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Correlation between folic acid and homocysteine level in patients with type 2 diabetes

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Abstract

This study analyzes the association between folic acid and homocysteine level in patients with type 2 diabetes. In this study were included 27 diabetic patients and 24 non-diabetic patients. Diabetic patients had a significant increase of the value of glucose ($p<0.0001$) and the value of HbA1c ($p<0.0001$). Significant difference is also observed in the concentration of homocysteine between the two groups of patients included in the study ($p=0.0280$), while no significant difference is observed with respect to folic acid concentration ($p=0.3324$). The results showed homocysteine level as a risk factor for many other disorders. While in diabetic patients, compared to normal healthy patients without diabetes, folic acid levels do not show a significant change. Our findings suggest that in patients with type 2 diabetes we have an increase in the level of homocysteine, respectively in addition to treatment with appropriate therapy insulin and metformin. Appropriate clinical condition for the development and progression of various disorders. Therefore, accurate treatment and evaluation of folic acid and homocysteine levels are key indicators for various related diseases in any patient affected by type 2 diabetes.

Keywords: Folic acid; Homocysteine; Type 2 diabetes

Introduction

Commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time [1]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and the onset of macrovascular diseases [2]. There are a large number of factors that lead to the onset of diabetes, such as IGT (Impaired glucose tolerance) as a common condition that greatly increases risk for the subsequent development of type 2 diabetes. Individuals with IGT manifest abnormalities in both insulin action and early insulin secretion similar to those seen in patients with type 2 diabetes. These abnormalities not only precede diabetes, they predict it as well [3].

The level of homocysteine and folic acid, as well as other metabolites, could be a risk factors accounting for chronic complications in diabetic patients. Nevertheless, it is necessary to perform more prospective and intervention studies to clarify the independent risk of those metabolites and thus assay alternative treatments [4]. The tags of this research were to determine the correlation between homocysteine and folic acid in patients with diabetes, particularly the incidence of hyperhomocysteinemia. The samples included in the research were analyzed for the level of homocysteine. Normal fasting levels of blood total homocysteine are considered to be 5<15 µmol/L, whereas European laboratories tend to use a value of 12 µmol/L as the cutoff value for normal fasting total homocysteine in adults [5].

Moreover, human epidemiological and controlled trial investigations, and the resultant scientific commentary, have focused almost exclusively on the small sub-set of vitamins (B9/B12/B6) that are the most prominent (but not the exclusive) B-vitamins involved in homocysteine metabolism [6]. The term folic acid includes 150 components of the family of pteroilglutamate, which participate in cell replication by enzymatic activity in purine base synthesis for DNA and are an important co-factor for transamination in the conversion of aminoacids, particularly homocysteine to methionine [7]. The biological activity of folic acid in the body depends upon dihydrofolate reductase action in the liver which converts folate into tetrahydrofolate. [8]. In cases where we have alternations in the metabolism of folic acid and other nutrients that are important as cofactors with homocysteine, then we encounter a deficiency in methyltetrahydrofolate and increase of homocysteine level [9] . Clinical interaction of hyperhomocysteinemia has as its main mechanism the creation of arterothrombosis causing damage to epithelial tissue through the formation of free radicals, platelet activation and oxidative modifications in LDL [10,11].

Patients included in the study after being diagnosed with type 2 diabetes were treated with the respective insulin and metformin therapy. This is important because several studies by different authors show that long-term use of metformin leads to an increased risk of vitamin B12 and folic acid deficiency, indirectly affecting homocysteine metabolism [12]. Although there is a wide debate about the interaction of insulin therapy and metformin, if we consider the results achieved by Wulfele et al, and other researches which had reported that treatment with metformin or in combination with insulin leads to a decrease in vitamin B12 and folate levels, whereas in an increase in homocysteine level, whereas treatment of patients with insulin alone has not shown this significant change [13,14].

Acceptable and sustained treatment of these patients and avoidance of related disorders will be achieved when countless metabolic parameters will be analyzed, because continuous interactions aggravates and worsen the condition of patients. Therefore, other ongoing research as this will determine more accurately the therapy and the course of the disease, especially the prevention of related disorders.

Materials and Methods

In this retrospective study which was performed in the Biochemical Diagnostic Laboratory at the Clinical Hospital of Tetova were included 27 diabetic patients (experimental group - 14 males and 13 females) and 24 non-diabetic patients (control group- 13 males and 11 females). The mean age of the patients included in the study was between 37 and 83 years. Diabetic patients were diagnosed with Type 2 diabetes and were hospitalised and performed routine tests to control diabetes. From the all survived patients were taken a blood samples (after 12 hours of starvation), 3 ml with anticoagulant K3EDTA, where HbA1c was measured by spectrophotometric method and a 6 ml blood test tube for obtaining of the serum, where was measured the concentration of glucose, folic acid and homocysteine.

Serum glucose concentration was measured on the Siemens RXL apparatus by the spectrophotometric method. Homocysteine concentration was measured by the Immulite 2000 apparatus by the EACLIA method (elektrochemiluminescence immuno assay), while serum folate was measured in the Advia Centaur apparatus by the DCLIA method (direct chemiluminiscent immuno assay).

Statistical processing of data was performed by statistical program SPSS version 26. For all variables was calculated the mean value, median, standard deviation, standard error, variance, rank, mode, minimum and maximum values, p-value and coefficient and Pearson. The value of $p < 0.05$ was considered statistically reliable.

The reference values of the analyzed parameters had normal reference intervals as follows: glucose level 3.5 – 6.1 mmol/L, HbA1c level 4.5 – 6.2%, folic acid level > 5.38 ng/ml, and the level of homocysteine 5-12 µmol/L.

Results and Discussion

Our study included 27 diabetic patients (experimental group) and 24 non-diabetic patients (a control group). The results obtained from the non-diabetic and diabetic patients are presented in **Table 1.**

From our results it is seen that the value of glucose (5.079±0.630 vs 8.955±3.174; p<0.0001) and the value of HbA1c (5.445±0.300 vs 7.322±1.010 ; p<0.0001) are higher in diabetic patients. Significant difference is also observed in the concentration of homocysteine between the two groups of patients included in the study (14.625±3.704 vs 17.177±4.291; p=0.0280), while no significant difference is observed with respect to folic acid concentration (12.891±3.042vs11.929±3.865;p=0.3324).

Table 1: Values of glucose, HbA1c, folic acid and homocysteine in diabetic and non-diabetic patients.

	non-diabetic patients				*Diabetic patients*			
	Glucose	**HbA1c**	**Folic acid**	**Homocysteine**	**Glucose**	**HbA1c**	**Folic acid**	**Homocysteine**
Average value	5.079	5.445	12.891	14.625	8.955	7.322	11.929	17.177
Standard error	0.128	0.061	0.621	0.756	0.610	0.194	0.743	0.825
Median	5.150	5.350	12.695	14.60	8.400	6.900	11.300	16.600
Modi	4.90	5.10	7.38	13.60	6.9	6.30	10.80	13.20
Standard deviation	0.630	0.300	3.042	3.704	3.174	1.010	3.865	4.291
Variance	0.397	0.090	9.258	13.721	10.076	1.020	14.944	18.420
Range	2.20	0.90	14.54	16.20	14.00	3.20	15.51	18.70
Minimum value	3.90	5.0	7.38	7.40	5.80	6.00	6.26	11.00
Maximum value	6.10	5.90	21.92	23.60	19.80	9.20	21.77	29.70

Table 2: Comparison of glucose, HbA1c, folic acid and homocysteine concentrations.

	Non-diabetic patients	**N**	**Diabetic patients**	**N**	**P**
Glucose	5.079±0.630	24	8.955±3.174	27	<0.0001
HbA1c	5.445±0.300	24	7.322±1.010	27	<0.0001
Folic acid	12.891±3.042	24	11.929±3.865	27	0.3324
Homocysteine	14.625±3.704	24	17.177±4.291	27	0.0280

***n-number of patients ; p- statistical significance**

Table 3: Correlation between folic acid and homocysteine in non-diabetic and diabetic patients.

Correlation		R	P
Folic acid vs. Homocysteine	**Non-diabetic patients**	0.239	0.260
	Diabetic patients	-0.217	0.276

The correlation between folic acid and homocysteine is shown in **Table 2**. Pearson coefficient for folic acid and homocysteine in non-diabetic patients is 0.239, it is a statistically insignificant positive correlation, p=0.260. While in diabetic patients the Pearson coefficient is -0.217, it is a negative correlation with insignificant statistical significance, p=0.276. **(Table 3)**

The results of our study revealed significantly increased concetration of serum homocisteine as well as higher prevalence of hyperhomocysteinemia in patints with type 2 diebetes comparet to non-diabetic patients. In addition, the increase in homocysteine level could be explained by the decreases in folate and vitamin B12 [13]. Thus, we can conclude that there is a strong positive relationship between the acid folic and homocysteine level in the type 2 diabetic patients. The clinical significance of this coondition shows a higher risk for the indicidence of related diseases which affect various organs, making it clear that the level of homocysteine, glucose and in particular no changes in the level of folic acid, are a determining risk factors for the onset in the progression of the diabetes and other diseases [15,16].

Also, from this study we conclude that standard therapy with insulin and theis dose has a positive impact on the concentartion of the studied variables. The exact pathogenesis of the standard therapy is multifactorial but it involves reduction of serum vitamin B12 concetration by induction of malabsorption by alterning bacterial flora [17], by the stimulation of the increased transportation and utility of Vitamin B12 by cells [18], by increasing the activity of enzymes of transsulfuration and remethylation reactions and hence by speeing up conversion of homocysteine to methionine and cysteine [19].

Conclusion

This and many other studies remain to demonstrate the correlation between increased homocysteine levels, no significant change in the folic acid level and the effect of appropriate therapy in patients with type 2 diabetes, treating and preventing this disorder and other related disorders.

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