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Research Article

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Infra-Clinical Vitamin B12 Deficiency and Microangiopathic Profile, is this a New Risk Factor in Type 2 Diabetics? Algerian Experience

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Abstract

Introduction: *Type 2 diabetes has multifactorial complications, in which hyperhomocysteinemia is an emerging risk factor that may be secondary to various conditions such as vitamin B12 deficiency, which appears oftenly as an asymptomatic setting and less specific in diabetics. Vitamin B12 deficiency definition has been revisited because its level does not reflect the intracellular status of vitamin B12, and an intracellular cofactor must be included systematically. Subclinical deficiency of vitamin B12 has recently been identified as a new clinic-biological entity that can affect micro and macro-angiopathic complications of diabetes indirectly through hyperhomocysteinemia.*

Materials and methods: *40 diabetic patients were screened for an infra-clinicalvitaminB12 deficiency subdivided into two groups each containing 16 patients, the first group having a deficit and the second having a normal level of vitamin B12. They were compared according to the frequency of micro-antipathy (retinopathy, nephropathy, peripheral neuropathy).*

Results: *No significant difference was found for the different microangiopathic lesions; nevertheless the subclinical deficit seems to be a risk factor for peripheral neuropathy.*

Conclusion: *In this study with a very modest sample. We attempted to approach the link between the borderline deficit of vitamin B12 and micro-angiopathic complications. In these results, even though the risk trend does not seem to be developing, the prospects for more extensive studies, both prospective and fundamental, should be encouraged.*

Keywords: Hyperhomocysteinemia, Vitamin B12 Borderline Deficit, Microangiopathic Complications.

Introduction

Type 2 diabetes is a metabolic disorder characterized by chronic hyperglycemia secondary to both early insulin resistance and late relative progressive insulinopenia.

Although micro and macro angiopathic complications are a major concern, the therapeutic approach is still complex because of comorbidities, particularly metabolic ones, which are flowing around hyperglycemia, besides HTA (Blood Hypertension), dyslipidemia and hyperhomocysteinemia, which seem to be recruited in this Risk Profile area

Hyperhomocysteinemia has recently emerged as a risk factor for diabetic micro and macro angiopathy, provided exclusively from the diet from essential amino acid methionine. Enzymatic systems are necessary for its purification or methionine demethylation thanks to vitamins B12 and B9.

After internalization via its receptor, vitamin B12 intracellular ensures intra-mitochondrial actions acting as enzymatic activator but also a cytosolic action represented by the demethylation of homocysteine to methionine in conjunction with folate [1].

During the synthesis of homocysteine, creatinine genesis from amino acid arginine, which partly explains the contribution of hyperhomocysteinemia in the creatinine excess observed during diabetic nephropathy [2].

Currently the definition of vitamin B12 deficiency has been revisited because the plasma vitamin B12 level does not reflect the intracellular vitamin B12 status; it is in this sense that Fedosov et al developed in 2015 a new classification of the deficit in vitamin B12 which roughly distinguishes 3 stages among which the subclinical subgroup .We were interested into the infra-clinical subgroupin our study in our study in order to establish its link with the diabetic micro angiopathy [1].

The subclinical deficit is defined clinically by the absence of

hematological or neurological signs, biochemically by a level of vitamin B12 (119-186) pmol / l; homocysteine (13.6-19.2) umol/l; holotranscobalamin (20-37) pmol / l; MMA: Methyl malonyl acid (0.35-0.84) umol / l; the latter represents the most specific and sensitive intracellular cofactor to define vitamin B12 deficiency nevertheless authors have retained Homocysteine as a cofactor to be assayed in first intention after the dosage of vitamin B12 for economic reasons and in case of anomaly to complete by other dosages more specific and less disturbed by glycemic imbalance or other vitamin deficits such as vitamin B9 deficiency that must be eliminated systematically before retaining the excess of homocysteine as an effect related to vitamin B12 deficiency [1].

Some authors have expressed a poor correlation between the level of vitamin B12 and homocysteine nevertheless these two parameters seem to maintain a good negative correlation between the margins of the thresholds defining the infra clinical deficit in vitamin B12 [3].

Materials and methods

The objective of our pilot study is to establish the link between micro-angiopathic and subclinical vitamin B12 deficiency. A type 2 diabetic population followed at the Mustapha Pasha University Hospital Center, Algiers, subdivided into two homogeneous groups each containing 16 patients, the first of which is diabetic deficient in vitamin B12 and the second diabetic with a normal level of vitamin B12. They were compared according to several parameters such as age, sex ratio, duration of evolution of diabetes, vitamin B12 level, homocysteine level as well as micro-angiopathic complications: retinopathy diagnosed by the fundus, nephropathy attested by albuminuria and creatinine clearance based on MDRD (Modification of Diet in Renal Disease) and peripheral neuropathy: DN4 score (neuropathic pain in 4 questions) of pain and examination of podiatry sensitivity (Table 1).

Table 1: Comparative Table of General Characteristics of Patients in Both Groups

Parameters (Total: 40 patients)	Diabetic Group with Deficiency in Vit B12 (n1: 16)	Diabetic group without deficit of vit B12 (n2: 16)	P
Mean Age	64 years	51 years	0.0002
Sexe ratio	11 F / 5 M	12 F / 4 M	NS
Diabetes duration	9 years (2-20)	11 years (3-16)	0.26
Vitamin B12	167pmol/l (123-264)	279.2 pmol/l (207-529)	0.066
Homocysteine	19umol/l (14.2-25.7)	10.36 umol/l (6.78-13.6)	0.000

Abbreviations: Vit B12: Vitamin B12, n: number of patients, p: significance index, NS: not significant, F: Female M: Male

We have taken homocysteine as an intracellular cofactor of vitamin B12 for two reasons: the availability of this dose in our health structure and also the negative correlation between vitamin B12 deficiency and hyperhomocysteinemia between the margins of the Borderline deficit of vitamin B12.

We used Epi Info to compare statistical variables and calculate correlations.

Results

The deficit group was significantly older than subjects with normal vitamin B12 levels. The distribution by sex and duration of diabetes was similar between the two groups: mostly women with diabetes older than 10 years on average respectively.

The analysis of microangiopathies did not find any difference between the two groups whatever the stage of nephropathy or diabetic retinopathy (odds ratio: 0.5 / p: Not Significant), without correlation between the creatinine and vitamin levels. B12 or homocysteine (r: - 0.198 / 0.43 respectively). In contrast to peripheral neuropathy, for which subclinical deficit is a risk factor (odds ratio: 7 / p: Not Significant) (Figure 1 & 2).

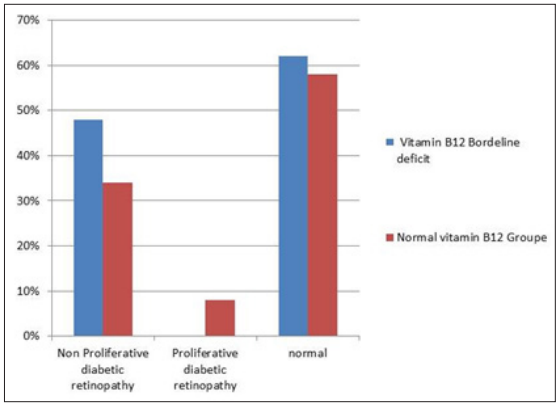

Figure 1: Graph comparing the severity of diabetic retinopathy between the moderately vitamin B12 deficient group and the normal-rate group.

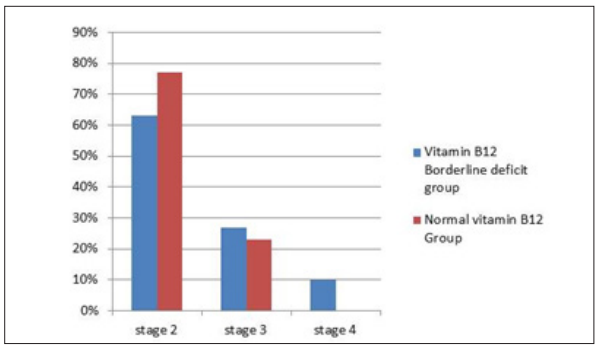

Figure 2: Graph comparing diabetic nephropathy at different stages between the group with subclinical vitamin B12 deficiency and those with a normal rate.

Considering that the causes of peripheral neuropathy in diabetes are multiple: as it appears that in the group having a normal level of vitamin B12, glycemic imbalance is a risk factor for diabetic neuropathy (Odds ratio: 1.5) versus Vitamin B12 deficient group (odds ratio: 0.83) in which vitamin deficiency appears to reduce the influence of glycemic imbalance on peripheral neuropathy (Figure 3).

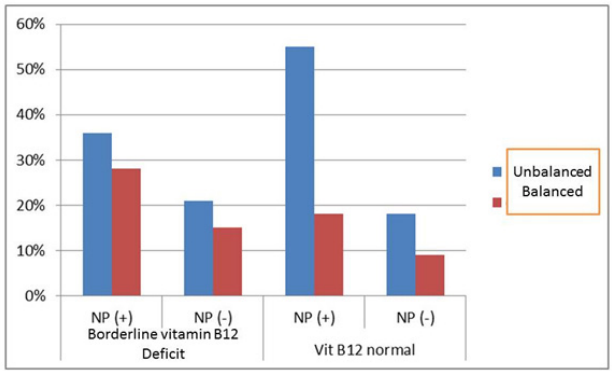

Figure 3: The frequency of glycemic imbalance as an etiological factor of peripheral neuropathy in the vitamin B12 deficient group versus normal Vit B12 group.

In our series, hyperhomocysteinemia is not correlated with glycemic imbalance, which is explained by the major contribution of vitamin deficiency.

Finally, the multifactorial nature of microangiopathy, whatever the organ concerned, makes it necessary to eliminate the other factors influencing its appearance; the comparison of the two groups did not detect any differences, which made it possible to eliminate the biases (Table 2).

Table 2: Comparative table of the different parameters influencing multifactorial microangiopathy

Parameters	Infra-clinical Vit B12 deficit	Vitamin B12 Normal Group	P
Total Cholesterol (g/l)	1.67	1.75	0.68
LDL Cholesterol (g/l)	0.88	1.02	0.24
Triglyceridemia (g/l)	1.5	1.4	0.66
HbA1C (Mean)	9.5%	10.55%	0.23
HTA	46.67%	58.33%	0.58

Abbreviation: HTA: Blood Hypertension, HbA1C: glycated hemoglobin, g/l:Gramm / liter, Vit B12: Vitamin B12, p: significance index

Discussion

The lack of correlation between infra-clinical vitamin B12 deficiency and diabetic retinopathy or nephropathy is explained by the moderate rise in homocysteine insufficient to cause this type of complication [4]. Nevertheless several studies have shown the existence of a link between retinopathy, nephropathy and hyperhomocysteinemia above the thresholds 16.3umol / l and 14 umol / l respectively [4, 5].

The suggested mechanism for nephropathy is indirect based on the consequences of oxidative stress such as matrix accumulation and intra-glomerular hypertension as well as endothelial dysfunction and vascular stiffness [6].

In the same way, impaired renal function accentuates hyper homocysteine not only by lowering its clearance but also by altering its remethylation [7].

With regard to diabetic retinopathy, a direct effect has been demonstrated for folate deficiency by destabilizing the genes by demethylation, a source of aggravation of the retinal proliferative process [8].

Subclinical vitamin B12 deficiency appears to be a risk factor for peripheral neuropathy in diabetics, contrary to its definition which only retains the subclinical deficit in the absence of neurological and haematological signs [1]. an exception to this rule in diabetics patients, which can be explained by a cumulative amount of metabolic neuronal aggression, as well as the subclinical deficit, which by definition is insufficient to cause neurological disorders, may become so in conjunction with the glycemic imbalance.

Therapeutic studies comparing the effect of vitamin B12 on peripheral neuropathy have been shown to be mediocre versus placebo in view of the important psychogenic component [9]. As for the non-improvement of the EMG (electromyogram) pattern never found, this is due to the late electrical effect of vitamin B12 [10].

Conclusion

In the present state, it is premature to conclude that moderate hyperhomocysteinemia secondary to subclinical vitamin B12 deficiency is an independent risk factor for diabetic microangiopathy of multifactorial origin, regardless of ethnic particularities and our insufficient strength. . The tendency to risk remains to be better defined.

Different hypotheses have suggested an indirect link via oxidative stress; however advantages of both prospective and fundamental clinical studies seem necessary to highlight the signaling pathways and regulatory agents involved in triggering and exacerbating the micro-angiopathy during subclinical vitamin B12 deficiency. This will better elucidate the link cause and effect.

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