

## Vitamin B12 Deficiency and Peripheral Neuropathy in patients with Type 2 Diabetes Mellitus Treated with Metformin. An integrative review

### Deficiência de Vitamina B12 e Neuropatia Periférica em pacientes com Diabetes Mellitus Tipo 2 Tratados com Metformina. Uma revisão integrativa

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#### **Maria Júlia Lima Eugenio Dias**

Graduanda de Medicina

Institution: Centro de Pesquisa Avançada em Medicina da União das  
Faculdades dos Grandes Lagos (CEPAM-UNILAGO)

Address: Rua Dr. Eduardo Nielsen, 960, Jardim Novo Aeroporto, São José do Rio  
Preto - SP, CEP: 15030-070

E-mail: mjlimadias@outlook.com

#### **Bruna Letícia Buzati Pereira**

Livre-Docente

Institution: Centro de Pesquisa Avançada em Medicina da União das  
Faculdades dos Grandes Lagos (CEPAM/ UNILAGO)

Address: Rua Dr. Eduardo Nielsen, 960, Jardim Novo Aeroporto, São José do Rio  
Preto - SP, CEP: 15030-070

E-mail: brunabuzati@hotmail.com

#### **Silvana Regina Perez Orrico**

Livre-Docente

Institution: Centro de Pesquisa Avançada em Medicina da União das  
Faculdades dos Grandes Lagos (CEPAM/ UNILAGO)

Address: Rua Dr. Eduardo Nielsen, 960, Jardim Novo Aeroporto, São José do Rio  
Preto - SP, CEP: 15030-070

E-mail: silvana.regina@unilago.edu.br

#### **ABSTRACT**

*Background/Purpose:* Type 2 diabetes mellitus (T2DM) is a worldwide pathology with several complications, and 50% of patients with T2DM develop peripheral neuropathy (PN) in the long term. The present study aimed to review the literature on the association between PN and vitamin B12 deficiency in patients with T2DM treated with metformin. *Materials and methods:* A literature review was carried out in the PubMed Central, Cochrane, Scielo, Scopus and Embase databases, from 2015 to 2021. We found 755 studies, of which 16 were included. *Results:* The serum level of vitamin B12 was lower in individuals with at least one neurological symptom. Treatment with metformin was associated with reduced serum vitamin B12 levels, and its use was defined as a probable cause of PN due to reduced vitamin B12. Studies that performed supplementation with methylcobalamin demonstrated significant improvement in neuropathic symptoms. Vitamin B12 supplementation therapy for diabetic patients undergoing metformin treatment has been suggested. *Conclusion:* Deficiency of vitamin B12 associated to

metformin can be considered a risk factor for PN. Periodically evaluation of serum levels of vitamin B12 is recommended for patients on metformin treatment.

**Keywords:** Diabetic mellitus, Diabetic neuropathy, Metformin, Peripheral neuropathy, Vitamin B12 deficiency.

## RESUMO

*Introdução/Propósito:* O diabetes mellitus tipo 2 (DM2) é uma patologia mundial com diversas complicações, e 50% dos pacientes com DM2 desenvolvem neuropatia periférica (NP) a longo prazo. O presente estudo teve como objetivo revisar a literatura sobre a associação entre NP e deficiência de vitamina B12 em pacientes com DM2 tratados com metformina. *Materiais e métodos:* Foi realizada revisão da literatura nas bases de dados PubMed Central, Cochrane, Scielo, Scopus e Embase, no período de 2015 a 2021. Foram encontrados 755 estudos, dos quais 16 foram incluídos. *Resultados:* O nível sérico de vitamina B12 foi menor em indivíduos com pelo menos um sintoma neurológico. O tratamento com metformina foi associado à redução dos níveis séricos de vitamina B12, e seu uso foi definido como provável causa de NP devido à redução da vitamina B12. Estudos que realizaram suplementação com metilcobalamina demonstraram melhora significativa dos sintomas neuropáticos. Foi sugerida a terapia de suplementação de vitamina B12 para pacientes diabéticos em tratamento com metformina. *Conclusão:* A deficiência de vitamina B12 associada à metformina pode ser considerada um fator de risco para PN. A avaliação periódica dos níveis séricos de vitamina B12 é recomendada para pacientes em tratamento com metformina.

**Palavras-chave:** Diabético mellitus, Neuropatia diabética, Metformina, Neuropatia periférica, Deficiência de vitamina B12.

## 1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and multifactorial metabolic disorder that is on the rise all over the world and characterized by insulin resistance, representing 90% of all cases of diabetes [1]. Peripheral neuropathy (PN) is the most common complication, affecting approximately 50% of patients and accounting for two-thirds of non-traumatic amputations and disabilities [2].

PN includes several syndromes that affect the peripheral nervous system and are characterized by dysfunction of one or more nerves resulting in pain, muscle atrophy, decreased deep tendon reflexes, vasomotor symptoms, and sensory disturbances (such as paresthesias and dysesthesias). In the end, it evolves to a reduction in protective sensitivity. PN has no defined etiology and may be related to several diseases, including diabetes, alcoholism and viral infections [3]. About 31% of patients with PN have diabetes, resulting in diabetic foot associated with ulcers, infections and/or amputations [2,4].

The Toronto Consensus defined typical diabetic peripheral neuropathy (DPN) as an asymmetric sensory and motor polyneuropathy that occurs due to changes in microvasculature

and to metabolic disturbances triggered by the ongoing hyperglycemic state. It generates a high cost for public health, as patients with neuropathy have a treatment that is difficult to control and manage. Therefore, the goal should be the identification of risk factors for its development and the prevention and control of sequelae [2,5].

Furthermore, metformin (1,1-dimethylbiguanide), a drug belonging to the biguanide class, is used as a first option for the treatment of T2DM and acts by decreasing hepatic gluconeogenesis and improving the peripheral utilization of glucose. However, in addition to side effects, such as nausea, abdominal discomfort, and lactic acidosis, metformin may inhibit the absorption of vitamin B12 in the ileum [6]. Vitamin B12 or cobalamin, also known as cyanocobalamin, is a water-soluble molecule important for the maintenance of the blood, nervous and cardiovascular systems. Its deficiency is associated with anemia, memory deficits, cognitive dysfunction, dementia and depressive disorders. [5,6].

Prolonged use of metformin then becomes a probable cause of vitamin B12 deficiency, as the drug modifies the action of calcium on ileal cells, altering the absorption of vitamin B12 intrinsic factor. However, despite numerous evidence on the reduction of vitamin B12 levels with the use of metformin. The proposed hypotheses include changes in small bowel motility due to hypocalcemia and competitive inactivation of its absorption. Thus, some studies have sought to determine the dose and duration of treatment with metformin that may be nutritionally harmful [7-9].

Several studies have demonstrated the link between vitamin B12 reduction and neuropathy in patients with T2DM. Bearing in mind that many individuals with diabetes receive treatment with metformin, which is a drug that can lead to reduced plasma levels of vitamin B12, a potential health problem may arise: neuropathy [3,7,8].

In view of the alarming panorama of 537 million individuals with diabetes worldwide in contemporary times, with a forecast to increase to 783 million in 2045 [1], there is an urgent need to prevent and treat possible complications associated with diabetes. The present study aims to review the literature on the association between PN and vitamin B12 deficiency in patients with T2DM.

## **2 MATERIALS AND METHODS**

The eligibility of the studies occurred according to the Population, Intervention, Comparison, Outcome, Study (PICOS) criterion.

Participant (Population): Individuals over 18 years of age, of both genders, without distinction of race or origin, and with T2DM for more than 5 years using hypoglycemic medication.

I (exposure, intervention): Individuals with vitamin B12 deficiency.

C (control): Individuals without vitamin B12 deficiency.

O (outcome): Presence of PN.

Study type (S): Articles in English or Spanish were selected. Prospective or retrospective, analytical observational studies (cohort, case-control, and cross-sectional) and systematic review with meta-analysis, which evaluated the correlation between PN and vitamin B12 deficiency in patients with T2DM, were considered eligible. In addition, interventional studies, such as clinical trials, describing the effect of vitamin B12 supplementation on PN in patients with T2DM were also considered. The search was limited to human studies.

Inclusion criteria were individuals with T2DM, serum dosage of vitamin B12, clinical and/or laboratory neurological assessment, and description of medications used.

The following were excluded: expert opinion, case reports, single case experimental, case series, descriptive studies, prediabetic individuals, individuals with type 1 diabetes mellitus or other types of diabetes, or pregnancy.

Sources and Research Methods: A systematic search was conducted on the PUBMED (US National Library of Medicine), SCIELO (Scientific Electronic Library), COCHRANE LIBRARY, SCOPUS and EMBASE platforms using the descriptors “peripheral neuropathy,” “diabetic peripheral neuropathy,” “diabetic neuropathy,” “type 2 diabetes,” “vitamin B12,” “vitamin B12 deficiency,” and Boolean operators and/or. Articles published from January 2015 to December 2021 were collected. In addition to the cited bases, a search was performed by manual scanning of the reference lists of identified articles.

### 3 RESULTS

A total of 755 articles were found in the aforementioned databases, 61 of which were removed because they were duplicates, 473 were excluded after reading the abstract and 221 were analyzed for inclusion and exclusion criteria (Figure 1). Of these, 16 articles were selected and the characteristics of the studies are described in Table 1 and Table 2.

Figure 1: Selection of studies

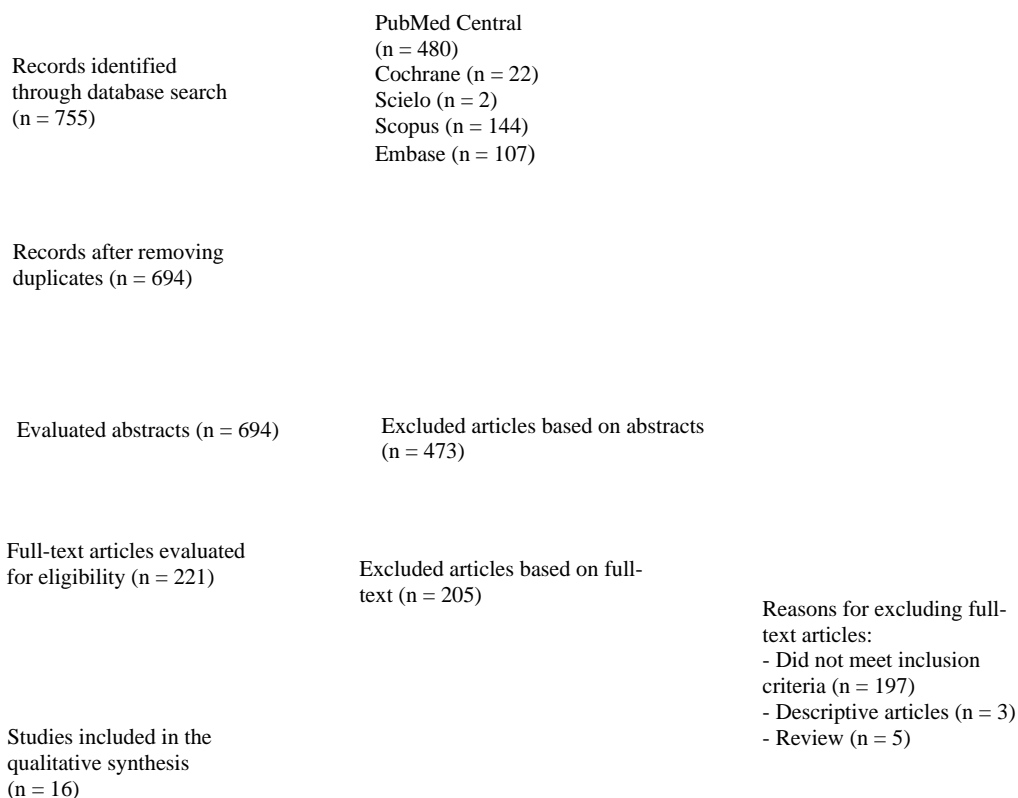


Table 1: Relationship between Vitamin B12 Deficiency and Peripheral Neuropathy

Author/ year	Country	Type of study	Patients	Method of peripheral neuropathy assessment	Metformin	Results
Russo et al., 2015 [10]	Italy	Cross-sectional	263 T2DM patients 30% with PND	Measurement of ulnar (motor and sensory), tibial and peroneal conduction velocity	124 patients on metformin treatment > 6 months (monotherapy or combined with another hypoglycemic agent)	Vitamin B12 levels were not associated with DPN Metformin-treated subjects showed significantly lower levels of vitamin B12, but the prevalence of PND was not different when compared to those not treated with the drug (33% vs. 27%).
Roy et al., 2016 [11]	India	Cross-sectional	90 patients with T2DM	NCV	Group Metformin > 6 months: 35 Group Metformin + another hypoglycemic agent: 20 Group no metformin: 35	Metformin causes reduced cobalamin levels, leading to peripheral neuropathy in individuals with T2DM. 54.28% of patients treated with metformin and 35% of the metformin + another hypoglycemic agent group had peripheral neuropathy.

<b>Ahmed et al., 2016 [12]</b>	South Africa	Cross-sectional	121 patients with T2DM Vitamin B12 deficiency (< 150 pmol/L): 28.1% of the total sample	NTSS-6 Peripheral neuropathy: NTSS-6 > 6	Average daily dose: 2,4 g Average duration of use: 9,6 years	Vitamin B12 deficiency was not associated with peripheral neuropathy. Approximately one-third of patients using metformin had vitamin B12 deficiency.
<b>Raizada et al., 2017 [13]</b>	India	Cross-sectional	183 patients with T2DM Vitamin B12 deficiency (< 150 pmol/L): 35.5% of the metformin group 33.8% of the non-metformin group	DNS DNE	Metformin group: 121 Non-metformin group: 62	No relationship between vitamin B12 deficiency and peripheral neuropathy. Metformin use is associated with lower serum vitamin B12 levels.
<b>Zalaket et al., 2017 [14]</b>	Lebanon	Cohort	200 patients with T2DM Vitamin B12 deficiency: 22,5% Boundary values: 33%	Questionnaire with neurological symptoms (peripheral, autonomic, sensory and motor)	Entire sample on metformin	Lower serum levels of vitamin B12 in individuals with at least one neurological symptom. The longer the use of metformin was, the lower the level of vitamin B12.
<b>Gupta et al., 2017 [15]</b>	India	Prospective, observational study	50 patients with T2DM Vitamin B12 deficiency (< 150 pmol/L): 56%	TCNS NCV TCSS	Entire sample on metformin treatment for at least 6 months	Higher incidence of peripheral neuropathy for individuals with B12 deficiency The longer the duration of metformin treatment was, the lower the serum level of B12 and the greater the chance of developing DPN.
<b>Metaxas et al., 2017 [16]</b>	Switzerland	Cross-sectional	50 patients with T2DM Vitamin B12 deficiency (< 200 pmol/L): 38%	NSS NDS	29 patients were treated with metformin 21 patients were not treated with metformin	No significant difference between vitamin B12, HoloTc and homocysteine levels in patients with mild, moderate and severe neuropathy. Age and duration of DM influenced the occurrence of severe neuropathy. Lower plasma levels of B12 and HoloTc in the group using metformin.
<b>Alharbi et al., 2018 [17]</b>	Qatar	Retrospective observational study	412 individuals with T2DM Vitamin B12 deficiency: 7.8% of the total sample, 9.4% in metformin users and 2.2% in non-metformin users	TCSS	319 metformin users 93 non-metformin users	Peripheral neuropathy was not associated with vitamin B12 deficiency or metformin use. Low vitamin B12 levels were associated with metformin dose and treatment time.

<b>Out et al., 2018 [18]</b>	Netherlands	Randomized controlled clinical trial (4.3 years)	390 patients with T2DM on previous insulin treatment  Vitamin B12 deficiency: 2.6% in the placebo group and 1% in the metformin group at baseline	Valk Score: absent (0 points); light (1-9 points); moderate (10-18 points) or severe (19-33 points)	Metformin group: 196  Placebo group: 194  Treatment period: 4.3 years  Average dose: 2050 mg	Metformin use resulted in increased serum MMA levels. It was associated with a small increase of a neuropathy score.
<b>Nareddy et al., 2018 [6]</b>	India	Cross-sectional	50 patients with T2DM	Subjective evidence of neuropathy	Categorized metformin use by treatment time: < 2 years 2-5 years 5-8 years ≥ 8 years	Neuropathy was not related to metformin-induced vitamin B12 deficiency.  Substantial reduction in vitamin B12 levels for patients with longer duration of metformin use (5-8 years), with a greater effect for men.
<b>Yang et al., 2019 [19]</b>	China	Meta-analysis	31 studies  5500 patients with T2DM	Not described	Metformin group: 2709 patients (425 patients with daily dose ≥ 2000 mg)  Not metformin group: 2195 patients  Average dosage: 1135 ± 496 mg  Average duration of treatment: 72 ± 62 months	No significant differences in the risk of peripheral neuropathy between populations with and without metformin treatment.  Daily dose and longer treatment time with metformin were risk factors for vitamin B12 deficiency. No relationship between vitamin B12 deficiency and peripheral neuropathy.  Peripheral neuropathy was associated with longer duration of diabetes.
<b>Khalaf et al., 2019 [9]</b>	Iraq	Cross-sectional	66 patients with T2DM  Mean duration of DM: 104 ± 71.8 months Vitamin B12 deficiency: 29% of total sample	NMSI	Average dosage: 1135 ± 496 mg  Average duration of treatment: 72 ± 62 months	Peripheral neuropathy was associated with longer duration of diabetes.
<b>Miyan et al., 2020 [20]</b>	Pakistan	Cross-sectional	932 patients with T2DM  Vitamin B12 deficiency (< 200 pg/mL): 3.3% of total sample, 3.9% in metformin users 2.1% in no metformin-users	Douleur Neuropathique 4 (DN4)  DNS  VPT	Metformin users for > 2 years: 645  No metformin-users: 287	Metformin users with vitamin B12 deficiency: VPT score > 25 or DN4 ≥ 4 significantly higher compared to no metformin-users.  Greater vitamin B12 deficiency in individuals with T2DM using metformin.  Lower B12 levels associated with metformin duration and dose.

<b>Hashem et al., 2021 [21]</b>	Egypt	Case-control, prospective, analytical, observational	150 patients with T2DM Vitamin B12 deficiency (<210 pmol/L): 33% in metformin users 4% in no metformin users	TCSS Electrophysiological studies	Metformin users for >6 months: 75 No metformin users: 75	Metformin-treated patients: significantly lower plasma cobalamine and significantly higher levels of homocysteine. Significant inverse relationship between severity DPN and cobalamine level. Severity of DPN was directly related to higher levels of MMA and homocysteine.
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T2DM: Type 2 Diabetes Mellitus; DPN: Diabetic Peripheral Neuropathy; MMA: Methylmalonic Acid; HoloTc: Holotranscobalamin; VPT: Vibratory Perception Threshold; DN4: Douler Neuropathique 4; NPS: Neuropathic Pain Scale; HbA1c: Glycated Hemoglobin; NCV: Nerve Conduction Velocity Test; NTSS-6: Neuropathy Total Symptom Score 6; DNS: Diabetic Neuropathy Symptom Score; DNE: Diabetic Neuropathy Examination Score; NSS: Neuropathy Symptom Score; NDS: Neuropathy Disability Score; TCNS: Toronto Clinical Neuropathy Score; NMSI: Neuropathy Michigan Score Index; TCSS: Toronto Clinical Score System.

Table 2: Effect of Vitamin B12 Supplementation on Peripheral Neuropathy

Author	Country	Type of study	Patients	Method of peripheral neuropathy assessment	Vitamin B12 supplementation	Results
<b>Chauhan et al., 2018 [22]</b>	India	Open-labeled prospective study	50 patients with T2DM Evidence of peripheral neuropathy: 64%	DNS Questionnaire SAS Questionnaire Standardized Nerve Conduction Ankle reflex-peripheral neuropathy test DNE	1.5 mg/day of methylcobalamin for 3 months for patients with peripheral neuropathy	Significant improvement in symptoms of polyneuropathy. (DNS $1.63 \pm 0.75 \times 1.41 \pm 0.80$ ; SAS $4.94 \pm 2.60 \times 4.59 \pm 2.39$ ; END $3.34 \pm 1.73 \times 3.06 \pm 1.54$ ) after 3 months of methylcobalamin therapy.
<b>Didangelos et al., 2021 [23]</b>	Switzerland	Randomized controlled clinical trial	90 patients with T2DM on metformin treatment for at least 4 years	SNCV SNAP VPT CARTs ESCH and ESCF MNSIQ and MNSIE QL Pain Score	Methylcobalamin group: 44 subjects 1 mg/day of methylcobalamin for 12 months  Placebo group: 46 subjects	Vitamin B12 supplementation led to significant improvement in VPT, MNSIQ, QOL, pain score, SNCV, SNAP and ESCF.  CARTs and MNSIE improved but not significantly, without improvement in the placebo group.  There was a significant increase in vitamin B12 levels in the active treatment group.

DNS: Diabetic Neuropathy Symptom; SAS: Survey of Autonomic Symptoms; DNE: Diabetic Neuropathy Examination; SNCV: Sural Nerve Conduction Velocity; SNAP: Sural Nerve Action Potential; VPT: Vibration Perception Threshold; CARTs: Cardiovascular Autonomic Reflex Tests; MNSIQ and MNSIE: Michigan Neuropathy Screening Instrument Questionnaire and Examination; ESCH and ESCF: Electrochemical Skin Conductance in Hands and Feet; QL: Quality of Life



### 3.1 RELATIONSHIP BETWEEN VITAMIN B12 DEFICIENCY AND PERIPHERAL NEUROPATHY

A total of 14 studies that evaluated the relationship between vitamin B12 deficiency and PN were included in this review (Table 1). The results show that only six studies showed this correlation directly or indirectly [11,14,15,18,20,21].

In a study evaluating, in addition to vitamin B12 levels, the levels of holotranscobalamin (a bioactive form of vitamin B12) and homocysteine (elevated levels in vitamin B12 deficiency) and their relationship with PN (Neuropathy Symptom Score [NSS] and Neuropathy Disability Score [NDS]), no significant differences were found between vitamin B12 and homocysteine levels in patients with mild, moderate, or severe PN [16].

### 3.2 RELATIONSHIP BETWEEN METFORMIN AND PERIPHERAL NEUROPATHY

Two studies related the use of metformin as a cause of PN due to the reduction of vitamin B12 [11,15], while two studies associated metformin use with the severity of PN, also related to vitamin B12 or methylmalonic acid levels [18,20]. On the other hand, four of the 14 studies did not find a higher risk of developing PN in the population receiving metformin, although they found a relationship between the drug's use and vitamin B12 deficiency [6,10,17,19].

According to a study, even short-term treatment with metformin causes a reduction in cobalamin (vitamin B12) and folic acid levels and an increase in serum homocysteine, leading to PN due to reduced nerve conduction velocity in individuals with T2DM [11].

On the other hand, one study showed that subjects treated with metformin for a period longer than 6 months had significantly lower levels of vitamin B12. However, the prevalence of DPN was not different when comparing subjects treated or not with the drug (33% vs. 27%). In this study, PN was associated with other factors, such as age and duration of diabetes [10].

### 3.3 RELATIONSHIP BETWEEN METFORMIN AND VITAMIN B12 DEFICIENCY

Of the 14 studies described in Table I, 13 studies showed that the use of metformin, which is a hypoglycemic medication widely used in the treatment of T2DM, is intrinsically linked to considerably reduced levels of serum vitamin B12 [6,10-21].

One study showed that the use of metformin leads not only to a reduction in vitamin B12 levels but also to an increase in methylmalonic acid (MMA), which is a more specific marker of tissue vitamin B12 deficiency and is associated with worsening of polyneuropathy [18].

Duration of treatment and dose of metformin are related to increased risk of vitamin B12 deficiency. According to six studies, the longer the treatment time was, the lower the serum concentration of vitamin B12 [6,14,15,17,19,20].

### 3.4 RELATIONSHIP BETWEEN VITAMIN B12 SUPPLEMENTATION AND PERIPHERAL NEUROPATHY

In the databases used in this review and within the inclusion and exclusion criteria, only two studies were found that performed vitamin B12 supplementation in patients with PN [22,23]. Both studies showed significant improvement in PN symptoms (Table 2).

## 4 DISCUSSION

Peripheral neuropathy is the most common chronic complication of diabetes, with approximately 10–20% of patients having severe symptoms [2,4]. Among the main risk factors for the development of DPN are duration of diabetes, advanced age, high glycated hemoglobin, smoking, diabetic retinopathy, high body mass index (BMI), altered fasting plasma glucose, high diastolic blood pressure, low vitamin B12 levels, metformin use, increased serum levels of MMA and homocysteine and decreased holotranscobalamin [2,5,7].

In the present review, the direct relationship between vitamin B12 deficiency and PN in diabetic patients in use of metformin was not proven for the most studies. It is important to highlight that the studies had different designs, most being cross-sectional, with only one randomized clinical trial. In addition, the method of evaluation of PN in the studies was heterogeneous, and the populations were unequal in terms of important factors, such as duration of diabetes and level of metabolic control, which may have contributed to the outcomes presented.

Another important factor for the results found were the methods for measuring vitamin B12 deficiency. Reduced levels of holotranscobalamin and increased levels of homocysteine can be considered as the best markers for vitamin B12 deficiency, especially in the older population, being more suggestive of tissue deficiency of the vitamin [10,16,18].

Metformin therapy is the first option for the treatment of T2DM and long-term therapy with the hypoglycemic agent (more than 2 years) has been shown to significantly reduce plasma levels of vitamin B12, which can lead to PN, cognitive impairment, and subacute bone marrow degeneration with macrocytic anemia. Even short-term therapy is capable of promoting a decrease in serum levels of vitamin B12 and folic acid, as well as an increase in homocysteine

levels, which requires special attention for patients using hypoglycemic agents and who have other predisposing factors for the onset of DPN [11].

Most of the studies shown in Table I related treatment with metformin to the reduction of serum levels of vitamin B12, increasing, according to the authors, the chances of developing PN [6,11–21]. Thus, although no direct relationship was found between vitamin B12 deficiency and PN in these studies, the authors define vitamin deficiency as a probable risk factor. Vitamin B12 deficiency is intrinsically linked to the metformin dose and duration of use [6,15,17,19–21].

On the other hand, oral methylcobalamin supplementation demonstrated beneficial effects on somatosensory symptoms, such as pain and paresthesias, in addition to improving the clinical parameters of the tests used to evaluate PN, without adverse effects associated with supplementation [22,23].

Other studies evaluated the effect of supplementation with the combination of L-methylfolate, methylcobalamin (active form of vitamin B12) and pyridoxal-5-phosphate (active form of vitamin B6) in individuals with DPN and found that the vitamin compound resulted in an improvement in symptoms and quality of life [24,25].

In the present review, most studies highlight the role of vitamin B12 in the treatment or prevention of PN, particularly in patients with diabetes treated with metformin. Oral vitamin B12 supplementation therapy is advised in patients being treated with the hypoglycemic agent, justifying that it preserves the patient's autonomy, has a reduced cost and is lower risk to patients using anticoagulants [6,9–11,14,19,22,23].

Studies recommend that serum levels of vitamin B12 be checked periodically in patients using metformin. [15,26]. Infante et al (2021) have proposed a list of criteria for screening and testing of vitamin B12 status in metformin-treated patients, among them duration of metformin therapy of  $\geq 5$  years, age  $\geq 65$  years and metformin dose  $\geq 1500$  mg/d for a period of at least 6 months [26]. Gupta et al. (2018) also indicate that diabetic patients undergoing treatment with the hypoglycemic agent, even in the absence of signs and symptoms of neuropathy, should be evaluated with electrophysiological tests [15]. In addition, the parenteral or sublingual routes should be considered in case of deficiency, because the enteral mechanisms are compromised by the interaction of metformin [15,26].

Establishing the origin of vitamin B12 deficiency is complex, as it can be related to nutritional deficiency, inadequate absorption or the use of medications. Current guidelines recognize this disadvantage related to the use of metformin; however, the hypoglycemic agent remains one of the main treatments for T2DM due to numerous advantages.

In order for the influence of vitamin B12 deficiency on the occurrence of DPN to be properly evaluated, it is understood that other studies should be carried out with more homogeneous populations regarding the duration and metabolic control of diabetes, with more sensitive and specific methods of measuring the vitamin levels, as well as the use of methods of evaluation of PN of recognized accuracy. This does not exclude the importance, demonstrated here, of carrying out periodic assessments of vitamin B12 levels for patients with diabetes, particularly those using metformin, seeking to prevent one of the predisposing factors to the onset of PN.

## **5 CONCLUSION**

The use of metformin is intrinsically related to the decrease in serum levels of vitamin B12, which can lead to deleterious clinical outcomes, such as PN. Despite the controversy over whether vitamin B12 deficiency leads to PN, it can be considered a risk factor. Periodic assessment of serum concentrations of vitamin B12 in diabetic patients are strongly recommended, particularly in metformin users. Supplementation and increased serum concentrations of vitamin B12 demonstrated positive effects on the symptoms and physical limitations of DPN.

## **LIMITATIONS**

This literature review has some limitations related to the studies included such as heterogeneous populations, non-assessment of glycemic control in some studies, different forms of laboratory analysis of vitamin B12, lack of information on the use of dietary supplements and drugs for metabolic control and lack of a standard in the diagnosis of DPN. In addition, the reference value to determine vitamin B12 deficiency showed small differences between studies.

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