INTERNATIONAL JOURNAL OF EXPLORING EMERGING TRENDS IN ENGINEERING
Peer-Reviewed, Refereed, Indexed and International Journal, https://ijoeete.com/
|ISSN No. 2394-0573 |Volume: 1, Issue: 01 | January - June 2022

ROLE OF VITAMIN B ON INCIPIENT NEUROPATHY IN PATIENTS OF TYPE 2 DIABETES

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ABSTRACT

A total of 120 persons with type 2 diabetes (including 46 patients with microalbuminuria) and 52 non-diabetic control participants had their levels of vitamins B6, B1, B12, associated vitamins, and biomarkers (including total homocysteine, methylmalonic acid) tested. Diabetic patients had lower levels of pyridoxal 5′-phosphate (PLP) in their blood (median: 22.7 nmol/L; 26.8 nmol/L; 39.5 nmol/L, non-diabetic control; p 0.0001) than in healthy controls (median: 39.5 nmol/L). 63%, 58%, and 25% of the diabetic groups with and without microalbuminuria and the control group had low PLP (30 nmol/L), respectively. P 0.0001 showed that plasma levels of pyridoxine and pyridoxal were lower, whereas pyridoxamine, pyridoxamine 5′-phosphate, and pyridoxic acid in both the diabetes and control groups were higher (p 0.001). Low levels of vitamin B12 and excessive levels of methylmalonic acid were uncommon in any of the study groups, whereas thiamine deficiency was common in all. Diabetes patients had higher levels of C-reactive protein and soluble vascular cell adhesion molecule-1 (p 0.05 vs. healthy control), according to the research.

KEYWORDS: Vitamin B deficiency Type 2 diabetes Microalbuminuria Pyridoxal 5′-phosphate

INTRODUCTION

There are a number of reactions triggered by high blood glucose levels, including oxidative stress and the formation of advanced glycosylated end products, which have been linked to structural and functional changes in the blood vessels that eventually lead to organ dysfunction, particularly in the heart, nerves and eyes, and the kidneys. When it comes to developing countries, diabetic kidney disease is the most common cause of kidney failure and end-stage renal disease. Microalbuminuria (greater than 300 mg/day), GFR decrease, and hypertension are the hallmarks of this condition. Numerous newly diagnosed patients with type 2 diabetes may already have incipient nephropathy (microalbuminuria) due to undiagnosed diabetes and poor glucose tolerance that occurred prior to their current diabetes diagnosis. Diabetes patients diagnosed with microalbuminuria had 6.5 percent prevalence upon diagnosis, and it rose to about 25 percent 10 years later, according to the UK Prospective Diabetes Study (UKPDS).

LITERATURE REVIEW

Triantafyllos Didangelos (2021)," For one year, the effect of giving patients with diabetic neuropathy 1000 g/day of oral B12 (methylcobalamin) to normalize their vitamin B12 levels will be examined (DN). Methods and patients 90 patients with type 2 diabetes who had been on motorman for at least four years and had both peripheral and autonomic DN were randomized to receive either B12 or a placebo in this double-blind, placebo-controlled study. The B12 levels in all of the patients were below 400 mol/L. In addition to undergoing SNCV, SNAP, and VPT assessments, the participants also conducted cardiovascular autonomic reflex tests (CARTs: mean circular resultant (MCR), Valsalva test, postural index, and orthostatic hypotension). The SUDOSCAN, which measures electrochemical skin conductance in the hands and feet, was used to test sudomotor function (ESCH and ESCF, respectively). To assess QoL and pain intensity, we also employed the Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE) (pain score).

Elena Beltramo (2021) Thiamine and diabetes have been linked since the 1940s, when the first reports of this association were published. Thiamine deficiency has been linked to diabetic neuropathy for some time now, and a number of pilot studies have been conducted to see if it can help. It wasn't until the end of the '90s that the use of thiamine and its lipophilic derivative benfotiamine for this problem acquired widespread acceptance. As far back as 1996, there were indications that thiamine could be used to treat diabetic microangiopathy using in vitro and animal models; since then, a number of studies have been published on the topic.

Stephanie Farah, Kaissar Yammine (2021) a total of 997 individuals from 14 different randomized controlled trials were included in the analysis. For pain and dysesthesia outcomes, the pooled odds ratios were 3.1 and 3.04, respectively, with a 95 percent confidence interval of 1.197–8.089. The weighted difference between two experiments for the amplitude change in electromyography of the sensory sural nerve was 0.37 (95 percent CI, 0.034–0.709). The intervention group experienced an increase in peak latency changes. On average, two research studies found that interventions improved velocity by 95 percent confidence intervals (0.310–0.831). The electromyography motor results of the tibial nerve were in favors of vitamin B supplementation, whereas the fibular nerve was not.

Lata Kanyal Butola (2021) Vitamin B12 deficiency is more common in those with type 2 diabetes, according to research. First-line therapy for patients with type 2 diabetes mellitus (T2DM) worldwide is metformin, which is the most often given anti-diabetic medicine. Metformin can be used to treat a variety of conditions, including insulin resistance and polycystic ovarian syndrome (PCOS). If you're looking for a medication that can help you lose weight and protect your arteries from the damage caused by carbohydrates, then Metformin is a good option. Metformin users, for example, are at risk of anaemia if they've been taking the drug for a long time. Metformin-related vitamin B12 deficiency could be to blame. Vitamin B12 malabsorption is expected to affect 30 percent of people on long-term metformin therapy, with a 14 percent to 30 percent decrease in serum vitamin B12.

Ranadheer Chowdary P (2019) about 44% of older diabetics suffer from diabetic peripheral neuropathy. Patients with a more pronounced neuropathic deficit may not have any symptoms at all, while others with DPN may experience excruciatingly painful symptoms. A deficiency of Vitamin B12 (also known as cobalamin), which results in a deficiency of methylcobalamin, has been linked to substantial neurological disease, particularly peripheral neuropathy. Diabetic neuropathy can also occur as a result of this condition. Metformin, an anti-diabetic drug, may cause Vitamin B12 insufficiency in people with DPN. This was a randomised, double-blind, placebo-controlled study. Per-protocol analysis will ensure that all two parallel trial arms are enrolled. A combination of metformin 500 mg BD, pregabalin 75 mg, and cyanocobalamin 100 mg OD was used as the intervention paradigm. Nine months of follow-up care will be provided to each patient. At the same time intervals, serum Vitamin B12 levels will be tested.

MATERIALS AND METHODS

2.1. Study population

Participants (18 years old) with type 2 diabetes who had were diagnosed for at least five years, had HbA1c levels under 10% (86 m mol/mol), and had BMIs ranging from 19–40 kg/m2 were recruited from three general and internal medicine clinics in Germany between January and September 2011. Non-diabetic control volunteers were also recruited from the study participants' families and friends. A keratinize clearance of 10 mL/min or lower was considered end stage renal disease; those who drank more than 50 units of alcohol per week, had significant co morbidities, a history of renal and/or pancreatic transplants, or were taking vitamin B supplements (including multivitamins) were excluded from this study. There was no need to recruit pregnant and breastfeeding women, as well as women who were planning to get pregnant. Patients with and without microalbuminuria (urine albumin excretion of 30–300 g/mg keratinize) were separated based on their urinary albumin excretion, which was found to be normal in the majority of the patients.

2.2. Blood and urine sampling

Before breakfast, a sample of blood and urine was collected. Glucose, HbA1c, and creatinine concentrations were determined by drawing 5 mL of venous blood from diabetics.

2.3. Analytical methods

Colorimetric assays for total cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were used to measure ALT and ASt concentrations in the blood. The results of the automated enzymatic colorimetric assay for ALT and ASt were used to determine the concentrations of ALT and ASt in the blood. As per the manufacturer's instructions, quantitative sandwich enzyme immunoassays (Quantikine®, R&D Systems Abingdon, and UK) were used to assess Cystatin C and sVCAM-1 and CRP. High-performance liquid chromatography (HPLC, Dionex UltiMate 3000, Thermo Scientific) was used to determine thiamine, thiamine monophosphate (TMP), and thiamine pyrophosphate (TPP) via precolumn derivatization to the corresponding thiochromes using potassium ferricyanide under alkaline conditions [19]. PLP, PMP, pyridoxine, pyridoxamine,

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pyridoxal, and pyridoxic acid were quantified by HPLC (Dionex UltiMate 3000, Thermo Scientific) with fluorimetric detection following post-column derivatization using sodium metabisulfite.

2.4. Statistical analysis

All participants who had blood and urine samples drawn and analysed had their study goals assessed on a protocol-by-protocol basis. Patients with type 2 diabetes (both those with and those without microalbuminuria) were compared to non-diabetic control participants to see if plasma PLP levels dropped. Based on an expected 20% drop in PLP concentration in patients with diabetes and microalbuminuria (N = 52) for statistical power of 0.90, the study group size was decided to be N = 52 for significance at the 5% level. In order to get an idea of what was going on, we looked at all of the other variables. In order to compare the differences in demographics, vital signs, and analyte levels between diabetic patients and non-diabetic control subjects, as well as between patients receiving metformin therapy and those not, non-parametric methods (two-sided Wilcoxon rank sum test or Fisher's exact test) were used. Correlation analyses were conducted between PLP and age, BMI, and body mass index (BMI). SAS® for Windows 9.3.1 was used to perform statistical analyses (SAS Institute Inc., Cary, NC, USA).

RESULTS

3.1. Demographic and medical characteristics of the study population

There were 174 participants in this study, including diabetics with and without microalbuminuria, as well as non-diabetic controls. Two patients were omitted from the study because they failed to meet the criteria for inclusion according to the protocol. Table 1 provides an overview of the research groups' characteristics. Patients with and without microalbuminuria had similar age, body mass index (BMI), smoking history, and drinking habits. Patients with type 2 diabetes were younger than control participants on average. Of the 120 patients with diabetes, just 4 (3.3% of the total) were under the age of 50, whereas only 34 of the control participants were that age (65.4 percent of 52 subjects). In addition, 103 patients with diabetes (85.8%) and 17 control subjects (BMI > 25 kg/m2) were both overweight or obese (BMI > 25 kg/m2) (32.7 percent). Drinking more alcohol was more common in the control group (p 0.05) than in the diabetic groups. HbA1c levels were stable in most patients, with an average of 7.3% in those with and without microalbuminuria; this corresponds to 65 m mol/mol. In patients with type 2diabetes and microalbuminuria, the median serum keratinizes and median glomerular filtration rate did not indicate severe or advanced renal disease.

Table 1 Characteristics of patients with type 2 diabetes with and without microalbuminuria and non-diabetic control subjects

Characteristic	**Type 2 diabetes with MA (*N* = 46)**	**Type 2 diabetes without MA (*N* = 74)**	**Healthy control (*N* = 52)**
Sex, male/female (*N*)	23/23	38/36	18/34
Age (years)	72 (51, 86)***	71 (47, 83)***	43 (19, 73)
BMI (kg/m^2)	30 (21, 39)***	29 (22, 38)***	24 (19, 36)
Smoker, never/former/current (*N*)	37/7/2*	57/9/8*	42/0/10
Alcohol, none/moderate/excessive (*N*)	32/14/0*	53/21/0*	22/30/0
Systolic BP (mmHg)	140 (100, 180)***	140 (110, 180)***	121 (100, 150)

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Characteristic	Type 2 diabetes with MA (*N* = 46)	Type 2 diabetes without MA (*N* = 74)	Healthy control (*N* = 52)
Diastolic BP (mmHg)	80 (70, 100)	80 (60, 100)*	80 (55, 93)
Heart rate (b pm)	70 (50, 96)	70 (45, 98)*	68 (42, 92)
Fasting glucose (m mol/L)	8.0 (3.3, 15.0)	7.4 (3.1, 15.2)	All negative
HbA1c (%)	7.3 (5.8, 9.9)	7.1 (5.5, 9.9)	n. d.
Serum keratinize (μ mol/L)	84.0 (53.0, 168.0)	79.6 (44.2, 159.1)	n. d.
Urinary albumin/total protein (mg/L)	50 (30, 100)	20 (0, 20)	All negative
GFR (m L/min)	69 (25, 214)	80 (39, 143)	n. d.
Medication, MET/PPI/ACE (*N*)	17/4/20	37/3/26	0/1/1

Vitamin B status

Table 3 lists the median levels of the vitamins or biomarkers B6, B1, and B12 in plasma or serum. 63% (N = 29) of the diabetes group with microalbuminuria, 58% (N = 43) of diabetics, and 25% (N = 13) of the control group were found to have low plasma PLP (30 n mol/L). The vitamin B6 vitamins PLP, pyridoxine, and pyridoxal had significantly lower median plasma concentrations in both diabetes groups than in the control group (p 0.0001, all parameters); median PLP was 43 percent lower in patients with microalbuminuria and 32 percent lower in patients without microalbuminuria. In contrast, the diabetic groups had considerably greater median plasma levels of pyridoxamine, PMP, and periodic acid than the control group (p 0.001). There were no significant relationships between plasma PLP and age, BMI, or weight in diabetic patients or in the control group. Pyridoxine levels were significantly higher in men than in women with diabetes and microalbuminuria (mean: 42.1 n mol/L vs. 29.7 n mol/L; p = 0.0134). PMP (mean: 30.1 vs. 19.8 mol/g creatinine; p = 0.0245) and periodic acid (mean: 30.1 vs. 19.6 mol/g keratinize; P = 0.0218) were more frequently excreted in the urine of women than males in the control group. Periodic acid was the most abundant urinary excreted vitamin B6 metabolite; other vitamin B6 vitamins excreted in minor quantities (see Table 4). Patients with diabetes had considerably higher urine periodic acid as a percentage of total urinary vitamin B6 than non-diabetic control participants (with microalbuminuria: 75%; without microalbuminuria: 77%, p 0.0001). (63 percent) Clinically significant decreases in urine pyridoxal concentrations (p 0.05) were found in patients with diabetes and microalbuminuria, as well as urinary PMP concentrations that were 82% and 71% lower in the former group compared to the control group, respectively (p 0.0001).

Table 3 Plasma concentrations of vitamin B1 and B6, serum concentrations of vitamin B12, and plasma concentrations of MMA and total homocysteine

Parameter	Type 2 diabetes with MA (*N* = 46)	Type 2 diabetes without MA (*N* = 74)	Healthy control (*N* = 52)
Vitamin B_6 (n mol/L)			
PLP	22.7 (4.5, 206.4)***	26.8 (1.3, 166.0)***	39.5 (15.1, 448.5)

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Parameter	Type 2 diabetes with MA (*N* = 46)	Type 2 diabetes without MA (*N* = 74)	Healthy control (*N* = 52)
Pyridoxine[a]	6.5 (1.1, 372.4)***	7.4 (1.3, 473.6)***	12.4 (6.7, 33.5)
Pyridoxal	11.8 (2.7, 115.1)***	12.4 (3.3, 46.1)***	22.6 (11.2, 119.1)
Pyridoxamine[b]	1.5 (0.1, 21.9)***	1.6 (0.4, 15.9)***	0.8 (0.1, 80.7)
PMP	10.7 (0.9, 56.1)***	9.6 (1.1, 42.2)***	1.4 (0.2, 57.6)
Pyridoxic acid	33.5 (14.1, 486.9)***	30.7 (13.3, 174.7)**	21.1 (10.1, 255.5)
Vitamin B_1 (n mol/L)			
Thiamine	15.4 (6.2, 83.4)***	15.5 (8.3, 55.3)***	10.8 (4.9, 33.9)
TMP	2.3 (0.4, 21.1)***	3.3 (0.4, 11.8)***	5.6 (1.1, 13.2)
TPP	8.9 (5.0, 21.2)*	8.5 (4.1, 16.1)**	6.4 (2.2, 16.8)
Vitamin B_{12}			
Total coalmine (p mol/L)	223 (101, 553)	218 (102, 1043)	246 (71, 526)
HoloTC (p mol/L)[c]	67 (12, 251)	74 (8, 246)	58 (7, 280)
MMA (µ mol/L)	0.25 (0.05, 1.56)	0.22 (0.02, 1.36)	0.21 (0.05, 3.33)
Total homocysteine (µ mol/L)	7.1 (3.1, 14.1)**	6.4 (3.4, 13.7)	5.6 (2.4, 19.5)

Ninety-eight percent of those with diabetes and microalbuminuria and one hundred percent of those without diabetes and microalbuminuria had low plasma thiamine (70 n mol/ L). Patients with microalbuminuria had 43 percent higher median plasma thiamine levels than control participants, while patients without microalbuminuria had a 44 percent higher median plasma thiamine level. Both groups with diabetes had significantly greater TPP levels (p 0.05) and decreased TMP levels (p 0.0001) compared to the control group. Patients with microalbuminuria had the lowest urine thiamine concentration, but there were no significant differences between the diabetes groups and the control group ($p > 0.05$; Table 4)

There was a prevalence of 8.7 percent (N = 4) of vitamin B12 deficiency in the diabetic group with microalbuminuria, 6.8 percent (N = 5) in the diabetes group without microalbuminuria, and 5.8 percent (N = 3) in the control group. Between the diabetic and control groups, the median levels of vitamin B12 (cobalamin) and its active form, holoTC, were comparable ($p > 0.05$). MMA levels in the blood, a sign of vitamin B12 deficiency ($p > 0.05$ when compared to

controls), were identical in all three groups. As compared to non-diabetic control subjects, diabetic patients with microalbuminuria had a considerably higher median plasma concentration of total homocysteine ($p = 0.001$). For both patients with and without microalbuminuria, treatment with metformin resulted in lower median serum levels of vitamin B12 and holoTC ($p > 0.05$ in all comparisons; 188, 227, and 62 p mol/L, respectively; 62 pmol/L, respectively) (p vs. no metformin, vitamin B12, and 63 p mol/L, respectively) (p vs. no metformin, vitamin B12, and MMA and total homocysteine concentrations in the plasma of metformin-treated and non-treated subjects were not significantly different ($p > 0.05$).

CONCLUSION

Our research found that patients with type 2 diabetes, particularly those who had microalbuminuria as an early sign of nephropathy, had a shortage in PLP. Vitamin B1 deficiency was also shown to be related with type 2 diabetes, as was a relative rise in PMP and periodic acid. Diabetic nephropathy may be diagnosed early if inflammation and endothelial dysfunction are present. For the time being, researchers are unsure of how vitamin B and inflammation-related pathways interact. Additionally, further research is needed to understand the causes of B vitamin shortage in diabetes, as well as to evaluate the possible advantages and hazards of supplemental treatment for the prevention of micro vascular problems associated with diabetes.

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