

THE ASSOCIATION BETWEEN RETINOPATHY, HYPERTENSION, AND DIABETES DURATION IN TYPE 2 DIABETICS: 6-YEARS OF EXPERIENCE⁺

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Background: Morbidity and mortality in diabetes are caused mainly by its vascular complications, both in the microcirculation and in the large vessels with accelerated atherosclerosis. Diabetic retinopathy is the clinical hallmark of microangiopathy which may lead to blindness.

Materials and method: This study was designed in type 2 diabetic patients who were on regular control and treatment in the diabetes clinic of Turgut Ozal Medical Center between June 1994 and February 2000. Six hundred and forty-seven type 2 diabetic patients (274 males and 373 females), aged 53.50 ± 11.02 years were evaluated. The mean diabetes duration was 7.90 ± 6.27 years. Patients were categorized according to the presence of retinopathy.

Results: Retinopathy was encountered in 181 patients (27.97%) (79 males and 102 females), aged 57.63 ± 10.18 years. Their mean diabetes duration were 12.98 ± 6.41 years. Four hundred and sixty-six patients (195 males and 271 females), aged 51.90 ± 10.93 years formed the non-retinopathy group. The mean diabetes duration were 5.93 ± 4.98 years. Hypertension was present in 210 of patients (45.06%) without retinopathy and in 130 patients (71.82%) with retinopathy. In terms of grading of retinopathy, background retinopathy was encountered in 93 (51.4%) patients, preproliferative retinopathy was encountered in 46 (25.4%) patients, and proliferative retinopathy was encountered in 42 (23.2%) patients. When retinopathy was compared with diabetes duration, background retinopathy was highly encountered in patients with a duration of 6-10 years, preproliferative retinopathy was seen the most in 11-15 years, and proliferative retinopathy was found to be higher in >15 years. When presence of hypertension was investigated in these patients, we found out that 52.4% of patients in group 1 (patients with diabetes duration of 0-5 years), 75.4% of patients in group 2 (6-10 years), 64% of patients in group 3 (11-15 years), and 85.3% of patients in group 4 (>15 years) were hypertensive.

Conclusion: The presence of hypertension should be investigated in patients with diabetic retinopathy and if present, should be treated aggressively. We need further studies in diabetic patients to consider the frequency and stage of retinopathy in normotensive, hypertensive, and aggressively treated hypertensive groups.

Key Words: Type 2 diabetes, duration, retinopathy, hypertension

Tip 2 diyabetli hastalarda retinopati, hipertansiyon ve hastalık süresi arasındaki ilişki: 6 yıllık deneyim

Amaç: Artmış ateroskleroz ile birlikte hem mikrosirkülasyonda, hem de büyük damarlardaki vasküler komplikasyonlar diyabet morbidite ve mortalitesine neden olmaktadır. Körlüğe neden olabilen diyabetik retinopati, mikroangiopatinin de klinik bir göstergesidir.

Materyal ve Metod: Çalışmamızda, Turgut Özal Tıp Merkezi Diyabet Kliniğinde, Haziran 1994 ile Şubat 2000 tarihleri arasında takip edilen, ortalama yaşları 53.50 ± 11.02 yıl olan 647 diyabetik hasta (274 erkek ve 373 bayan) değerlendirildi. Ortalama hastalık süreleri 7.90 ± 6.27 yıl idi. Hastalar, retinopati varlığına göre gruplandırıldı.

Bulgular: Retinopati saptanan 181 hastanın (%27.97) (79 erkek ve 102 bayan) ortalama yaşları 57.63 ± 10.18 yıl ve ortalama diyabet süreleri 12.98 ± 6.41 yıl idi. Retinopati saptanmayan 466 hastanın (195 erkek ve 271 bayan) ortalama yaşları 51.90 ± 10.93 yıl ve ortalama hastalık süreleri 5.93 ± 4.98 yıl idi. Hipertansiyon, retinopati saptanmayan hastaların 210'unda (%45,06) ve retinopati saptanan hastaların 130'unda (%71.82) tesbit edildi. Retinopati sınıflaması yapıldığında, hastaların 93'ünde (%51,4) background retinopati, 46'sında preproliferatif retinopati (%25,4) ve 42'sinde (%23,2) proliferatif retinopati saptandı. Retinopati, diyabet süresi ile karşılaştırıldığında, background retinopati özellikle hastalık süresi 6-10 yıl arası olan hastalarda en fazla görülürken, preproliferatif retinopati 11-15 yıl ve proliferatif retinopati >15 yıldan fazla hastalık süresi olan gruplarda en fazla görüldü. Aynı hasta gruplarında hipertansiyon araştırıldığında, grup 1'de (diyabet süresi 0-5 yıl olan hastalar) %52,4, grup 2'de (6-10 yıl) %75,4, grup 3'de (11-15 yıl) %64 ve grup 4'de (>15 yıl) %85,3 olarak bulundu.

Sonuç: Diyabetik retinopati hastalarda, hipertansiyon varlığı araştırılmalı ve saptandığında yoğun bir şekilde tedavi edilmelidir. Normotansif, hipertansif ve yoğun tedavi edilen hipertansif gruplarda, diyabetik retinopati sıklığı ve evrelendirilmesi çalışmaları yapılmalıdır.

Anahtar Kelimeler: Tip 2 diyabet, süre, retinopati, hipertansiyon.

INTRODUCTION

Morbidity and mortality in diabetes are caused mainly by its vascular complications, both in the microcirculation and in the large vessels with accelerated atherosclerosis.¹ Diabetes mellitus is the leading cause of new cases of blindness for people between the ages of 20 and 64 years.² Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes mellitus. The diabetes duration is a significant risk factor for the development of retinopathy.² After 20 years of diabetes, nearly all patients with type 1, and more than 60 percent of patients with type 2 diabetes, have some degree of retinopathy.³ The retinopathy is usually categorized as background, preproliferative, or proliferative which presumably represent different stages of the same pathophysiological process.⁴ Visual loss can now be largely prevented by laser photocoagulation and vitreoretinal surgery.⁵ The aim of the present study was to evaluate the association between retinopathy, hypertension, diabetes duration, and grading of diabetic retinopathy in a group of well-characterized patients.

SUBJECTS AND METHODS

Study Participants:

This study was designed in type 2 diabetic patients who were on regular control and treatment in the diabetes clinic of Turgut Ozal Medical Center between June 1994 and February 2000. Six hundred and forty-seven type 2 diabetic patients were evaluated in the cross-sectional descriptive study. We investigated the effects of diabetes duration and hypertension in patients with and without retinopathy which have clear effects on prognosis of both micro- and macrovascular complications. Patients with other chronic diseases were excluded from the study. Retinal examination was performed within the last 6 months by the same experienced ophthalmologist. Diabetic patients were treated by diet, oral antidiabetic drugs, or insulin. None of the hypertensive patients

received any other medical treatment apart from antihypertensive drugs.

Hypertension:

Hypertension was diagnosed according to the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) ($\geq 140/90$ mmHg).

Grading of Retinopathy:

On the basis of the clinical grading of all lesions, overall retinopathy was graded on a scale after induction of cycloplegia and mydriasis by phenylephrin 10% and tropicamid 1% eye drops. Consequently, the assignment of retinopathy grade was made according to the following guidelines:

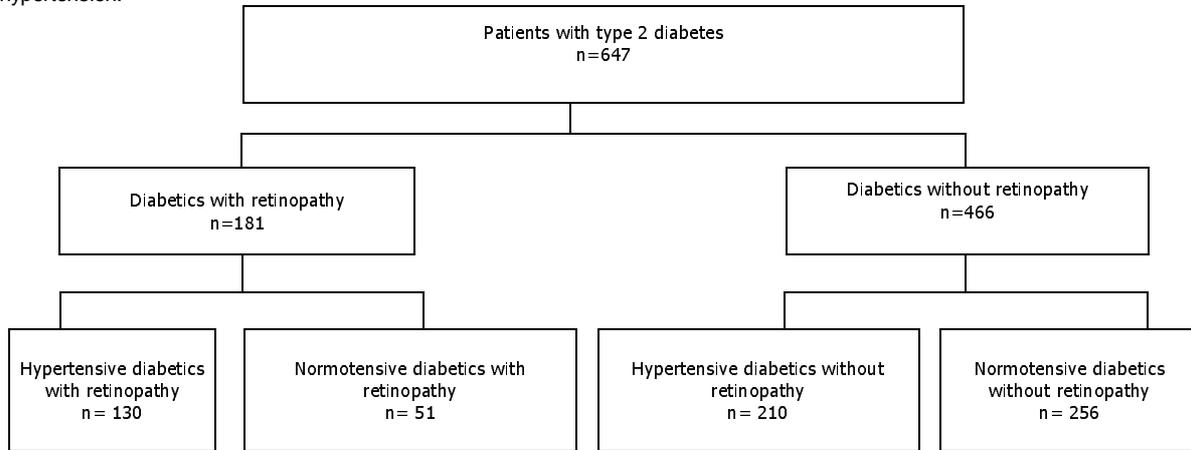
- A. Background diabetic changes were visualized ophthalmoscopically as microaneurysms, hemorrhage, focal hard exudates, and diffuse intraretinal edema.
- B. Preproliferative diabetic retinopathy was defined as a significant retinal microvascular ischemia in the absence of overt preretinal neovascularization. Multiple cotton-wool spots, dark blot haemorrhages, and intraretinal microvascular abnormalities are also added to this category.
- C. The hallmark of proliferative diabetic retinopathy was neovascularization of the retina or optic disc.

Statistical Analysis:

All data were analyzed using SPSS computational software. Intergroup comparisons were evaluated statistically by chi-square test, the difference between two population means test, and one-way ANOVA test. Results were expressed as mean \pm standard deviation. $p < 0.05$ was considered to be statistically significant.

RESULTS

Six hundred and forty-seven (274 males and 373 females) type 2 diabetic patients aged 53.50 ± 11.02 years were evaluated (Table 1).

Table 1. Study design and evaluation of patients with type 2 diabetes according to the presence of retinopathy and hypertension.

The mean diabetes duration was 7.90 ± 6.27 years. Patients were categorized according to the presence of retinopathy. Retinopathy was encountered in 181 patients (27.97%) (79 males and 102 females), aged 57.63 ± 10.18 years. Their mean diabetes duration were 12.98 ± 6.41 years. These patients were subgrouped according to the presence of hypertension. Hypertension was encountered in 130 patients (71.82%). The mean age of hypertensive patients with retinopathy were 59.23 ± 10.11 years and that of normotensive patients with retinopathy were 53.56 ± 9.27 years. The mean diabetes duration in the same groups were 13.52 ± 6.63 years in the hypertensive patients and 11.60 ± 5.63 years in the normotensive patients.

Four hundred and sixty-six patients (195 males and 271 females), aged 51.90 ± 10.93 years formed the non-retinopathy group. The mean diabetes duration were 5.93 ± 4.98 years. There was no statistically significant difference between male and female patients in terms of age and diabetes duration ($p > 0.05$) (53.58 ± 11.41 vs 50.69 ± 10.43 and 5.94 ± 5.02 vs 5.92 ± 4.96 years, respectively). Hypertension was present in 210 (45.06%) out of 466 patients without retinopathy. The mean age of hypertensive patients without retinopathy were 54.11 ± 11.31 years and normotensive patients without retinopathy were 50.08 ± 10.28 years. The mean diabetes duration in

the same groups were 6.31 ± 4.92 years in the hypertensive patients and 5.62 ± 5.01 years in the normotensive patients. There was only a statistically significant difference in the diabetes duration of hypertensive patients with and without retinopathy ($p < 0.05$).

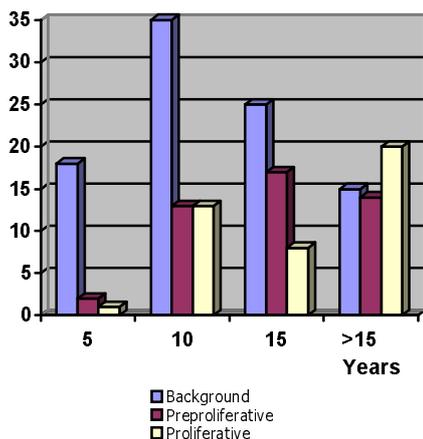
Hypertension was encountered in 340 (52.55%) out of 647 patients in the total diabetic population. When patients were categorized according to the presence of retinopathy, 130 patients (38.23%) were in the retinopathy group and 210 patients (61.77%) were in the non-retinopathy group. In terms of types of retinopathy, background retinopathy was encountered in 93 (51.4%) patients, preproliferative retinopathy was encountered in 46 (25.4%) patients, and proliferative retinopathy was encountered in 42 (23.2%) patients. There was no statistically significant difference between male and female patients in terms of age and diabetes duration ($p > 0.05$) (56.27 ± 12.02 vs 58.68 ± 8.40 and 13.26 ± 7.30 vs 12.76 ± 5.65 years, respectively). The duration of diabetes mellitus in patients with background retinopathy was found to be 9.90 ± 5.19 years in males and 8.69 ± 3.58 years in females, in patients with preproliferative retinopathy it was 17.31 ± 7.06 years in males and 14.40 ± 6.13 years in females, and in patients with proliferative retinopathy it was 18.73 ± 6.64 years in males and 15.70 ± 6.61 years in females (Table 2).

Table 2. The distribution of patients with and without retinopathy and diabetes duration in male and female patients.

Retinopathy vs Non-retinopathy	N	Male (Years) X + SD	Female (Years) X + SD
Background Retinopathy	93	9.90 ± 5.19	8.69 ± 3.58
Preproliferative Retinopathy	46	17.31 ± 7.06	14.40 ± 6.13
Proliferative Retinopathy	42	18.73 ± 6.64	15.70 ± 6.61
Total Retinopathy	181	13.26 ± 7.30	12.76 ± 5.65
Without Retinopathy	466	5.94 ± 5.02	5.92 ± 4.96

X : mean
SD : standard deviation

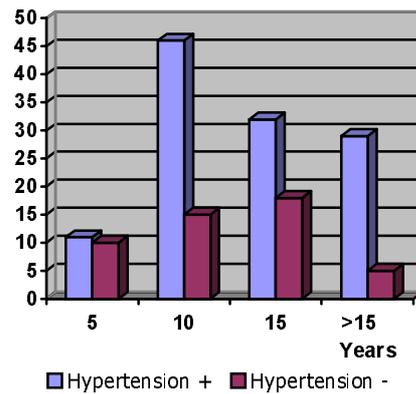
In order to determine the relationship between retinopathy and duration of diabetes, patients were categorized into 4 groups. Group 1 included patients with a diabetes duration of 0-5 years, group 2 included 6-10 years, group 3 included 11-15 years, and group 4 included ≥16 years. In group 1, background retinopathy was encountered in 85.7%, preproliferative retinopathy was in 9.5%, and proliferative retinopathy was in 4.8%. In group 2, background retinopathy was encountered in 57.4%, preproliferative retinopathy was in 21.3%, and proliferative retinopathy was in 21.3%. In group 3, background retinopathy was encountered in 50%, preproliferative retinopathy was in 34%, and proliferative retinopathy was in 16%. In group 4, background retinopathy was encountered in 30.61%, preproliferative retinopathy was in 28.57%, and proliferative retinopathy was in 40.82%. There was statistically significant difference in groups 1 and 3 (p< 0.05) (Figure 1).



*p<0.05

Figure 1. Number of patients with background, preproliferative, and proliferative retinopathy in comparison with the duration of diabetes.

When presence of hypertension was investigated in these groups, we found out that 52.4% of patients in group 1, 75.4% of patients in group 2, 64% of patients in group 3, and 85.3% of patients in group 4 were hypertensive. The only statistically significant difference was observed in group 1 (p< 0.05) (Figure 2).



*p<0.05

Figure 2. Number of hypertensive and non-hypertensive patients among patients with diabetic retinopathy.

DISCUSSION

Ophthalmic complications of diabetes include corneal abnormalities, glaucoma, neovascularization of the iris, cataracts, and optic nerve abnormalities, but by far the most frequent and potential cause of blindness is the diabetic retinopathy. Approximately 25% of all diabetics have some form of retinopathy³ In our study population, the rate is 27%. The incidence and severity increase consistently over time so that more than 90% of diabetics developed retinopathy at some time during their lives.³ It is known from the studies that early diagnosis and treatment of diabetic

retinopathy can slow its progression and help to prevent blindness.³

There is considerable epidemiological evidence suggesting that hypertension plays a significant role in the development and progression of diabetic nephropathy,⁶ retinopathy,^{7,8} cardiovascular disease,⁹⁻¹² and neuropathy¹³ in patients with type 2 diabetes mellitus. Hypertension is a frequent complication of diabetes and is often found in conjunction with retinopathy. Furthermore, several studies have demonstrated a significant increase in mortality in diabetic patients with hypertension.^{14,15} Duration of diabetes and poor blood glucose control are established risk factors for the development of retinopathy,¹⁶⁻¹⁹ but the pathogenetic mechanisms underlying the initiation and progression of this complication are still poorly understood.²⁷

The prevalence of background retinopathy increases with age, and after 25 to 30 years of disease at least 90% of patients have retinal lesions.²⁰ In type 1 diabetic patients, 99.5% of patients have some type of retinopathy after 15 years of disease, and 67% have proliferative retinopathy after 35 years.²¹

In our study, we detected a strong correlation between retinopathy grading and diabetes duration. Background retinopathy was highly encountered in group 2, preproliferative retinopathy was seen the most in group 3, and proliferative retinopathy was found to be higher in group 4. After 5 years, patients were at increased risk of developing retinopathy (Background retinopathy 51.4%, preproliferative retinopathy 25.4%, and proliferative retinopathy 23.2%). In a national study performed in Kırıkkale and İskenderun, the prevalence of retinopathy in patients with newly diagnosed diabetes mellitus was searched. Of those 55 patients, 10 patients (18.18%) were diagnosed to have retinopathy at the initial diagnosis of type 2 diabetes. Twenty-one patients (38.18%) were diagnosed to have hypertension. When diabetic patients with retinopathy were searched for the presence of hypertension, 3 patients (30%) were found to be hypertensive at the initial diagnosis of retinopathy.²² In our study, 52.4% of diabetic retinopathy patients with a disease

duration of 0-5 years were found to be hypertensive.

The four retinopathy groups were also compared for the presence of hypertension. Interestingly, in all groups, the frequency of hypertension was found to be higher (52.4%, 75.4%, 64.0%, and 85.3%, respectively). In group 4, only 14.7% of patients were not hypertensive.

Diabetics are often affected by both diabetes and hypertension which are also independent risk factors for morbidity (micro- and macrovascular) and mortality. People with type 2 diabetes make up the greatest proportion of those with hypertension.²³ It is often found in conjunction with retinopathy. Nevertheless, retinopathy also occurs in the absence of hypertension.³ Hypertension appears to be a significant contributor to the development and progression of diabetic complications.²⁴ The role of blood pressure elevation in the incidence and progression of diabetic retinopathy is not clearly established and the results have been conflicting.²⁵⁻²⁷

Hypertension may also play a role in the evolution of diabetic retinopathy by increasing retinal blood flow.^{29,30} Kohner et al³¹ reported that the severity of retinopathy was found to be associated with increased systolic and diastolic blood pressures. Patients with microvascular retinal pathology may also have renal involvement and secondary higher systolic blood pressures. However, they also found that increased urine albumin concentrations showed only a weak association with retinopathy in women and no association in men. The authors concluded that higher systolic blood pressure per se was probably an important determinant of retinopathy. On the other hand, Norgaard et al³² attempted to separate the possible effects of hypertension and of increased urinary albumin loss on diabetic retinopathy by comparing hypertensive, normoalbuminuric IDDM patients with normotensive, normoalbuminuric patients and found no statistically significant difference in prevalence of diabetic retinopathy, thus claiming that hypertension is not associated with increased retinal changes.

Although blood pressure and urinary albumin excretion are closely related, the association between blood pressure and diabetic retinopathy is present also when coexisting renal disease is excluded and the relationship between retinopathy and hypertension may not be confined to patients with elevated urinary albumin excretion.²⁸ However, evaluation of a possible independent relationship between retinopathy and blood pressure elevation is rendered impossible without precise information albumin excretion, since confounding by coexisting incipient renal disease can not be ruled out.²⁸

The presence of hypertension should be investigated in patients with diabetic retinopathy and if present, should be treated aggressively. We need further studies in diabetic patients to consider the frequency and stage of retinopathy in normotensive, hypertensive, and aggressively treated hypertensive groups. Prospective studies are also needed in order to further evaluate the association between blood pressure elevation and diabetic retinopathy and control studies designed to evaluate whether antihypertensive therapy may impede or prevent development and progression of diabetic retinopathy would be of interest.

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