Volume 1, Issue 1, April 2023 ISSN (E): XXXX-XXXX

TREATMENT OF TYPE 2 DIABETES WITH METFORMIN

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Abstract
Metformin is a first line treatment for diabetes. As a positive additional effect, it reduces the risk of vascular pathology and mortality and exhibits a geroprotective effect. The appointment of metformin is a pathogenetic therapy for type 2 diabetes, due to the effect of reducing insulin resistance, increasing peripheral glucose utilization by tissues, reducing gluconeogenesis and reducing glucose production by the liver. Epidemiological and randomized studies have shown that long-term treatment with metformin significantly increases the risk of decreased blood levels of vitamin B12 and the risk of folate deficiency, contributing to the progression of diabetic peripheral neuropathy..

Introduction

Diabetes mellitus is a global problem all over the world. The term "Cachara diabetes" as defined by the World Health Organization (WHO) means a metabolic disorder of multiple etiologies, which is characterized by chronic hypergliemia with impaired metabolism of carbohydrates, fats and proteins as a result of impaired insulin secretion and / insulin action. Diabetes is the only non-communicable disease (meaning especially dangerous infections - plague, smallpox, etc.) taken under the control of the United Nations (UN)

Type 2 diabetes mellitus (DM), the most common endocrine disease, is a serious medical and social problem due to the widespread progressive increase in morbidity, chronic course and high frequency of disabling complications [1; 4]. According to forecasts, 2011–2019 Science for Education Today (until 2018: Bulletin of Novosibirsk State Pedagogical University) Science for Education Today 2019, vol. 9, © no. 1 http://sciforedu.ru ISSN 2658-6762 210 by 2040 their total number will reach 642 million[1] [4]. Every 6 seconds. One person dies in the world from diabetes mellitus and its complications[2] .

Атлас диабета IDF. 7-е изд. 2015 [Электронный ресурс]. URL: http://www.diabetesatlas.org (дата обращения: 09.12.2018) 2 Там же. 3 Petri C., Stefani L., Bini V., Mascherini G., Francini L., De Angelis M., Galanti G. Life style and nutrition habits

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in type 2 diabetes [Электронный ресурс]. URL: https://www.researchgate.net/publication/278024473 (дата обращения: 09.12.2018)

As of 01.01.2019. 230,610 patients with diabetes are registered in Uzbekistan:
18,349 patients with type 1 diabetes (T1DM), and 212,261 patients with type 2 diabetes (T2DM). According to screening studies, the prevalence of type 2 diabetes in Uzbekistan has increased by 1.6 times over the past 14 years and, according to the latest data (2015), is 7.9% among people over 35 years of age. According to the National Register of Board of Directors (2007, 2010), as well as
according to the annual reports of the regional dispensaries of the Republicof UzbekistanBekistan, about 80% of patients do not reach the target indicators of carbohydrate metabolism, which contributes to the development of various diabetic and cardiovascular complications, shortening the life of patients, high **[Clinical Recommendation for Treatment of Type 2 Diabetes Mellitus.Ruk.dlya Doctors 2019.Tashkent].**

Over the past 15 years, there have been revolutionary discoveries in diabetology in the field of research on the pathogenesis of type 2 diabetes, accompanied by the development of new classes of hypoglycemic drugs that have radically changed the treatment algorithm.

Metformin is a 1st-line treatment for diabetes. As a positive additional effect, it reduces the risk of vascular pathology and mortality and exhibits a geroprotective effect. Metformin monotherapy is recommended against the background of lifestyle changes in HbA1c <9%. The appointment of metformin is a pathogenetic therapy for type 2 diabetes, due to the effect of reducing insulin resistance, increasing peripheral utilization of glucose by tissues, reducing gluconeogenesis and reducing glucose production by the liver. In addition to reducing fasting and post-meal glycemia (without a significant risk of hypoglycemia), metformin significantly reduces risk factors for cardiovascular disease. Level HbA1c decreases in monotherapy with metformin up to 2%.

To reduce side effects (metallic taste in the mouth, nausea, diarrhea, flatulence), the dose of metformin should be titrated from 500 mg to a maximum of 2550-3000 mg. It should be noted that when taken after meals, the frequency of occurrence decreases
side effects. The effectiveness of the drug should be evaluated
on the 3-4th day of admission.

Contraindications

►► СД1
►► кетоацидоз
►► Pregnancy and lactation
►► liver pathology (increase in ALT >2.5 times)
►► kidney CKD C 3b-5 (GFR <45 ml/min/1.73 m2)
►► chronic heart failure III-IV degree.
►► severe anemia
►► alcoholism

The drug is integrated into the complex therapy of polycystic ovaries, treatment of infertility in women associated with insulin resistance and glucose tolerance. However, long-term use of metformin (months and years) helps to reduce the levels of vitamin B12 in the blood, disrupts the absorption of thiamine and other B vitamins [1]. Epidemiological and randomized studies have shown that long-term treatment with metformin significantly increases the risk of lowering blood levels of vitamin B12 and the risk of folate deficiency, contributing to the progression of diabetic peripheral polyneuropathy [2].

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Clinical practice shows that 10–30% of patients who took metformin often have blood levels of cobalamin below 200 pmol/L [3]. At the same time, vitamin B12 and other B vitamins (in particular, B1 and B6) are essential for maintaining sugar metabolism [4], especially in patients with diabetes. Further, the results of fundamental studies of the effect of metformin on the homeostasis of vitamin B12, the clinical consequences of taking metformin related to hypovitaminosis B12, and clinical studies of the relationship between metformin and hypovitaminosis B12 are consistently considered.

Body

Fundamental studies of the effect of metformin on vitamin B12 homeostasis Malabsorption of vitamin B12 during malabsorption, recorded as abnormal results of the Schilling test (which quantifies the absorption of vitamin B12 with an isotopic label in the presence of an intrinsic factor and without it), are a typical side effect of biguanide therapy in patients with type 2 diabetes mellitus (T2DM) [5], including buformin [6] and metformin [7].

In experimental and clinical studies, it has been shown that biguanides such as phenformin, buformin, metformin do not change the volume of stool or the excretion of fat through the gastrointestinal tract (GIT), but significantly reduce the content of bile acids in intestinal transit. This is due to an excessive increase in the deconjugation of glycocholic acid, which is a conjugate of cholic acid and glycine. During the deconjugation of glycocholic acid, glycine is detached, and 90–95% of cholic acid is absorbed in the intestine into the blood and enters the liver through the portal vein [8].

As a result, the content of fatty acids in intestinal transit decreases, which significantly impairs the absorption of all fat-soluble micronutrients (vitamins A, D, K, etc.). In particular, the lack of bile acids somewhat reduces the absorption of vitamin B12 in the small intestine [9], which is consistent with the peculiarities of the chemical structure of vitamin B12 (see Fig. 1). In the experiment, guinea pigs received saline, or phenformin, or metformin (subcutaneously or orally). Bile acid excretion was assessed using 14 C-cholic acid. Parenteral and oral administration of biguanides has been shown to cause malabsorption of bile acids and vitamin B12 [10]. Discontinuation of treatment with biguanides or the introduction of antibiotics normalizes the deconjugation of bile acids. The effect of antibiotics on the deconjugation of bile acids suggests that the overgrowth of opportunistic bacteria in the small intestine leads to the binding of vitamin B12 by pathogenic bacteria, which is reflected in the abnormal results of the Schilling test [7].

An experimental study showed that metformin disrupts the redistribution of vitamin B12 in the body, increasing, in particular, the accumulation of B12 in the liver. After daily subcutaneous injections of metformin or placebo (saline), vitamin B12 levels decreased by 22% (range 370 to 289 μmol/L, 95% confidence interval CI 47–383, p=0.001). The animals were then given vitamin B12 with an isotopic label (57 Co) per os. After metformin injections, the amount of B12 in the liver was 36% higher (p=0.007) and in the kidneys was 34% lower (p=0.013) compared to the placebo group (Fig. 2). At the same time, there was no significant difference between the groups in the total amount of absorbed vitamin B12 [11]. Thus, metformin may not impair the absorption of vitamin B12, but nevertheless cause disturbances in its physiological compartmentalization. In particular, under the influence of metformin, there is a decrease in the levels of vitamin B12 in the kidneys and blood serum. As a result, the peripheral nerves do not receive enough cobalamin and its derivatives. It can also be noted that the accumulation of B12 in the liver and erythrocytes [12],

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which occurs under the action of metformin, may contribute to the geroprotective effects of this drug [13]

Changes in the homeostasis of vitamin B12 are characteristic of biguanides, but not of other drugs for the treatment of type 2 diabetes. Treatment of patients with type 2 diabetes (n=165) with metformin or rosiglitazone for 6 weeks showed that both drugs significantly reduced the levels of triglycerides, low-density lipoproteins (LDL), total cholesterol, HbA1c and insulin. The use of metformin was associated with an increase in homocysteine levels (+2.4 μmol/L), a decrease in folate levels (-1.04 ng/ml) and vitamin B12 (-20 pg/ml). On the contrary, the level of homocysteine decreased (-0.92 μmol/L), while the levels of folate and vitamin B12 remained unchanged [14].

It is important to note that the absorption of the vitamin B 12 complex with the cobalamin transporter protein in the intestine depends on the concentration of Ca2+ ions. Therefore, calcium subsidies help to improve the absorption of B12 while taking metformin [15]. Reduced calcium supply is common among patients with diabetes and in elderly patients. Consequences of taking metformin related to hypovitaminosis B12 Vitamin B12 deficiency is usually accompanied by: relevant clinical manifestations (usually neurological).

The most common causes of hypovitaminosis B12 are indigestion, pancreatic insufficiency, chronic drug treatment not only with metformin, but also with drugs from the group of proton pump inhibitors (PPIs) and other drugs that reduce the acidity of gastric juice [16].The combination of metformin with histamine H2 receptor antagonists or PPIs is especially dangerous in polyneuropathy, which develops as a result of malabsorption of vitamin B12 and / or in severe form hypovitaminosis B12 [17].

Metformin and PPI treatment in patients with type 2 diabetes (n=231) is associated with a 3-fold higher risk of developing hypovitaminosis B12 (less than 180 pg/ml, 22.5% of patients) than in the control group (n=231, 7.4%) [18]. Even relatively short-term treatment with metformin (6 months) causes a decrease in cobalamin levels and an increase in serum homocysteine. Within 2 years of metformin treatment in patients with type 2 diabetes (n=90), the risk of peripheral neuropathy significantly increased [19]. In the groups of patients with established malabsorption of cobalamin from food (n=80) and patients with cobalamin deficiency (n=127), serum vitamin B12 levels were 153±74 pg/ml (95% CI 35–200 pg/ml), and homocysteine levels reached very high levels of 20.6±15.7 μmol/L (95% CI 8–97 μmol/L).

The main clinical manifestations of vitamin B12 deficiency were peripheral polyneuropathy (46%), asthenia (19%), stroke (12%), dementia (10%), leg edema (11%) and gastrointestinal diseases (8%). The most typical comorbid conditions associated with B12 deficiency were atrophic gastritis (39%, often with signs of Helicobacter pylori infection – 12%) and alcohol abuse (14%) [20]

In patients with diabetes and polyneuropathy due to atherosclerosis, serum vitamin B12 levels were significantly lower when taking metformin (ra ($p<0.001$)

An increase in cobalamin levels for every 25 pmol/L was associated with a 6% reduction in the risk of neuropathy (risk ratio – RR 0.94, 95% CI 0.88–1.00, p=0.034) [21]. A systematic analysis of 43 studies of the association between serum vitamin B12 levels and cognitive impairment showed that low levels of B12 (less than 250 pmol/L) are significantly associated with Alzheimer's disease, vascular dementia and Parkinson's disease. The use of metformin helps to reduce serum levels of vitamin B12 and, accordingly, increases the risk of cognitive impairment. Vitamin B12 supplements, administered orally or parenterally at a high dose (1 mg / day), effectively correct vitamin deficiency and contribute to prevention

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cognitive impairment in patients with pre-existing vitamin B 12 deficiency (less than 150 pmol/L) [22]

The following case clearly illustrates that malabsorption/redistribution of vitamin B12 during long-term treatment with metformin can lead to megaloblastic anemia [23]. Patient A., 47 years old (height 1.57 m, body weight 88 kg) with symptoms of polyuria and polydipsia against the background of high venous blood glucose levels (10 mmol/l in the postprandial 21-hour test), was prescribed a low-calorie diet (1000 kcal) containing 100 g/day of carbohydrates.

Despite following the diet for 1 year, the patient regularly had hyperglycemia, as a result of which metformin (500 mg / day) was prescribed. After 8 years of metformin therapy, the patient developed severe clinical symptoms of anemia without peripheral neuropathy. The results of laboratory tests showed: hemoglobin level 89 g / dl, average erythrocyte volume (MCV) 106 fl (norm 84-99), intracellular hemoglobin (MCH) 36 pg (norm 30-35 pg), bilirubin 164 μmol / l (norm 3-21 μmol / l), lactate dehydrogenase 680 units (norm 220-440), serum iron concentration 10 μmol / l (norm 14-25 μmol / l). The patient's serum vitamin B12 levels were only 60 pmol/L with a lower normal limit of 150 pmol/L.

A general blood test showed that red blood cells were enlarged, megaloblastic forms were noted. A modified combination Schilling test showed that when a test dose of vitamin B12 was administered from the body per day, only 6.2% was excreted in the urine at a rate of 10-32%. Studies using barium sulfate as radiopaque indicated the presence of a symptom of flocculation and adhesion of food transit in the proximal ileum. At the same time, local intestinal lesions in the patient were not established.

After treatment with cyanocobalamin at a dose of 1000 μg/day for 1 month and then maintenance monthly single injections (1000 μg/month), serum vitamin B12 levels increased to 1000 ng/l, hemoglobin to 139 g/dl against the background of the disappearance of clinical and laboratory manifestations of anemia [24]. In patients with type 2 diabetes treated with metformin, cobalamin levels greater than 150 μmol/L were associated with a reduced risk of depression (RR 0.42, 95% CI 0.23–0.78) and better preservation of cognitive functions [25]. Clinical studies of the relationship between metformin and hypovitaminosis B12. The incidence of vitamin B12 deficiency (concentrations less than 150 μmol/L) in patients with type 2 diabetes was 28%, and metformin was a significant risk factor for hypovitaminosis B12 (RR 1.96, 95% CI 0.99–3.88, p=0.053) [26]. In another study, in patients with type 2 diabetes taking metformin (n=231), vitamin B12 deficiency (levels less than 180 pg/ml) was also more common (22.5%) than in healthy participants (n=231, 7.4%, p <0.05) [27] Even short-term use of metformin by patients with type 2 diabetes (1–3 months) leads to a decrease in the level of B vitamins in the blood. For example, in the group of patients with type 2 diabetes undergoing insulin treatment (n=745), metformin was taken for 16 weeks. Compared with the placebo group, metformin was associated with a significant reduction in folate levels (-7%, 95% CI 1.4 to -13, p=0.024) and vitamin B12 (-14%, 95% CI 4.2 to -24, p < 0.0001) against an increase in homocysteine levels (+4%, 95% CI 0.2–8, p=0.039) [28] An analysis of a multicenter cohort (n=2510, participants over 50 years of age) showed that the use of metformin in patients with diabetes was associated with reduced serum concentrations of vitamin B12 (average 409 pmol/L) compared with the group of patients with T2DM who did not take metformin (average 485 pmol/L, p<0.01).

Adjuvant therapy of type 2 diabetes with vitamin B12 as part of multivitamin complexes led to a significant increase in serum B12 levels (509 pmol/l) compared with a subgroup of patients who did not receive B12 subsidies (376 pmol/l, p <0.01)

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Vitamin B12-containing multivitamins were associated with a more than 6-fold reduction in the risk of hypovitaminosis B12 (levels less than 220 pmol/L) (RR 0.14, 95% CI 0.04–0.54) [29].

A systematic review and meta-analysis of 17 studies confirmed the relationship between metformin and vitamin B12 deficiency in patients with type 2 diabetes. In particular, a meta-analysis showed a statistically significant effect of a 57 pmol/L reduction in serum vitamin B12 levels (95% CI -35 to -79 pmol/L) associated with metformin use for only 2–3 months [30]

Analysis of data from the Diabetes Prevention Program Outcomes Study (DPPOS) cohort (n=3210) confirmed that long-term use of metformin (1700 mg/day, 5 years) is associated with vitamin B12 deficiency. Thus, vitamin B12 levels of less than 150 pmol/L were observed much more often (4.3%) in patients treated with metformin than in the placebo group (2.3%, p <0.05) [31]

A randomized trial conducted as part of the DPPOS project confirmed the results of the cohort study.

The cohort was randomized to receive metformin (n=1073) or placebo (n=1082) for 3 years. The use of metformin was indeed associated with an increased risk of vitamin B12 deficiency [32]. A meta-analysis of 6 randomized controlled trials confirmed that serum vitamin B12 concentrations were significantly lower in patients treated with metformin than in those treated with placebo or rosiglitazone (mean difference -54 pmol/L, 95% CI -81 to -26 pmol/L, p=0.0001). Subgroup analyses indicated 4 studies in which patients received a lower dose of metformin (less than 2000 mg/day) and 2 studies in which patients received a higher dose (2000 mg/day or more).

A distinct dose-dependent effect was observed: at doses of metformin less than 2000 mg/day, vitamin B12 concentrations decreased by an average of -37.99 pmol/L (95% CI -57 to -18 pmol/L, p=0.0001), and at doses greater than 2000 mg/day – by -78.62 pmol/L (95% CI 106–51 pmol/L,

A meta-analysis of 29 studies (n=8089) showed an increase in the number of cases of B12 deficiency in the group of participants, metformin (RR 2.45, 95% CI 1.74 to 3.44, p < 0.0001 In the metformin group, serum B12 levels were lower by an average of 65 pmol/L (95% CI -78 to -54 pmol/L, pp<0.00001

The results of this meta-analysis also confirmed the statistically significant effects of metformin on the formation of B12 deficiency [34]. A randomized trial showed that sublingual intake of vitamin B12 supplements (1 mg per day, 3 months) in patients with type 2 diabetes treated with metformin led to a significant increase in serum vitamin B12 levels (372±103 pmol/l, control – 242±40 pmol/l, p <0.04)

A cross-sectional study of patients with diabetes taking metformin (n=550, average dose 1306 mg/day, average duration of 64 months) showed that an increase in the daily dose of metformin by 1 μg/day was associated (p <0.001) with an average decrease in serum cobalamin levels by 0.042 pmol/L (95% CI -0.060 to -0.023 pmol/L) [36].

Conclusion

Metformin is a drug for thetreatment of type 2 diabetes. The drug is included in the complextherapy of type 2 diabetes and conditions associated with insulin resistance and glucose tolerance. Metformin is actively used as a geroprotector. Treatment with metformin is often prolonged. The maximum daily dose of metformin is 3000 mg / day. Patients receive metformin more often in doses of more than 850-1500 mg / sut, which can lead to a violation of the

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metabolism of vitamin B12 in the body in patients and, in particular, to a decrease in serum B12 levels, with the development of irreversible consequences.

General practitioners, endocrinologists, hepatologists should monitor the homeostasis of Vitamin B12 in patients taking metformin and inform patients about the correct prevention.

Literature

1. Alston TA. Does metformin interfere with thiamine? Arch Intern Med 2003; 163 (8): 983.
2. Xu L, Huang Z, He X et al. Adverse effect of metformin therapy on serum vitamin B12 and folate: short-term treatment causes disadvantages? Med Hypotheses 2013; 81 (2): 149–51.
3. Buvat DR. Use of metformin is a cause of vitamin B12 deficiency. Am Fam Physician 2004; 69 (2): 264; author reply 26.
4. Громова о. а., торшин и. ю., прокопович о. а. синергидные нейропротекторные эффекты тиамина, пиридоксина и цианокобаламина в рамках протеома человека. неврология и ревматология (прил. к журн. Consilium Medicum). 2016; 2: 76–84. / Gromova O.A., Torshin I.Yu., Prokopovich O.A. Synergistic neuroprotective effects of thiamine, pyridoxine and cyanocobalamin within the human proteome. Neurology and Rheumatology (Suppl. Consilium Medicum). 2016; 2: 76–84. [in Russian]
5. Adams JF, Clark JS, Ireland JT et al. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. Diabetologia 1983; 24 ((1): 16–8.
6. Muller P, Fischer H, Sorger D. Vitamin B12-level in serum of diabetics receiving long-term buformin therapy. Z Gesamte Inn Med 1981; 36 (6): 226–8.
7. Caspary WF, Zavada I, Reimold W et al. Alteration of bile acid metabolism and vitaminB12-absorption in diabetics on biguanides. Diabetologia 1977; 13 (3): 187–93.
8. маев и. в., самсонов а. а. Болезни двенадцатиперстной кишки. м.: медпресс-информ, 2005. / Maev I.V., Samsonov A.A. Bolezni dvenadtsatiperstnoi kishki. M.: MEDpress-inform, 2005. [in Russian]
9. Kapadia CR, Essandoh LK. Active absorption of vitamin B12 and conjugated bile salts by guinea pig ileum occurs in villous and not crypt cells. Dig Dis Sci 1988; 33 (11): 1377–82.
10. Tomkin GH. Comparison of the effect of parenteral with oral biguanide therapy on vitamin B12 and bile acid absorption. Ir J Med Sci 1976; 145 (1): 340.
11. Greibe E, Miller JW, Foutouhi SH et al. Metformin increases liver accumulation of vitamin B12 – an experimental study in rats. Biochimie 2013; 95 (5): 1062–5.
12. Obeid R, Jung J, Falk J et al. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie 2013; 95 (5): 1056–61.
13. Novelle M, Ali A, Diéguez C et al. Metformin: A Hopeful Promise in Aging Research. Cold Spring Harb Perspect Med 2016; 6 (3): a025932. DOI: 10.1101/cshperspect.a025932
14. Sahin M, Tutuncu NB, Ertugrul D et al. Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus. J Diabetes Complications 2007; 21 (2): 118–23.
15. Bauman WA, Shaw S, Jayatilleke E et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care 2000; 23 (9): 1227–31.
16. Rufenacht P, Mach-Pascual S, Iten A. Vitamin B12 deficiency: a challenging diagnosis and treatment. Rev Med Suisse 2008; 4 (175): 2212–4, 2216–7.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

17. Zdilla MJ. Metformin With Either Histamine H2-Receptor Antagonists or Proton Pump Inhibitors: A Polypharmacy Recipe for Neuropathy via Vitamin B12 Depletion. Clin Diabetes 2015; 33 (2): 90–5.
18. Damiao CP, Rodrigues AO, Pinheiro MF et al. Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin: a cross-sectional study. Sao Paulo Med J 2016; 134 (6): 473–9.
19. Roy RP, Ghosh K, Ghosh M et al. Study of Vitamin B12 deficiency and peripheral neuropathy in metformin-treated early Type 2 diabetes mellitus. Indian J Endocrinol Metab 2016;
20 (5): 631–7. 20. Andres E, Perrin AE, Demangeat C et al. The syndrome of food-cobalamin malabsorption revisited in a department of internal medicine. A monocentric cohort study of 80 patients. Eur J Intern Med 2003; 14 (4): 221–6.
21. Hansen CS, Jensen JS, Ridderstrale M et al. Vitamin B12 deficiency is associated with cardiovascular autonomic neuropathy in patients with type 2 diabetes. J Diabetes Complications 2017; 31 (1): 202–8. 22. Moore E, Mander A, Ames D et al. Cognitive impairment and vitamin B12: a review. Int Psychogeriatr 2012; 24 (4): 541–56.
23. Mourits-Andersen T, Ditzel J. Megaloblastic anemia caused by malabsorption of vitamin B12 during long-term metformin therapy. Ugeskr Laeger 1983; 145 (1): 25–6.
24. Callaghan TS, Hadden DR, Tomkin GH. Megaloblastic anaemia due to vitamin B12 malabsorption associated with long-term metformin treatment. Br Med J 1980; 280 (6225): 1214–5.
25. Biemans E, Hart HE, Rutten GE et al. Cobalamin status and its relation with depression, cognition and neuropathy in patients with type 2 diabetes mellitus using metformin. Acta Diabetol 2015; 52 (2): 383–93.
26. 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.
27. Damiao CP, Rodrigues AO, Pinheiro MF et al. Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin: a cross-sectional study. Sao Paulo Med J 2016; Sao Paulo: S1516-318020160050.
28. Wulffele MG, Kooy A, Lehert P et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med 2003; 254 (5): 455–63.
29. Kancherla V, Garn JV, Zakai NA et al. Multivitamin Use and Serum Vitamin B12 Concentrations in Older-Adult Metformin Users in REGARDS, 2003–2007. PLoS One 2016; 11 (8): e0160802.
30. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab 2016; 42 (5): 316–27.
31. Holmes D. Diabetes: Metformin linked to vitamin B12 deficiency. Nat Rev Endocrinol 2016; 12 (6): 312.
32. 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.
33. Liu Q, Li S, Quan H, Li J. Vitamin B12 status in metformin treated patients: systematic review. PLoS One 2014; 9 (6): e100379.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

34. 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 (1): 93–102. O.A.Gromova et al. / Consilium Medicum. 2017; 19 (4): 58–64.

35. Parry-Strong A, Langdana F, Haeusler S et al. Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial. N Z Med J 2016; 129 (1436): 67–75.

36. Beulens JW, Hart HE, Kuijs R et al. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. Acta Diabetol 2015; 52 (1): 47–53.

37. Doskina, E.V. Diabetic polyneuropathy and B12-deficient states: fundamentals of pathogenesis, ways of treatment and prevention. Pharmateca. 2011; 20: 38–43. / Doskina E.V. Diabeticheskaia polineiropatiia i B12-defitsitnye sostoianiia: osnovy patogeneza, puti lecheniia i profilaktiki. Farmateka. 2011; 20: 38–43. [in Russian]

38. Pankratova Y.V. Long-term treatment with metformin in patients with type 2 diabetes mellitus and vitamin B12: a randomized placebo-controlled trial. obesity and metabolism. 2012; 4: 56–7. /

39. Clinical guidelines for the treatment of type 2 diabetes mellitus. 2019 year Tashkent.

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