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Is it necessary to be afraid of vitamin B_{12} deficiency during metformin treatment?

ABSTRACT

Metformin, a biguanide derivative, is the most frequently used antihyperglycaemic agent in the world. Various adverse effects can occur during the drug therapy. One of them is vitamin B_{12} deficiency, which may be either asymptomatic (biochemical) or may lead to neurological and/or haematological disorders. Causal diagnosis of these disorders is hampered due to the fact that nervous system symptoms are similar to neurological complications developing over the course of diabetes mellitus. It is estimated that 5.8 to 33% of metformin treated patients have a low (below the reference level) serum vitamin B_{12} concentration. The interrelation between vitamin B_{12} deficiency and metformin usage has been known for decades and over that time many studies have been carried out to assess the issue. Unfortunately, these studies were mainly observational, retrospective and performed on nonhomogeneous groups of patients. Recently a meta-analysis of studies concerning only diabetic patients was performed and it demonstrated the existence of a relationship between metformin treatment and vitamin B_{12} deficiency. Nevertheless, further well-designed, large-scale, randomized studies performed on a homogenous group of patients and employing homogenous criteria for diagnosing vitamin B_{12} deficiency are necessary in order to decide whether serum vitamin B_{12} concentration should be routinely checked among metformin treated patients. (Clin Diabetol 2016; 5, 6: 195–198)

Key words: metformin, vitamin B_{12}, type 2 diabetes mellitus

Introduction

Metformin, a biguanide derivative, has been used in treatment of type 2 diabetes for over fifty years, and its effectiveness, safety of administration and beneficial effect on e.g. metabolic disorders, cardiovascular system, promoting reduction of body weight or postulated anti-cancer action made it the first-line medication according to international and Polish standards of care for patients with diabetes. Therefore it is one of the most frequently used antihyperglycaemic agents in the world [1–3]. Adverse effects of metformin include gastrointestinal disorders and possible lactic acidosis, though the risk of the latter is low, approximately 3.3–4.3/100,000 patient-years. Another adverse effect related to long-term administration of metformin is a potential risk of vitamin B_{12} deficiency [4, 5]. Vitamin B_{12} deficiency may be clinically significant if concentration of this vitamin in blood serum falls below 150 pmol/L. The accepted lower limit of reference levels of serum vitamin B_{12} concentration is typically 150–220 pmol/L. According to the National Diet and Nutrition Survey conducted in the UK in 2004, 20% of men and 27% of women (UK residents) aged 19–64 years, had a vitamin B_{12} concentration below 200 pmol/L [3]. Similarly, the EPIC (European Prospective Investigation into Nutrition and Cancer) study, carried out at 23 centres

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in 10 European countries, indicated that 5% adults under the age of 60 had a vitamin B_{12} concentration below 175 pmol/L [6, 7]. Water-soluble vitamin B_{12}, so-called cobalamin, plays a fundamental role in the process of DNA synthesis and proper functioning of haematopoietic and nervous systems [5]. Symptoms of the classic form of vitamin B_{12} deficiency include disorders such as macrocytic anaemia, peripheral neuropathy, depression and cognitive function impairment; however, not all patients with low serum vitamin B_{12} concentration exhibit clinical symptoms of deficiency [8]. Unfortunately, with respect to metformin, despite the fact that the occurrence of vitamin B_{12} deficiency related to treatment using this drug has been known for over 40 years, prevalence and clinical significance of this phenomenon is not fully known. Results of studies carried out among type 2 diabetic patients estimate that vitamin B_{12} deficiency diagnosed via laboratory tests concerns 5.8% to 33% of tested patients [9, 10]. Such a wide range stems most likely from the fact that the criteria for defining vitamin B_{12} deficiency in those tests were not homogeneous. This paper attempts to systematize available information concerning the effect of metformin administration on vitamin B_{12} deficiency and the scale of this phenomenon.

Role of vitamin B_{12} in the human body

Vitamin B_{12} performs its biological action through two primary enzymatic pathways: methylation of homocysteine to methionine and conversion of methylmalonyl coenzyme A (CoA) to succinyl coenzyme A. In the first of these processes, vitamin B_{12} is a cofactor facilitating methylation of homocysteine to methionine, which is subsequently activated to S-adenosyl methionine, which in turn donates methyl groups to their acceptors such as myelin, neurotransmitters and membrane phospholipids. This is why a metabolically significant vitamin B_{12} deficiency results in impaired methylation and increased homocysteine concentration in cells and blood serum; homocysteine, in turn, has a negative effect on neurons and vascular endothelium. As for the second mentioned metabolic pathway, vitamin B_{12} deficiency leads to increased methylmalonic acid (MMA) concentration in the blood serum and impaired synthesis of neuronal membrane fatty acids [11]. Furthermore, vitamin B_{12} is essential for synthesis of monoamines or neurotransmitters such as serotonin or dopamine which are not being synthesized correctly when the deficiency of vitamin B_{12} exists [12]. The above information explains why vitamin B_{12} deficiency results in symptoms of a nervous system disorder, which may manifest as autonomic and peripheral neuropathy, dementia and mental disorders [11]. Moreover, hyperhomocysteinaemia is linked with increased risk of cardiovascular events due to its toxic effect on blood cells and vessels [13, 14].

Potential mechanisms of vitamin B_{12} deficiency

The primary source of vitamin B_{12} for humans are animal proteins. After ingestion, vitamin B_{12} is released from the proteins using pepsin and gastric acid. Next, it binds to the R-protein produced by salivary glands and travels to the duodenum, where in an alkaline environment and with the use of pancreatic proteases the R-protein is hydrolysed and vitamin B_{12} is released and binds to the intrinsic factor (IF) produced by the parietal cells of the stomach. The intrinsic factor-vitamin B_{12} complex is resistant to proteolytic degradation. The complex binds to a specific receptor in the mucosa of the terminal ileum, where vitamin B_{12} is absorbed, a process intermediated by calcium ions. Vitamin B_{12} is then released through degradation of IF. The freed vitamin B_{12} binds yet to another transport protein, so-called transcobalamin II (TC-II), and is released into circulation. The vitamin B_{12}-TC-II complex, also called holo-TCII, is actively taken up by the liver, bone marrow and other cells of the body. Vitamin B_{12} is primarily stored in the liver, up to 90% of total vitamin B_{12} content in the body [5, 15]. Any factor disrupting gastrointestinal absorption of vitamin B_{12} may lead to its deficiency. Vitamin B_{12} deficiency is therefore caused by e.g. insufficient supply of vitamin B_{12} in the diet, which is often observed in case of vegetarians and alcoholics, disorder of gastrointestinal absorption of this vitamin, which may be caused by chronic inflammation of the gastric mucosa, coeliac disease, chronic pancreatitis or treatment using drugs such as metformin or proton pump inhibitors. Not all patients diagnosed with vitamin B_{12} deficiency in the blood serum will exhibit symptoms of it. The symptoms of this vitamin deficiency typically occur only after its reserves stored in the liver had been exhausted, which may take between 1 up to 5 years; during that time serum vitamin B_{12} concentration may be low without producing any symptoms [16].

Metformin may increase the risk of vitamin B_{12} deficiency via several mechanisms. Stimulation of small intestine bacterial overgrowth (SIBO) is one of these mechanisms. SIBO causes maldigestion and malabsorption, which in turn lead to vitamin B_{12} deficiency. It is postulated that dysbacteriosis of the gastrointestinal tract is caused by changes in peristalsis of the gastrointestinal tract or increased glucose concentration in the small intestine. Metformin may also lead to competitive inhibition or inactivation of vitamin B_{12} absorption through reducing the amount of intrinsic

factor [17]. Furthermore, it has been shown that metformin might inhibit calcium-dependent absorption of the vitamin B_{12}-intrinsic factor complex in the distal ileum. Calcium cations are an obligatory factor in the process of vitamin B_{12}-intrinsic factor complex binding to the surface receptors of distal ileal enterocytes [18]. Additionally, the risk of vitamin B_{12} deficiency increases with age, daily metformin dose and duration of its administration [19, 20].

Vitamin B_{12} deficiency in metformin treated patients — the scale of the problem

For many years, studies concerning the relationship between metformin and vitamin B_{12} deficiency among type 2 diabetic patients were mostly observational, case-control and retrospective, and studied groups typically comprised few subjects; only several studies were prospective, placebo-controlled and randomized. Most randomized studies featured groups comprising few subjects and generally were not continued for longer than 6 months [20–22]. Niafar et al., authors of one of the recently performed meta-analyses of the above studies, note that an important factor limiting their comparability is the fact that administered metformin doses were not homogeneous. The studies also utilized different cut-off points for defining vitamin B_{12} deficiency. In most studies, vitamin B_{12} concentration level lower than 150 pmol/L was considered as deficiency; however, this criterion varied between 74–221 pmol/L. In turn, nonhomogeneous criteria for diagnosing vitamin B_{12} deficiency inevitably lead to overestimating or underestimating its actual incidence. Moreover, most studies did not include information concerning the initial level of vitamin B_{12} concentration, before metformin treatment commenced [23]. Furthermore, studied groups were not homogeneous, since in many cases not only type 2 diabetic patients, but also other patient populations treated with metformin had been included.

In 2016, Aroda et al. published the results of a secondary analysis of DPP (Diabetes Prevention Program)/ /DPPOS (Diabetes Prevention Program Outcomes Study), which assessed the risk of vitamin B_{12} deficiency in patients at risk of type 2 diabetes treated with metformin. This was the biggest and longest (average period of observation was 13 years) cohort study assessing vitamin B_{12} concentration during metformin treatment conducted so far. Authors showed that administration of metformin was linked to vitamin B_{12} deficiency diagnosed via laboratory tests. Moreover, an increased homocysteine concentration in the blood serum was also observed, which suggests tissue vitamin B_{12} deficiency. Furthermore, on average 5 years after randomization, increased incidence of anaemia among patients treated using metformin was also noticed. However, vitamin B_{12} deficiency was also observed with lack of anaemia. Peripheral neuropathy was more frequent in patients with vitamin B_{12} deficiency, but it should be noted that it occurred in a small group of patients (13 out of 56 metformin treated patients), in whose cases vitamin B_{12} deficiency occurred after 9 years of observing over one thousand patients treated with metformin [24].

Over 20 years ago, De Fronzo et al. carried out one of the first randomized studies among patients with type 2 diabetes aiming to assess incidence of vitamin B_{12} deficiency. They found that serum vitamin B_{12} concentration of metformin treated patients was reduced by 22% and 29% compared to placebo and glyburide, respectively [25].

A study carried out by Jager et al. is the biggest randomized prospective study assessing the relationship between metformin treatment and incidence of vitamin B_{12} deficiency among patients with type 2 diabetes performed so far. Its results demonstrated that, after more than 4 years of observation, metformin treatment was linked to a 19% reduction in serum vitamin B_{12} concentration, a 5% increase in homocysteine concentration and an 11-fold increase in risk of low vitamin B_{12} concentration compared to placebo [20]. In 2014, Liu et al., and in 2015, Niafar et al. performed meta-analyses of studies, where they clearly demonstrated that in fact there is a relationship between vitamin B_{12} deficiency and administration of metformin; however, analysed studies were carried out on nonhomogeneous groups of patients (e.g. patients with diabetes, polycystic ovary syndrome) [23, 26].

Only in 2016 Chapman et al. performed a systematic review and a meta-analysis of results of studies (observational and interventional) concerning the relationship between metformin and vitamin B_{12} deficiency carried out on a homogeneous group of type 2 diabetic patients [27]. Results of studies analysed by Chapman et al. indicated decreased vitamin B_{12} concentration and increased risk of borderline vitamin B_{12} concentration in case of patients treated with metformin. Most interventional studies were characterized by a short duration (up to 4 months), but their results suggested a significant decrease in serum vitamin B_{12} concentration while metformin was being administered. A meta-analysis of four interventional studies indicated a substantial decrease in vitamin B_{12} concentration of 57 pmol/L (95% CI: –35 to –79). Such a sharp reduction of vitamin B_{12} concentration could be clinically significant, causing a clear vitamin B_{12} deficiency (< 150 pmol/L) or a drop in concentration levels to borderline values (150–220 pmol/L) in case of patients

whose initial vitamin B_{12} concentration was between 207–277 pmol/L.

Results of meta-analysis performed by Chapman et al. are consistent with results of meta-analyses performed by Niafar et al. and Liu et al., who analysed studies carried out not only among patients with diabetes. Similar results in different groups of patients might indicate that the effect of metformin on vitamin B_{12} deficiency does not vary depending on studied patient population [27].

Summary

Current clinical recommendations concerning care for patients with diabetes do not require screening for vitamin B_{12} deficiency to be performed in case of patients treated with biguanide derivative. When clinical symptoms, such as macrocytic anaemia, peripheral neuropathy or mental disorders, occur in long-term metformin treated patients, marking serum vitamin B_{12} concentration is worth considering [23].

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