THE ASSOCIATION BETWEEN OPHTHALMIC, RENAL COMPLICATIONS AND PLASMA HOMOCYSTEINE CONCENTRATION IN TYPE 2 DIABETES PATIENTS

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Summary

Objectives: To investigate the relationship between plasma Hcy concentration and some ophthalmic and renal complications in patients with T2DM. ***Subjects and methods:*** 395 patients with type 2 diabetes treated as inpatients at the National Hospital of Endocrinology who were clinically examined for their organs and performed basic tests to diagnose and assess their disease status. An ophthalmologist examined to determine cataracts, diabetic retinopathy (DR), and macular edema. Test for albuminuria, estimate glomerular filtration rate (eGFR), and quantify plasma Hcy in μmol/L. ***Results:*** The incidence of DR was encountered 45.8%; macular edema encountered 9.4%; cataract 73.4%; positive albuminuria 37.0%; eGFR decreased < 60 mL/min: 22.5%. The concentration of Hcy increased significantly in patients with albuminuria, and eGFR < 60 mL/min. The rate of increase of Hcy in the group of patients with DR and cataracts was higher than in the group of patients without DR and cataracts. ***Conclusion:*** Ophthalmic and renal complications are common in patients with type 2 diabetes, especially patients with DR, positive albuminuria, and decreased glomerular filtration rate. In patients with type 2 diabetes, an increase in plasma Hcy levels is significantly associated with some ophthalmic and renal complications.

* *Keywords: Type 2 diabetes mellitus; Diabetic retinopathy; Cataracts; Macular edema; Plasma Hcy levels; Albuminuria.*

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INTRODUCTION

Type 2 diabetes is a chronic metabolic disease characterized by prolonged hyperglycemia. In the progression, T2DM often appears to cause vascular complications, especially small blood vessels, including ophthalmic and renal complications. In addition to prolonged hyperglycemia, atherosclerosis is the leading cause of vascular complications in general and small blood vessels in particular. Among the risk factors for target organ complications in patients with T2DM, it is found that Hcy levels play an essential role, which is considered a non-traditional risk factor. Diabetes mellitus 2 with retinal complications can cause increased homocysteine, reaching 75.4 % of cases [1]. Common ophthalmic complications caused by diabetes mellitus 2 are DR, cataracts, and macular edema. The most common renal complications caused by type 2 diabetes are albuminuria and decreased glomerular filtration rate. In the abovementioned ophthalmic and renal complications, there is an effect of Hcy with the expression of increased blood concentration. The study aims: *1) To analyze the rate of some ophthalmic and renal complications and plasma Hcy concentration in patients with type 2 diabetes. 2) To investigate the relationship between Hcy concentration and ophthalmic and renal complications in patients with type 2 diabetes.*

SUBJECTS AND METHODS

1. Subjects

395 inpatients with T2DM at the National Hospital of Endocrinology, that are qualified to be examined and do basic tests for diabetic diagnosis, ophthalmic and, renal complications identification. The patients are excluded from the research if their eyes are cloudy in transparent environments, and the retina cannot be seen during ophthalmoscopy

2. Methods

* *Research design:* Observational, descriptive, a cross-sectional.

* *Research content and steps:*

+ Take medical history.

+ Clinical examination of organs.

+ Ophthalmic examination with the following contents: measurement of vision; measurement of intraocular pressure; anterior partial examination using biomicroscopy, slit lamp, identifies abnormalities of cornea, anterior chamber, vitreous body; Examination of the posterior part of the body was dilated with Mydrin 1% solution, using Volk glass with the microscope, slit lamp to observe vitreous, retina, optic disc, identify lesions. The eye exam was performed by an ophthalmologist from the Ophthalmology Department of Military Hospital 103.

Method of assessing eye damage: Eyes that have been replaced by artificial cataracts are still counted as having cataracts. Identify the patient with eye damage as follows: If both sides have similar damage, then evaluate that patient has the corresponding eye damage. If both sides have lesions, but the extent is different, determine the patient with the injury based on the side with more severe severity; or only one eye has the disease to count the patient as having the disease.

+ Estimating eGFR by MDRD formula based on blood creatinine concentration, age, and adjusted for gender (unit mL/min).

+ Serum Hcy test. The normal value of plasma Hcy in the Department of Biochemistry - National Hospital of Endocrinology is 5 - 12 µmol/L.

** Diagnostic criteria and classification used in the study:*

Table 1: Classification of diabetic retinopathy according to ICO-2017 [2].

Diabetic retinopathy	**Signs can be seen on ophthalmoscopy with dilated pupils**
No apparent DR	No abnormalities
Mild non-proliferative DR	Only microaneurysms
Moderate non-proliferative DR	Microaneurysms and other signs (e.g., dot and glot hemorrhages, hard exudates, cotton wool spots), but less than severe non-proliferative DR
Severe non-proliferative DR	Moderate non-proliferative DR with any of the following: • Intraretinal hemorrhages (≥ 20 in each quadrant); • Definite venous beading (in 2 quadrants); • Intraretinal microvascular abnormalities (in 1 quadrant); • And no signs of proliferative retinopathy
Proliferative diabetes mellitus	Severe non-proliferative DR and 1 or more of the following: • Neovascularization • Vitreous/preretinal hemorrhage

Table 2: Classification of diabetic macular edema according to ICO-2017 [2].

Diabetic macular edema	**Signs can be seen on ophthalmoscopy with dilated pupils**
No DME	No retinal thickening or hard exudates in the macula
Noncentral-involved DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter
Central-involved DME	Retinal thickening in the macula that does involve the central subfield zone that is 1mm in diameter

+ Evaluate albuminuria, if albuminuria ≥ 20 mg/L is considered positive, If albuminuria < 20 mg/L is considered negative.

+ eGFR < 60 mL/min is considered to be decreased.

** Data processing and medical ethics in research:*

+ Analyze data using SPSS 23.0 software.

+ The topic has been approved by the Department of Joints - Endocrinology of Military Medical Academy and the Medical Ethics Council of the Central Hospital of Endocrinology.

RESULTS

Table 3: Age and sex characteristics of study subjects (n = 395).

Age group (years)	**Total**		**Male (n = 206)**		**Female (n = 189)**		**p**
	n	**%**	**n**	**%**	**n**	**%**	
≤ 40	23	5.8	13	6.3	10	5.3	> 0.05
41 - 60	165	41.8	88	42.7	77	40.7	
> 60	207	52.4	105	51.0	102	54.0	
Add	395	100.0	206	100.0	189	100.0	
The average age	60.5 ± 12.1		59.4 ± 12.2		61.6 ± 11.9		

+ The mean age of men and women is similar.

+ Patients of different ages, in which the highest percentage is > 60 years old.

Table 4: Rate of retinal damage.

Retinal disease diabetes	Right eye (n = 395)		Left eye (n = 395)		Ratio to the total number of eyes (n = 790)		Percentage by the patient (n = 395)	
	n	%	n	%	n	%	n	%
No apparent DR	220	55.7	220	55.7	440	55.7	214	54.2
Diabetic retinopathy	175	44.3	175	44.3	350	44.3	181	45.8
1. Non-proliferative DR:	161	92	164	93.7	325	92.9	164	90.6
Mild non-proliferative DR	75	46.6	78	47.6	153	47.1	72	43.9
Morderate non-proliferative DR	54	33.5	51	31.1	105	32.3	61	37.2
Severe non-proliferative DR	32	19.9	35	21.3	67	20.6	31	18.9
2. DR proliferative	14	8.0	11	6.3	25	7.1	17	9.4

+ The incidence of DR was lower than that of none DR. Among eyes with DR, the majority were non-proliferative. Among the non-proliferative DR, mild was found with the highest rate, and severe degree had the lowest rate.

Table 5: Percentage of patients with macular edema, cataracts (n = 395).

Eyes damage	Quantity (n)	Ratio (%)
Macular edema	37	9.4
Cataracts	290	73.4

+ The percentage of patients acquiring cataracts was high.

Table 6: Rate of kidney damage (n = 395).

Expression	Quantity (n)	Ratio (%)
Albuminuria (+)	146	37.0
eGFR < 60 mL/min	89	22.5

+ Two main manifestations of diabetic kidney damage, albuminuria (+) and decreased eGFR, were detected.

+ The rate of albuminuria (+) is higher than the decrease in eGFR

Table 7: Association of homocysteine levels with ophthalmic complications.

Hcy (µmol/L)	**No DR (n = 214)**	**Have DR (n = 181)**	**p**
Avarage value	9.91 ± 3.67	10.75 ± 4.71	0.077
> 12 (n, %)	46 (21.5)	55 (30.4)	0.044
≤ 12 (n, %)	168 (78.5)	126 (69.6)	
	No macular edema (n = 358)	**Macular edema (n = 37)**	
Avarage value	10.28 ± 4.25	10.41 ± 3.72	0.737
> 12 (n, %)	91 (25.4)	10 (27.0)	0.831
≤ 12 (n, %)	267 (74.6)	27 (73.0)	
	No cataracts (n = 105)	**Cataracts (n = 290)**	
Avarage value	9.72 ± 3.63	10.50 ± 4.37	0.107
> 12 (n, %)	18 (17.1)	83 (28.6)	0.021
≤ 12 (n, %)	87 (82.9)	207(71.4)	

+ The concentration of Hcy is not significantly related to DR, macular edema, or cataracts.

+ The rate of increase of Hcy in the group of patients with DR and cataracts was higher than in the group of patients without DR, and cataracts.

+ The rate of increase in Hcy was not significantly different between patients with and without macular edema.

Table 8: Relationship of homocysteine levels with albuminuria, glomerular filtration rate.

Hcy (µmol/L)	**Albuminuria (+) (n = 146)**	**Albuminuria (-) (n = 249)**	**p**
Avarage value	11.56 ± 5.13	9.55 ± 3.33	0.000
> 12 (n, %)	51 (34.9)	50 (20.1)	0.000
≤ 12 (n, %)	95 (65.1)	199 (79.2)	
	eGFR < 60 mL/min (n = 89)	**eGFR ≥ 60 mL/min (n = 306)**	
Avarage value	13.94 ± 5.65	9.49 ± 3.27	0.000
> 12 (n, %)	43 (48.3)	58 (19)	0.000
≤ 12 (n, %)	46 (51.7)	248 (81)	

+ Hcy concentration in patients with albuminuria (+); eGFR < 60 mL/min is higher than in patients without albuminuria and eGFR ≥ 60 mL/min.

+ The rate of increased Hcy in patients with albuminuria (+); eGFR < 60 mL/min are higher than those without albuminuria and eGFR ≥ 60 mL/min.

DISCUSSION

1. Damage to eyes and kidneys in patients with type 2 diabetes

** Ophthalmic damage in patients with type 2 diabetes:*

In patients with type 2 diabetes, the eye is one of the most common and early target organ damage. There are many different manifestations of eye damage described on examination and examination. The three most crucial and common types of eye damage include diabetic retinopathy, cataracts, and macular edema. Overall, DR was found in 35.4%, mainly non-proliferative DR, and macular edema ranged from 1.4 to 12.8% [3]. The rate of DR in the study was 45.8% also reached a high level, of which 90.6% belonged to non-proliferative DR. The prevalence of DR in some countries is high, such as Jordan at 64%, Yemen at 55%, Kuwait at 40%, Iraq 37% [4]. In Indonesia, the rate of macular edema in patients with type 2 diabetes was 17.1% [5]. Cataracts are complications of diabetes, mainly related to metabolism. Moreover, depending on the individualization of the patient, cataracts can be encountered at different rates. The overall rate of cataracts in diabetic patients is about 25%, but in some countries, the rate is as high as in India 65.7% [6]. The rate of cataract patients in the study was 73.4%, the number of eyes with cataracts accounted for the highest rate was 47.05%, and the number of eyes with an artificial lens replaced accounted for 9.2%. Thus, three important eye lesions common in the subject are also at an average high level compared with the general observations in the literature.

** Renal damage in patients with diabetes:*

The kidney is a common target organ for early complications. Two features characteristic of diabetic nephropathy include albuminuria and decreased eGFR. The incidence of renal complications varied depending on the type of patients surveyed. This study found that 37% of patients had positive albuminuria, 22.5% had decreased eGFR at < 60 mL/min. Renal complications in diabetic patients appear due to many different factors and mechanisms, the most

important of which is increased blood glucose, causing increased pressure in the glomerular capillaries and the whole system combined with the effects of cytokines or growth factors. Renal complication rates ranged from 20 to 60%, depending on the subjects observed [7]. Thus, in the studied patients, it was found that besides eye damage, kidney damage was also observed. These two types of complications often go hand in hand in patients with type 2 diabetes.

2. Association of homocysteine levels with eye and kidney complications in patients with type 2 diabetes

Ophthalmic and renal complications are caused by many factors, many of which have a common effect, and at the same time, increased Hcy is one of those factors. Therefore, Hcy concentration is related to ophthalmic and renal complications in general and some manifestations in particular. Increasing Hcy will cause increased oxidation leading to atherosclerosis causing vascular dysfunction [8]. The survey results showed that the concentration of Hcy in patients with DR, albuminuria (+), and reduction of eGFR were higher than in those without the above complications. In contrast, the concentration of Hcy was not significant with macular edema and cataract. Many authors also found that Hcy levels are associated with ophthalmic and renal complications, including DR. If the Hcy concentration is ≤ 16 µmol/L, the rate of DR is 12%, if the Hcy concentration is > 16 µmol/L, the rate of DR is 16.5%. Hcy levels increase when patients with type 2 diabetes have renal complications [9]. Thus, the survey results show that hcy levels are related to ophthalmic and renal complications, including BVM, albuminuria (+), and decreased glomerular filtration rate, the most obvious of which is renal complications.

CONCLUSION

A survey of 395 patients with type 2 diabetes found that the incidence of DR was 45.8%, of which 90.6% is non-proliferative DR, 9.4% is proliferative DR; macular edema was 9.4%; cataracts was 73.4%. Moreover, the rate of renal complications was 37% for albuminuria and 22.5% for eGFR decreased < 60 mL/min. Plasma Hcy concentration increased in patients with albuminuria (+), and decreased eGFR. The rate of increase of Hcy in the group of patients with DR and DR was higher than in the group of patients without DR, and cataracts. Lastly, there is no association between the rate of increased Hcy and macular edema.

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