Homocystein Levels in Diabetic Patients on Hemodialysis

Diyaliz Tedavisindeki Diyabetik Hastalarda Homosistein Düzeyleri

Neşe Ersöz Gülçelik*, Banu Kale Köroğlu**, Mansur Kayataş***

*Ankara Oncology Hospital, Endocrinology, Ankara, Turkey
**Süleyman Demirel University, Endocrinology, Isparta, Turkey
***Ankara Numune Hospital, Nephrology, Ankara, Turkey

Abstract

Objective: Atherosclerotic diseases (ASD) are the major risk factors for mortality and morbidity in diabetic patients on hemodialysis (HD). However, the extent of the role of hyperhomocystinemia as a risk factor for ASD is uncertain in diabetic HD patients. In this study we examined the association of homocysteine levels with ASD in diabetic HD patients.

Method: We enrolled 25 diabetic patients on HD (DM group) (12M, 13 F, mean age 60±8y) and 25 non-diabetic patients on HD (N group) (12M, 13 F, mean age 57±8 y). Patients are evaluated for atherosclerotic disease and urea, creatinin, albumin, total cholesterol, LDL, HDL, vitamin B 12, folic acid and homocysteine levels were measured.

Results: There was no difference between homocysteine levels of diabetic and non-diabetic HD patients (20.3±2.3mmol/ml vs. 18.2±1.1mmol/ml, p=0.467). The prevalence of ASD in diabetic HD patients was higher than non diabetic HD patients (72% vs. 44%, p=0.042). In DM group, the patients with ASD had significantly higher homocysteine levels than the patients without atherosclerosis (20.5±3.2mmol/ml vs. 14.4±1.6 mmol/ml, p=0,017). In N group, patients with ASD had significantly higher homocysteine levels than patients without ASD (21.7±2.8 mmol/ml vs. 16.3±3.0 mmol/ml, p=0.036).

Conclusion: We conclude that hyperhomocystinemia in diabetic and non-diabetic patients on HD may contribute to their excess incidence of ASD. *Turk Jem 2007; 11: 20-2*

Key words: Homocysteine, diabetes mellitus, hemodialysis

Özet

Giriş: Son dönem böbrek yetmezliği olan diyabetik hastalarda aterosklerotik hastalıklar önemli morbidite ve mortalite nedenlerindendir. Diyaliz tedavisindeki diyabetik hastalarda homosistein ve aterosklerotik hastalık ilişkisi ile ilgili çelişkili yayınlar mevcuttur. Bu çalışmamızda diyaliz tedavisindeki diyabetik hastalarda homosistein düzeylerinin aterosklerotik hastalıkla ilişkisini araştırdık.

Materyal-Metod: Çalışmaya diyaliz tedavisindeki 25 diyabetik hasta (12E, 13K, ort. yaş 60±8yıl) ve diyaliz tedavisindeki 25 diyabetik olmayan hasta (12E, 13K, ort. yaş 57±8 yıl) dahil edildi. Hastalar aterosklerotik hastalık açısından değerlendirildi. Kan örnekleri diyaliz öncesi alındı ve üre, kreatinin, albumin, total kolesterol, LDL, HDL, vitamin B12, folik asit ve homosistein düzeylerine bakıldı.

Bulgular: Diyabetik ve diyabetik olmayan diyaliz hastaları arasında homosistein düzeyleri açısından fark saptanmadı (20.3±2.3mmol/ml ve 18.2±1.1mmol/ml, p=0,467). Diyabetik diyaliz hastalarında aterosklerotik hastalık diyabetik olmayanlara göre daha fazla gözlendi (72% ve 44%, p=0.042). Diyabetik ve diyabetik olmayan diyaliz hastalarında aterosklerotik hastalığı olanlarda olmayanlara göre daha yüksek homosistein düzeyleri gözlendi (sırasıyla, 20.5±3.2mmol/ml vs 14.4±1.6 mmol/ml, p=0,017 ve 21.7±2.8 mmol/ml vs 16.3±3.0 mmol/ml, p=0,036).

Sonuç: Sonuç olarak diyabetik ve diyabetik olmayan diyaliz hastalarında homosistein düzeyi yüksekliği artmış aterosklerotik hastalık sıklığı ile birliktedir. Çalışmamızda diyabetik diyaliz hastalarında homosistein düzeyleri diyabetik olmayan diyaliz hastalarından farklı bulunmamıştır. *Turk Jem 2007; 11: 20-2*

Anahtar kelimeler: Homosistein, diabetes mellitus, hemodiyaliz

Introduction

Atherosclerotic diseases (ASD) are the major risk factors of mortality and morbidity in diabetic patients and patients on hemodialysis (HD) (1). Despite their widespread prevalence, traditional risk factors such as smoking, hypertension, dyslipidemia are relatively limited predictors of atherosclerotic disease specific mortality and morbidity in patients on HD (2). Hyperhomocysteinemia is an independent risk factor of ASD in diabetic patients (3-5). However, it is still controversial in

Address for Correspondence: Neşe Ersöz Gülçelik, Ankara Oncology Hospital, Endocrinology, Ankara, Turkey
Phone: +90 322 336 09 09 Fax: +90 322 345 49 79 E-mail: neseersoz@hotmail.com

end-stage kidney disease patients who underwent long-term dialysis (6-9). In this study we examined the significance of homocystein (Hcy) levels in predicting atherosclerotic cardiovascular disease in diabetic and non- diabetic HD patients.

Subjects and Methods

We evaluated 50 patients with end stage renal disease who received HD three times per week. The study population was restricted to patients whose urine volume was < 100 ml between HD sessions with almost no residual renal function. We divided the patients into two groups. Diabetic patients (DM group): (12 male, 13 female, mean age 59.6±7.9 y), non-diabetic patients (N group): (12 male, 13 female, mean age 56.7±8.7 y). Patients in both groups were adjusted for age and HD duration. Atherosclerotic disease was defined as a history of angina pectoris or myocardial infarction, ischemia on electrocardiography, calcification of vasculature on X-ray or a coronary artery bypass or angioplasty or a previous angiogram showing significant occlusive disease. Patients with atherosclerotic disease were defined as ASD (+) and patients without atherosclerotic diseases were assigned as ASD (-).

Levels of urea, creatinin, albumin, total cholesterol, LDL, HDL, ferritin, vitamin B 12, folic acid and Hcy levels were measured in all patients. Blood samples were obtained before HD from each patient. Homocysteine levels were measured by fluorimetric high performance liquid chromatography method.

The statistical analysis was performed using the SPSS 10.0 (SPSS, Inc., Chicago, IL) package. Results were expressed as mean values ± SD. Statistical analysis based on unpaired Student's t test and Pearson correlation analysis. P<0.05 was accepted as statistically significant.

Results

The characteristics of DM group and N group are shown on Table 1. In our study there was no difference between Hcy levels of diabetic and non-diabetic HD patients (20.3±2.3 mmol/ml vs. 18.2±1.1 mmol/ml, p=0.467). ASD (+) patients had higher Hcy levels than ASD (-) patients (22.1±2.8 mmol/ml vs. 15.3±4.6 µmol/ml, p=0.005). In DM group ASD (+) patients had higher Hcy levels than ASD (-) patients (20.5±3.2mmol/ml vs 14.4±1.6 mmol/ml, p=0.017). There was no difference in urea, creatinin, LDL, HDL, total cholesterol and ferritin levels between ASD (+) and ASD (-) patients in DM group. In N group ASD (+) patients had higher Hcy levels than ASD (-) patients (21.7±2.8 mmol/ml vs 16.3±3.0 mmol/ml, p=0.036). There was no difference in urea, creatinin, LDL, HDL, total cholesterol and ferritin levels between ASD (+) and ASD (-) patients in N group. Diabetic patients had higher incidence of ASD than non diabetic pateints (72% vs 44%, respectively, p=0.042). Hcy was associated with albumin levels (r=0.347, p<0.05). There was no correlation between Hcy levels and total cholesterol, LDL, HDL levels, hypertension and HD duration.

Discussion

Cardiovascular diseases are the major risk factors of mortality and morbidity in patients on HD and this is largely attributable to advanced atherosclerosis (10). Diabetic patients on HD are at higher risk for cardiovascular diseases since diabetes and end stage renal disease have additive impacts on the development and progression of atherosclerosis (11). Hyperhomocysteinemia is a cardiovascular risk factor in the general population, and in patients with diabetes (12,13). Because hyperhomocysteinemia is common in dialysis patients, hyperhomocysteinemia is emerging as an important risk factor for atherosclerotic disease in patients on HD. Previous analyses have provided conflicted data regarding the association between Hcy levels and atherosclerotic disease in HD patients. Dennis et al. reported that high Hcy levels in HD patients were associated with atherosclerotic and thrombotic diseases (7). Moustapha et al found that high Hcy levels were associated with cardiovascular mortality in HD patients (9). It has been proposed that this high prevalence of hyperhomocysteinemia in dialysis patients is one of the main reasons for the high rate of cardiovascular events and poor clinical outcome in these individuals. Sakurabayashi et al. found that hyperhomocysteinemia, along with advanced age,

Table 1. The characteristics of DM and N group patients

	DM group	N group	p-value
Patient (M,F)	25 (12:13)	25 (12:13)	-
Age	59.6 ± 7.9	56.7 ± 8.7	NS
Hemodialysis duration (month)	52.2 ± 5.7	69.2 ± 3.1	NS
BUN (mg/dl)	83.7 ± 8.2	84.7 ± 5.1	NS
Creatinin(mg/dl)	7.4 ± 1.9	7.9 ± 1.9	NS
Vitamin B12 (pg/ml)	679.3 ± 39.0	432.8 ± 81.3	NS
Folic asit (ng/ml)	12.4 ± 7.1	10.9 ± 6.1	NS
Albumin (g/L)	4.3 ± 0.5	4.6 ± 0.5	NS
TCholesterol(mg/dl)	161.7 ± 37.5	145.5 ± 43.9	NS
LDL (mg/dl)	78.0 ± 26.1	72.2 ± 27.6	NS
HDL (mg/dl)	27.7 ± 3.4	32.0 ± 5.9	NS
Homocysteine(mmol/L)	20.3±2.3	18.2±1.1	NS

DM group: diabetic group, N group: non-diabetic group, NS: not significant

systolic hypertension, and smoking worsen atherosclerosis in chronically uremic patients (12). Lee et al. reported an association between hyperhomocysteinemia and atherosclerotic disease in HD patients but failed to find a difference between diabetic and non diabetic HD patients according to Hcy levels (13). Our study is in line with Lee et al. as we could not find a difference in Hcy levels between diabetic and non diabetic HD patients.

Although some studies reported positive correlations between increased Hcy and higher rate of mortality in dialysis patients (10, 14), other studies failed to show such an association or found paradoxically reversed correlations. Sirrs et al. did not found any correlation between Hcy and vascular access complications in HD patients (15). However, they found significantly higher 9-month mortality in HD patients with Hcy levels higher than 27 micromol/L. Taruangsri et al. found that hyperhomocysteinemia is not an independent factor in the genesis of atherosclerosis in HD patients (16). Zadeh et al. showed that in HD patients, there is a paradoxically inverse association between poor clinical outcome and Hcy levels (17). Oishi et al. reported that diabetic dialysis patients had lower Hcy levels than non-diabetic dialysis patients and they suggested that this is because of a disorder in the demethylation pathway of Hcy (1).

In our study, there is a relationship between hyperhomocysteinemia and atherosclerosis in patients on HD. Diabetes itself being a risk factor for atherosclerosis brings out atherosclerotic risk factors of great importance in diabetic patients on HD. In vitro, homocysteine injures the endothelium through production of free radicals, suppression of nitric oxide production and Hcy also prevents anticoagulation function of endothelium, and oxidates low density lipoprotein cholesterol and causes atherosclerosis (18). Hyperhomocysteinemia, therefore, is a good indicator of risk for atherosclerosis in chronic uremic patients. There was no difference between diabetic patients and non diabetic patients according to Hcy levels. Hyperhomocysteinemia per se could not explain the increased cardiovascular mortality and morbidity rates seen in diabetic patients on HD. Traditional and non-traditional risk factors of atherosclerosis other than hcy levels may be the reason of the increased atherosclerosis in these patients.

In conclusion, high Hcy level is an independent risk factor for atherosclerosis in diabetic and non-diabetic patients on HD and hyperhomocystinemia may contribute to their excess incidence of ASD in these patients.

Table 2. Corralation between Hcy levels and other parameters

Parameters	Correlation	P value
Albumin	0.347	<0.05
Total cholesterol	0.067	NS
LDL	0.112	NS
HDL	0.180	NS
HD duration	0.109	NS

NS: not significant

References

1. Oishi K, Nagake Y, Yamasaki H, Fukuda S, Ichikawa H, Ota K, Makino H: The significance of serum homocysteine levels in diabetic patients on heamodialyses. Nephrol Dial Transplant 2000; 15: 851-5.
2. Bostom AG, Shemin D, Verhoef P, Nadeau MR, Jacques PF, Selhub J, Dworkin L, Rosenberg IH: Elevated fasting total plasma homocysteine levels and cardiovasculer disease outcomes in maintenance dialysis patients. Atherosclerosis and Thrombosis 1997; 11: 2554-8.
3. Yeromenko Y, Lavie L, Levy Y. Homocysteine and cardiovascular disease in patients with diabetes mellitus. Nutr Metab Cardiovasc Disease 2001; 11: 108-116.
4. Okada E, Oıda K, Tada H, Asazuma K, Eguchi K, Tohda G, Kosaka S, Takahashi S, Miyamori I: Hyperhomocysteinemia is a risk factor for coronary arteriosclerosis in Japanese patients with type 2 diabetes. Diabetes Care 1999; 22: 484-90.
5. Kark J D, Selhub J, Bostom A, Rosenberg I H: Plasma homocysteine and all-cause mortality in diabetes. Lancet 1999; 353: 1936-7.
6. Bachman J, Tepel M, Raidt H, Riezler R, Graefe U, Langer K, Zidek W: Hyperhomocysteinemia and the risk for vascular disease in hemodialysis patients. J Am Soc Nephrol 1995; 6:121-5.
7. Dennis W, Robinson K: Homocysteinemia and vascular disease in end stage renal disease. Kidney Int 1997; 50 (Suppl 57): 11-7.
8. Chauveau P, Chadefaux B, Coude M, Aupetit J, Hannedouche T, Kamoun P, Jungers P: Hyperhomocysteinemia, a risk factor for atherosclerosis in chronic uremic patients. Kidney Int 1993; 41 (Suppl 43): 72-7.
9. Moustapha A, NasoA, Nahlawi M: Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end stage renal disease. Circulation 1998; 20:138-41.
10. Foley RN; Parfrey PS; Harnett JD; Kent GM; Murray DC; Barre PE: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol 1996; 7: 728-36.
11. Shoji T, Kawagishi T, Emoto M: Additive impacts of diabetes and renal failura on carotid arherosclerosis. Atherosclerosis 2000; 153: 257-8.
12. Sakurabayashi T, Fujimoto M, Takaesu, Y, Haginoshita S, Goto S, Aoike I. Miyazaki S, Koda Y, Yuasa Y, Sakai S, Suzuki M, Hirasawa Y. Association Between Plasma Homocysteine Concentration and Carotid Atherosclerosis in Hemodialysis Patients. Japanese Circulation Journal 1999; 63: 692-6.
13. Lee CH, Chang HW, Wang IK, Lin CL, Chen TC, Wang PH. Diabetes mellitus, hyperhomocysteinemia and atherosclerotic vascular disease in Taiwanese chronic hemodialysis patients: A retrospective study. Renal failure 2004; 26:317-23.
14. Mallamaci F, Zoccali C, Tripepi G, Fermo I, Benedetto FA, Cataliotti A, Bellanuova I, Malatino LS, Soldarini A: Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. Kidney Int 2002; 61: 609-14.
15. Sirrs S, Duncan L, Djurdjev O, Nussbaumer G, Ganz G, Frohlich J, Levin A: Homocysteine and vascular access complications in hemodialysis patients: Insights into a complex metabolic relationship. Nephrol Dial Transplant 1999; 14: 738–43.
16. Taruangsri P, Ong-Ajyooth L, Ong-Ajyooth S, Chaiyasoot W, Leowattana W, Sritippayawan S, Vareesangthip K, Chanchairujira T, Vasuvattakul S, Shayakul C, Vanichakarn S. Relationship between hyperhomocysteinemia and atherosclerosis in chronic hemodialysis patients: J Med Assoc Thai 2005; 88:1373-81.
17. Kalantar-Zadeh K, Block G, Humphreys MH, Mcallıster CJ, Kopple JD. A Low, Rather than a High, Total Plasma Homocysteine Is an Indicator of Poor Outcome in Hemodialysis Patients. J Am Soc Nephrol 2004; 15: 442-453.
18. McCully KS: Homocysteine and vascular disease. Nat Med 1996; 2: 386– 389.