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ORIGINAL ARTICLE

Evaluation of Folic Acid in Diabetic Type II Patients with and without Neuropathy

LIHAZ GUL[1], JAHAN SARDAR[2], MUHAMMAD ZUBAIR[3], SAJID KHAN[4], ANEES MUHAMMAD[5], SUNDAS IFTEKHAR[6]
[1]*Clinical Technologist, Department of Pathology, Hayatabad Medical Complex, Peshawar, Pakistan.*
[2]*Assistant Professor of Medicine, Kuwait Teaching Hospital/Peshawar Medical College, Peshawar, Pakistan.*
[3]*Assistant Professor, Department of Pathology, Saidu Medical College/Saidu Group of Teaching Hospitals, Swat, Pakistan.*
[4]*Lecturer, Department of Biochemistry, Kabir Medical College/Gandhara University, Peshawar, Pakistan.*
[5]*Clinical Technologist, Department of Pathology, Naseerullah Khan Babar Memorial Hospital, Peshawar, Pakistan.*
[6]*Registrar, Pathology Department, Institute of Kidney Disease, Peshawar, Pakistan*
Corresponding author: Sundas Iftekhar, Email: Ifsa_malik@yahoo.com

ABSTRACT

As a result of peripheral neuropathy, diabetes-related mortality and morbidity rates increase. It is possible that a folate deficiency raises the risk of developing diabetic neuropathy since folate is required for the creation and maintenance of neurons. This study evaluated diabetic neuropathy and the role of folic acid in neuropathic and non-neuropathic diabetic individuals.

This study was conducted from October 2019 to March 2020 in Peshawar on both from neuropathic (n=105) and non-neuropathic patients (n=100) of having diabetes mellitus type II. Blood samples were collected for estimation of HBA1c, folate and random blood sugar (RBS).

Positive family history (87.6%), hypertension (53.3%), and dyslipidemia (54.3%) were more determined in neuropathic patients. HbA1c level was found high among neuropathic patients. Patients with diabetic neuropathy had a considerably greater frequency of folate insufficiency (16 percent).

A significant increase in the number of people with diabetic neuropathy who are folate deficient shows that folate plays a critical role in delaying the onset of diabetic neuropathy.

Keywords: Folic Acid, Diabetes, Neuropathy, Diabetic Neuropathy, HBA1c

INTRODUCTION

Diabetic individuals are at an increased risk of folate deficiency[1]. According to one study, 27% of diabetics had a folate deficiency[2]. Vitamin B12 deficiency can occur in diabetic people as a result of a folate deficiency[3]. Folate deficiency was reported to occur in between 12 and 23% of senior diabetic patients[4]. Another study found that diabetic individuals in Brazil had a higher prevalence of folate deficiency, up to 37%[5]. According to a study, those who consume more folate and vitamins B6 and B12 had a lower risk of developing type 2 diabetes[6]. Plasma folate concentrations have been associated with better nerve growth and the avoidance of peripheral neuropathy and nephropathy in diabetic patients[7]. A combination of folate, uridine monophosphate, and vitamin B12 has been shown to decrease the pain associated with diabetic neuropathy[8]. It decreases blood glucose levels and protects neurons and arteries from the oxidative damage caused by diabetes[9]. Increased folate levels have been reported in certain studies to treat endothelial dysfunction without lowering homocysteine plasma levels[10]. Folic acid enhances the antioxidant capacity of arteries by creating nitric oxide (NO), hence lowering the risk of atherosclerosis[11]. Numerous studies have demonstrated a 50% reduction in neuropathy in diabetics who take folate supplements[12].

Numerous studies have revealed a folate deficiency in diabetic patients with peripheral neuropathy[13]. Vitamin B complex medication can help manage the symptoms and consequences of diabetic peripheral neuropathy[14]. Folic acid reduces homocysteine levels, which are crucial for glycemic management in type 2 diabetes[15].

Folic acid deficiency has been connected to diabetic neuropathy[16]. 8% of individuals over the age of 55 have a higher risk of acquiring neuropathy, and the prevalence is increasing with time[17,18]. Folic acid is a vitamin that the body requires for a variety of metabolic functions. The subject of whether folic acid can aid diabetic neuropathy sufferers remains unresolved. Folic acid plays a key role in diabetic patients, and it is critical to understand this role for the future treatment of these individuals. To our knowledge, no research on the impact of folic acid in diabetic neuropathy has been conducted in our region. The researchers undertook this investigation to determine if individuals with and without diabetic neuropathy have elevated serum folic acid levels, as well as their risk factors.

MATERIALS AND METHODS

This descriptive comparative cross-sectional study was done between October 2019 and March 2020 by researchers from the Chemistry Department at the University of Peshawar and the Pathology Department at Hayatabad Medical Complex Hospital in Hayatabad Peshawar (six months duration). Patients with type I diabetes, gestational diabetes mellitus, chronic renal disease, or liver disease were excluded, whereas volunteers and verified type II diabetes patients were included. Folic acid levels were determined in all individuals with and without neuropathy. A total of 215 samples were calculated, including the control group, with a 5% margin of error. The study gained ethical clearance from the University of Peshawar and Hayatabad Medical Complex Hospital in Peshawar. After the ethics committee approved their enrollment, all patients were required to provide written and oral consent.

Blood was taken from participants' veins into K3 EDTA vacutainer tubes (Purple tops), sodium fluoride vacutainer tubes (Gray tops), and nonadditive vacutainer tubes (Red tops) for HbA1c, random blood sugar calculation, and serum folic acid measurement. Each participant's blood was extracted into these tubes. A new sample was used for

HbA1c analysis. Using an electrochemi-luminescence immunoassay, the Cobas-6000 biochemistry analyzer (Automatic biochemistry analyzer Cobas® 6000 series) was utilised to determine serum folate or folic acid. HbA1c levels were determined using HPLC-based analyzers (D10, Bio-Rad, USA).

Clinical significance was defined as a p-value of 0.005 or greater in the analysis of all data gathered and analysed. Following analysis, data were displayed in tables.

RESULTS

All neuropathic and non-neuropathic patients completed a pre-designed questionnaire about a variety of illnesses, including hypertension, cardiovascular disease, renalpathy, retinopathy, dyslipidemia, and family history. There were 53% of patients with hypertension and 87% with a positive family history of diabetes among the 100 neuropathic patients studied, as well as 54% with dyslipidemia among diabetic neuropathy patients, as well as 23% with cardio-vascular disease, 14% with nephropathy, and 13% with retinopathy. In comparison to diabetic neuropathic patients, diabetic neuropathic patients were more likely to have hypertension, a positive family history of diabetes, and dyslipidemia (Table. 1).

Table 1: History of co-morbidities in diabetic patients with neuropathy and without neuropathy

Morbidity	Group 1 % (n)		Group 2 % (n)		Total % (n)
	No	Yes	No	Yes	Yes
Cardiovascular Disease	76.2 (80)	23.8 (25)	86.0 (86)	14.0 (14)	19.0 (39)
Dyslipidemia	45.7 (48)	54.3 (57)	52.0 (52)	48.0 (48)	51.2 (105)
Family History	12.4 (13)	87.6 (92)	17.0 (17)	83.0 (83)	85.4 (175)
Hypertension	46.7 (49)	53.3 (56)	46.0 (46)	54.0 (54)	53.7 (110)
Nephropathy	86.7 (91)	13.3 (14)	86.0 (86)	14.0 (14)	13.7 (28)
Retinopathy	85.7 (90)	14.3 (15)	83.0 (83)	17.0 (17)	15.6 (32)

Group 1: Patients with neuropathy; Group 2: Patients without neuropathy

The duration of diabetes in all individuals with or without neuropathy was documented. 37.6 percent of diabetic patients have suffered in the last six to ten years, followed by 0-5 years (24.4 percent), 11-15 years (22.0 percent), 16-20 years (12.5 percent), and 21-30 years (05.5 percent) (Table. 2).

Table 2: Association of diabetic neuropathy with duration of diabetes in diabetic patient with Neuropathy and without Neuropathy

Duration of Diabetes	0-5 years % (n)	6-10 years % (n)	11-15 years % (n)	16-20 years % (n)	21-25 years % (n)	>25 years % (n)	Total % (n)
Diabetes with Neuropathy	21.9 (23)	34.3 (36)	21.0 (22)	15.2 (16)	4.8 (05)	2.9 (03)	100 (105)
Diabetes without Neuropathy	27.0 (27)	41.0 (41)	23.0 (23)	8.0 (08)	1.0 (01)	00 (00)	100 (100)
Total	24.4 (50)	37.6 (77)	22.0 (45)	12.5 (24)	04.0 (06)	01.5 (03)	100 (205)

Random blood sugar, HBA1c, and folic acid values were determined in neuropathic and non-neuropathic diabetics. When compared to non-neuropathic patients, neuropathic patients' random blood sugar levels were significantly lower than the range of 155510 mg/dl (297.9–67.06 mg/dl) for non-neuropathic patients. Folic acid levels decreased in neuropathic patients (10.8-6.73 ng/m) in compared to non-neuropathic individuals (1.6-36.0 ng/ml; 13.03-7.16 ng/m). HBA1c levels in patients with neuropathic diabetes mellitus were significantly greater than those in patients with nonneuropathic diabetes, ranging from 0.01-14.0 percent (9.9–2.06 percent) (Table. 3).

Table 3: Blood parameters of diabetic patients having Neuropathy and Non-Neuropathy Patients

Parameters		RBS Level mg/dl	HBA1c %	Folate Level ng/ml
Diabetic Neuropathy	Mean±S.D	285.1±102.45	10.7±1.97	10.8±6.73
	Range (Minimum-Maximum)	145-559	06.5-14.4	1.53-31.0
Non-Neuropathy	Mean±S.D	297.9±67.06	09.9±2.06	13.03±7.16
	Range (Minimum-Maximum)	155-510	01.1-14.0	01.6-36.0

Serum folic acid levels were determined in diabetic and nondiabetic neuropathic patients. 83.8 percent of the 105 people with diabetic neuropathic pain had normal folic acid levels, while 16.2 percent had low levels. On the other hand, no diabetic neuropathic people had detectable folic acid levels. Folic acid levels were also measured in individuals with non-diabetic neuropathy, and 93.0 percent of patients had normal levels; only 7.0 percent had lower-than-normal levels. Serum HbA1c values were also determined in patients with diabetic neuropathy and nonneuropathic patients with hyperglycemia. All diabetic neuropathy patients had a higher HbA1c level in their blood. In 99.0 percent of non-diabetic neuropathic patients, serum HbA1c values were excessively high. Similar to serum folic acid and HbA1c, random blood sugar was also assessed in diabetic neuropathic and non-diabetic neuropathic patients. There were raised serum glucose levels in 96.2 percent of diabetic neuropathic patients and 99 percent of non-diabetic neuropathic patients, respectively (Table 4).

Table 4: RBS, HBA1c, and Folate concentration Diabetic Neuropathic and non-Diabetic Neuropathic patients

Parameters	RBS Level			HBA1c			Folate Level		
Concentration	Low Level % (n)	Normal % (n)	High Level % (n)	Low Level % (n)	Normal % (n)	High Level % (n)	Low Level % (n)	Normal % (n)	High Level % (n)
Diabetic Neuropathy	0 (0)	3.8 (04)	96.2 (101)	0 (0)	0 (0)	100 (105)	16.2 (17)	83.8 (88)	0 (0)
Non-Diabetic Neuropathy	0 (0)	1.0 (01)	99.0 (99)	1.0 (01)	0 (0)	99.0 (99)	7.0 (07)	93.0 (93)	0 (0)

DISCUSSION

In this study of individuals with diabetic neuropathy, 53.5 percent had hypertension, 18.5 percent had cardiovascular disease, 14.5 percent had nephropathy, and 15.05 percent had retinopathy. According to study, those with diabetes and neuropathy are 85 percent more likely to have a family history of the disease than those without the disease. Individuals with diabetes and hypertension were at a greater risk of developing complications. Tesfaye et al., identified diabetes mellitus duration as a significant risk factor for diabetic peripheral neuropathy[19]. Diabetes type 2 has been linked to a number of health complications, including dyslipidemia and hypertension[20]. Diabetes is connected with insulin resistance, dyslipidemia, obesity, and genetic risk, as well as a variety of other multi-factor factors[21]. The Shah et al., study discovered a statistically significant link between cardiovascular disease and type 2 diabetes. Diabetes patients are more likely to develop cardiovascular disease than non-diabetics, owing to the presence of additional risk factors such as a family history of heart disease or hypertension, diabetes mellitus, and a history of smoking or statin usage[22].

Folic acid, more commonly referred to as vitamin B9, is a water-soluble vitamin that has been shown to help prevent a variety of diseases. Folic acid deficiency has been associated with a number of diseases, including cancer, cardiovascular disease, and insulin resistance[23]. It acts as a cofactor in a range of critical physiological reactions, including the synthesis of nucleotides and methionine[24]. According to study, folate is involved in both insulin resistance and diabetes complications such as retinopathy (sight loss)[23,24]. According to a study conducted in the United States, having a higher folate status in the body can significantly aid in the reduction of insulin resistance[23]. When individuals with non-proliferative retinopathy were compared to subjects without retinopathy, another study revealed a higher connection between folate levels and proliferative retinopathy[24].

Increases or decreases in folate levels have a deleterious effect on the DNA's integrity and structural stability. Numerous investigations have established a link between hypomethylation, DNA damage, and altered NO generation and impaired folate metabolism and deficient folate levels[24]. Numerous studies conducted on animal models have demonstrated that a diet deficient in folate might have a detrimental effect on the methylation of various genes related with diabetes. As a result, deficient folate levels may have an effect on diabetes issues by affecting the physiological system and resulting in a number of complications such as neuropathy[23].

Oxidative stress, which is caused by free radicals in the body, is a significant contributor to diabetes and associated consequences, such as diabetic neuropathy. In humans, oxidative stress has the potential to cause a variety of physiological problems, including DNA and brain damage[25]. Nuclear aberrations are more prevalent in diabetics with neuropathy than in diabetics without neuropathy, which may be explained by the increased oxidative stress in diabetics with neuropathy. Oxidative stress may contribute to neuropathic symptoms in diabetes patients via a variety of pathways[26]. Numerous studies have shown that folate can help the body cope with oxidative stress caused by free radicals[27]. It is likely that a deficiency in folate, which could result in an increase in oxidative stress, will aggravate diabetic neuropathy. Our previous study involved 105 patients with diabetic neuropathy and 100 non-neuropathic diabetic controls, and the results were reported in Diabetes Care. The levels of folate in the neuropathic and non-neuropathic groups were determined. When neuropathic patients were compared to non-neuropathic diabetic controls, it was discovered that neuropathic patients had considerably lower folic acid levels. Interestingly, our findings are similar with prior research that revealed decreased folic acid levels in diabetic patients with retinal impairment or problems[24]. Folic acid supplementation has been shown to considerably reduce the quantity of free radicals in the body in a prior study[25].

This study analysed only folate; no other vitamins or risk factors were included. Additionally, the study used a limited sample size and did not compare individuals with type I diabetes to those without the disease. While there are some differences in folate levels between patients with and without neuropathic disease, this study sheds light on why this is the case. Additionally, the HBA1c level was determined in neuropathic and non-neuropathic subjects.

CONCLUSION

In this study, folate insufficiency was found to be substantially related with neuropathic symptoms. Additional research is needed to elucidate the relationship between diabetes, neuropathy, and folic acid. Individuals with diabetes, both neuropathic and non-neuropathic, require the development of improved treatment choices.

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