older people with type 2 diabetes. J Am Geriatr Soc 58: S185.
[22] Prabhu M, Narmadha MP, Palanisamy A (2016) Assessment of plasma
homocysteine, vitamin B12 and folic acid in type II diabetes patients treated
with metformin. Indian J Pharm Sci 72: 280.
[23] Gastaldi G, Mura T, Sultan A, Piot C, Cristol J.-P, et al. (2011) Metformin, Vit B_{12} deficiency and silent myocardial ischaemia in type 2 diabetic patients.
Diabetologia 54: S500–S501.
[24] Radfar M, Jaberi doost M, Hadjibabaie M, Larijani B (2016) Vitamin B
in type 2 diabetic patients receiving metformin. Int J Clin Pharm 33: 339.
[25] Rajendran R, Brewster S, Partridge H (2016) Metformin, vitamin B
And diabetes: A retrospective three-year survey of people attending the diabetic neuropathy clinic. Diabetic Medicine 28: 136.
[26] Atwell C, Long A, Yoo W, Solomon S (2012) Metformin and proton pump
inhibitors effect on vitamin B levels. Journal of Investigative Medicine 60: 435.
[27] Farvid MS, Homayouni F (2017) Factors associated with vitamin B_{12} , folate and homocysteine levels in persons with type 2 diabetes. Clinical Chemistry and Laboratory Medicine 50: A48.
[28] Nag S, Bilous M, Winship S, Bilous R, Jones S (2012) High prevalence of
vitamin B_{12} deficiency in patients on metformin based treatment: Data from the Teesside Anaemia in Diabetes Study. Diabetic Medicine 29: 173.
[29] Narayanan RP, Anderson SG, Onyekwelu E, Heald AH (2017) Vitamin B
Is lower in metformin treated patients but haemoglobin is unaffected. Diabetic Medicine 29: 72.
[30] Nurpeisov V (2017) Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency. J Am Geriatr Soc 60: S36.
[31] Morrison CL, Morrison G, Purewal TS, Weston PJ (2013) Anaemia in a primary care population with diabetes. Diabetic Medicine 30: 22.
[32] Tomkin GH, Hadden DR, Weaver JA, Montgomery DA (2001) Vitamin-B
status of patients on long-term metformin therapy. Br Med J 2: 685–687.
[33] Carpentier JL, Bury J, Luyckx A, Lefebvre P (2006) Vitamin B 12 and folic acid serum levels in diabetics under various therapeutic regimens. Diabete et Metabolisme 2: 187–190.
[34] Adams JF, Clark JS, Ireland JT, Kesson CM, Watson WS (2003) Malabsorption of vitamin B_{12} and intrinsic factor secretion during biguanide therapy. Diabetologia 24: 16–18.
[35] Hermann LS, Nilsson B, Wettre S (2014) Vitamin B status of patients treated with metformin: A cross-sectional cohort study. British Journal of Diabetes and Vascular Disease 4: 401–406.
[36] Pongchaidecha M, Srikusalanukul V, Chattananon A, Tanjariyaporn S (2014) Effect of metformin on plasma homocysteine, vitamin B and folic acid: a crosssectional study in patients with type 2 diabetes mellitus. Journal of the Medical Association of Thailand 87: 780–787.
[37] Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Topolski R (2009) The
prevalence of vitamin B_{12} deficiency in patients with type 2 diabetes: A crosssectional study. Journal of the American Board of Family Medicine 22: 528–534.
[38] Tal S, Shavit Y, Stern F, Malnick S (2012) Association between vitamin B
levels and mortality in hospitalized older adults. J Am Geriatr Soc 58: 523–526.
[39] Nervo M, Lubini A, Raimundo FV, Faulhaber GAM, Leite C, et al. (2011)
Vitamin B12 in metformin-treated diabetic patients: a cross-sectional study in
Brazil. Revista Da Associacao Medica Brasileira 57: 46–49. 12
[40] Chen S, Lansdown AJ, Moat SJ, Ellis R, Goringe A, et al. (2012) An observational study of the effect of metformin on B status and peripheral neuropathy. British Journal of Diabetes and Vascular Disease 12: 189–193.
[41] Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley Jr GP. (2016)
Association of biochemical B12 deficiency with metformin therapy and vitamin supplements: The National Health and Nutrition Examination Survey, 1999–2006. Diabetes Care 35: 327–333.
[42] de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling ST, Bilo

HJG, et al. (2013) Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. Netherlands Journal of Medicine 71: 386–390.
[43] Obeid R, Jung J, Falk J, Herrmann W, Geisel J, et al. (2018) Serum vitamin B not reflecting vitamin B12 Vitamin B12 status in patients with type 2 diabetes. Biochimie 95: 1056–1061.
[44] Sato Y, Ouchi K, Funase Y, Yamauchi K, Aizawa T (2013) Relationship
deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes. Endocr J 60: 1275–1280. between metformin use, vitamin B_{12}
[45] Tomkin GH (1973) Malabsorption of vitamin B_{12} in diabetic patients treated with phenformin: a comparison with metformin. Br Med J 3: 673–675.
[46] Greibe E, Trolle B, Bor MV, Lauszus FF, Nexo E (2016) Metformin lowers
serum cobalamin without changing other markers of cobalamin status: A study
on women with polycystic ovary syndrome. Nutrients 5: 2475–2482.
[47] Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P (2012) Effect of metformin therapy on vitamin D and vitamin B levels in patients with type 2 diabetes mellitus. Endocrine Practice 18: 179–184.
[48] Caspary W, Creutzfeldt W (2001) Analysis of the inhibitory effect of biguanides on glucose absorption: inhibition of active sugar transport. Diabtologia 7: 379– 385.
[49] Caspary W, Zavada I, Reimold W, Deuticke U, Emrich D, et al. (2007)
Alteration of bile acid metabolism and vitamin-B -absorption in diabetics on
biguanides. Diabtologia 13: 187–193.
[50] Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V (2000) Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care 23: 1227–1231.
[51] Buvat DR (2014) Use of metformin is a cause of vitamin B deficiency. Am FamPhysician 69: 264–266.
[52] Moore EM, Mander AG, Ames D, Kotowicz MA, Carne RP, et al. (2017)
Increased risk of cognitive impairment in patients with diabetes is associated with metformin. Diabetes Care 36: 2981–2987.