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The Prevalence of Vitamin B12 Deficiency in Patients with Type 2 Diabetes on Metformin

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ABSTRACT

Introduction: Metformin is the first-line medical treatment for type 2 diabetes. However, it has recently been shown that metformin is responsible for a decrease in plasma vitamin B12 in these patients, with exposure to the hematological, neurological, and cardiovascular risks of that deficit. The aim of this study is to evaluate the prevalence of vitamin B12 deficiency in type 2 diabetics treated with metformin and to establish a correlation between vitamin status, dose, duration of metformin intake, and various clinico-biological parameters. Patients and methods: This is a prospective cross-sectional descriptive study of 200 types 2 diabetic patients recruited from the Endocrinology-Diabetology-and Metabolic Diseases and Internal Medicine departments of the Avicenna Military Hospital in Marrakech, over a 5-month period from November2017until March 2018. Patients were divided into 2 subgroups: a group treated with Metformin (Metformin+) (n=150) and a control group (Metformin -) (n=50). Clinical and therapeutic parameters were collected in the medical departments and the patients benefited from a complete biological assessment associated with the vitamin B12/folate dosage. Results: The prevalence of vitamin B12 deficiency in our study was about 14.4% in the metformin+ group (n=22) versus 8.5% in the metformin (-) group (n=4); the mean vitamin B12 concentration was 401.33+/-246.026 pg/ml in the metformin (+) group and was 496.58+/-305.86 pg/ml in the metformin (-) group. We have found a statistically significant association between vitamin B12 deficiency and the age of diabetes (p=0.023) as well as with the duration of metformin intake (p=0.025), but its association with the dose of Metformin received, as well as the rest of the biological workup has not been demonstrated. Conclusion: The prevalence of vitamin B12 deficiency is higher in type 2 diabetics treated with Metformin, compared to the control group. And that the deficiency depends essentially on the duration of the treatment and the length of time the patient has been diabetic. In the light of these results, it is desirable to screen for vitamin B12 deficiency from a threshold duration of 6.5 years.

INTRODUCTION:

Metformin is a biguanide widely used in the treatment of type 2 diabetes, it reduces basal and postprandial glycemia, improves peripheral insulin sensitivity, and thus, improves the risk of cardiovascular morbidity-mortality[1].

Metformin use longer than 4 months puts you at significant risk of vitamin B12 deficiency[1] The prevalence of vitamin B12 deficiency, in the diabetic population under Metformin treatment, is 6-30%[2]. The severity of the deficit depends essentially on the duration and the dose of the treatment [3].

Many authors have suggested that the decrease of the absorption of the VitB12/intrinsic factor complex could explain the mechanism of vitamin B12 deficiency in diabetic patients on Metformin. According to several authors, this decrease is due either to microbial pullulation following alteration of intestinal motility or to structural alteration of the intrinsic factor or the cubulin receptor[4].

Vitamin B12 deficiency is clinically manifested by neurological and neurocognitive signs, including depression, a dementia syndrome, and peripheral neuropathy due to the axonal demyelination; the latter is completely reversible after vitamin supplementation, unlike diabetic peripheral neuropathy, which causes definitive neuronal degeneration [5].

The objective of this study was to evaluate the prevalence of vitamin B12 deficiency in a population of type 2 diabetics treated with Metformin.

PATIENTS AND METHODS

Patients:

This is a cross-sectional and descriptive study of a population of 200 patients over 18 years of age, with type 2 diabetes mellitus(T2DM) in the department of endocrinology and metabolic diseases and the department of internal medicine of the Avicenna military hospital in Marrakech either during their hospitalization or during the outpatient consultation. Our study spanned a 5-month period from November 2017 to March 2018. Patients with known digestive pathology (digestive surgery, digestive inflammatory pathology, severe liver pathology), known megaloblastic anemia were excluded.

Methods:

The patients were thoroughly interviewed about age, sex, socioeconomic level, dietary habits, cardiovascular risk factors, diabetic information (duration of treatment, duration of Metformin treatment, and average dose during the last 6 months).

Clinical examination included weight measurement, height, BMI, waist circumference, blood pressure.

Diabetic neuropathy (retinopathy, nephropathy, neuropathy) was assessed during a specialized consultation.

Vitamin B12 dosage was performed by competitive enzyme-linked immunosorbent assay (Cobas/rock). The threshold of deficiency is 197pg/ml.

Other parameters were measured: folic acid, CBC with hemoglobin and mean corpuscular volume (MCV), fasting blood glucose and glycated hemoglobin, renal function and glomerular filtration rate, liver function, and lipid profile.

Statistics:

Summary statistics of the demographic and clinical characteristics of all patients were expressed as frequencies and proportions for categorical variables, mean ± SD or median, and interquartile for continuous variables. The optimal cut-off values of the continuous values were calculated by applying the receiver operating curve (ROC) analysis.

$P < 0.05$ was recognized as statistically significant. All these statistical calculations were performed using the SPSS 25.0 software (SPSS Inc, Chicago, USA).

Ethical consideration:

The study took into account the patient's written and informed consent, anonymity, and confidentiality of the data.

RESULTS

200 patients were enrolled, 150 of whom were treated with Metformin for more than 6 months. The socio-demographic, clinical, biological, and therapeutic characteristics of the Metformin patients compared to the Metformin (-) group were summarized in Table 1.

The mean plasma vitamin B12 concentration was 401.33±246.02 pg/ml in the Metformin(+) group, with 14% of patients with vit B12 deficiency, compared with a mean concentration of 496.58±305.86 pg/ml in the Metformin(-) group, with only 4% of patients with Vit B12 deficiency (p=0.027).

This effect was mainly dependent on the duration of treatment and not on the dose.

Table 2 and Table 3

The representation of the association of the duration of Metformin treatment and vitamin B12 deficiency in the form of a ROC curve shows a sensitivity of 0.82 and a specificity of 0.42, for a threshold value of 6.4 years and a Cut-off of 250pg/ml.

The correlation of Metformin treatment was statistically significant with BMI and waist circumference and vitamin B12 concentration, whereas it was non-significant with age, cardiovascular risk factors, degenerative complications, and the rest of the biological tests.

It should also be noted that the length of time that diabetes has been present is significantly associated with vitamin B12 deficiency, regardless of whether or not Metformin is taken. (p=0.023).

DISCUSSION

In our study, the prevalence of vitamin B12 deficiency in diabetic patients treated with Metformin is 14%, after an average of 6.5 years of use and an average dose of 2.35g.

In the literature, this rate varies greatly between 6-30% [2]. this margin is mainly due to the large variability of the cut-off value (150-300pg/ml) used to define the vitamin B12 deficiency, the average age of the study population, the dose and duration of treatment [6].

Our study showed that the use of Metformin does not expose to the occurrence of degenerative complications, especially neurodegenerative ones. This is consistent with several studies, which found no significant difference between the 2 groups Metformin (+) and Metformin (-) [6–8]. On the other hand, several studies have shown that Metformin can aggravate and accelerate diabetic neuropathy [9,10].

To explain these inconsistent results, many studies have been carried out in mouse models and have shown that Metformin has a neuroprotective effect [11]. it has shown also that Metformin can inhibit neuroapoptosis and stimulate neurogenesis [12,13]. Thus, the pathogenesis due to vitamin B12 deficiency is probably counterbalanced by the neuroprotective effect of Metformin.

The prevalence of anemia in our patients did not exceed 6% in the 2 groups Metformin (+) and Metformin (-) without significant statistical difference between the 2 subgroups. Thus, as has been demonstrated by several authors, treatment with Metformin does not increase the risk of anemia [14]. Indeed, the hematological complications of vitamin B12 deficiency are always deferred[15], and often lead to a delay in diagnosis even in severe vitamin B12 deficiency.

The cut-off value used to define vitamin B12 deficiency has been a topic of medical controversy. One study showed that 60% of patients may experience symptoms at a threshold value of 200pg/ml, and 90% below 100pg/ml [16]. Most authors recommend that the metabolites of vitamin B12 should be measured for any concentration below 300pg/ml, namely homocysteine and methylmalonic acid [17,18]. Unfortunately, the determination of these metabolites is very expensive. Additionally, it has been shown that Metformin can directly increase serum homocysteine concentrations, without being due to vitamin B12 deficiency [19].

In our study, the average reduction in serum vit B12 concentrations between the Metformin (+) and Metformin (-) groups was -96pg/ml. Joshua found in a meta-analysis comparing 6 studies, a mean reduction of -54pg/ml (-81pg/ml to -26pg/ml) [19].

In a large study in South Korea, hypovitaminosis due to Metformin was dose and duration dependent at a threshold of 4 years and 1100mg/d [4]. Other studies have shown that the effect of Metformin dose is more significant than duration [3,14,20], Ting et Al suggested that each 1-g/d metformin dose increment conferred an odds ratio of 2.88 (95% confidence interval, 2.15-3.87) for developing vitamin B(12) deficiency[20].

Unfortunately, our study could not relate the dose-dependent effect of Metformin on the prevalence of vit B12 deficiency. This is probably due to the small sample size, or to the presence of factors influencing plasma vit B12 concentrations that biased the results of the study.

It has been shown in our study that the duration of treatment with Metformin is strongly related to the occurrence of vitamin deficiency from a threshold value of 6.5 years. This finding has been demonstrated by several authors who have advocated screening for vitamin B12 deficiency in all chronic diabetics treated for a long time with Metformin [20–25].

CONCLUSION

Our study confirmed the time-dependent effect of Metformin on the increase in the prevalence of vitamin B12 deficiency, and the need to perform a screening test after a threshold duration of 6.5 years.

The effect of the daily dose of Metformin received was not demonstrated, nor was the link between this treatment and the occurrence of hematological, neurological, and cardiovascular complications, which prompts the re-evaluation of these parameters on a larger sample.

TABLES AND FIGURES:

Table 1: the clinical, demographic, and biological characteristics of diabetic patients Metformin (+) and Metformin (-).

	Metformin (+) group	Metformin (-) group	*P*
Age	58,27±9,10	56,48±14,74	0,42
Weight	81,88±13,2	74,48±15,75	
Waist circumference	94,27±11,86	88,48±10,33	0,032
BMI	29,65±6,42	26,63±4,80	0,003
Cardiovascular disease			
Hypertension	63 (42%)	15 (30%)	
Smoking	15 (10%)	10 (20%)	
Dyslipidemia	47 (31,33%)	7 (14%)	
sedentary lifestyle	5 (3,33%)	1 (2%)	
age of diabete	244,21±167,09	99,40±83,70	0,000001
degenerative complications			
Microangiopathy	32 (21,33%)	7 (14%)	0,25
Macroangiopathy	9 (6%)	4 (8%)	0,74
Biological tests			

Vitamin B12 (pg/ml)	401,33±246,02	496,58±305,86	0,027
Vitamin B12 deficiency	22 (14%)	4 (8%)	
Folic acid (ng/ml)	7,42± 3,07	7,27±3,33	0,77
Folic acid deficiency	26 (17%)	10 (20%)	
Hemoglobin (g/dl)	13,63±1,47	13,49±1,54	0,57
Anemia	8 (6,1%)	3 (5,33%)	
VGM (fl)	85,06±6,20	85,88±6,20	0,42
TCMH (pg/GR)	28,11±2,42	28,39±2,41	0,47
CCMH (g/dl)	32,37±1,56	32±1,33	0,27
GAJ (mmol/l)	9,32±0,74	9,37±0,40	0,94
Glyquated hemoglobin (%)	8,05±1,8	8,67±2,6	0,12
total Cholesterol (mmol/l)	4,92±2,34	5,36±2,63	0,26
Triglyceride (mmol/l)	1,51±0,90	1,44±0,62	0,64
HDL (mmol/l)	1,31±0,67	1,41±0,67	0,35
LDL (mmol/l)	2,83±1,52	7,01±6,57	0,27
Urea (mmol/l)	7,82±13,81	6,61±4,32	0,42
Creatinine (µmol/l)	83,71±77,79	75,05±39,42	0,45
Microalbuminuria	2,36±4,64	3,62±7,22	0,26

Table 2: The correlation between vitamin B12 deficiency and the received dose of Metformin.

		Dose reçue de la Metformine			
		<1000	1000-1500	1500-2000	>2000
Dosage vit B12 (pg/ml)	<197	146,20±23,15	122,06±85,83	131,23±75,16	106,03±33,23
	≥250	523,16±93,16	323,25±65,16	456,16±327,66	298,16±163,16

Table 3: The correlation between vitamin B12 deficiency and duration of treatment with Metformin

	vit B 12	Durée (ans)	*P*
Dosage vit B12	<250	13±7,61	0,007
	≥250	9,31±6,61	

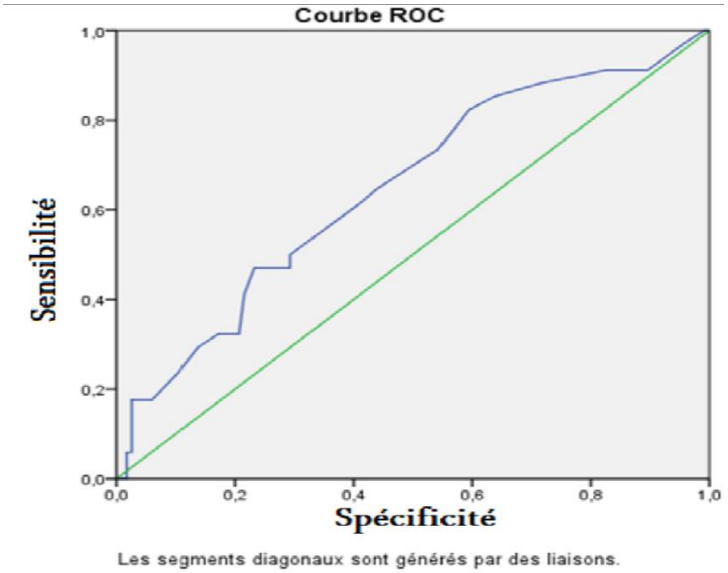

Figure 1: ROC curve representing the association between vitamin B12 deficiency and metformin treatment duration

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