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Serum and vitreous resistin levels in patients with proliferative diabetic retinopathy

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ABSTRACT

Aim: The aim of the study was to investigate the serum and vitreous levels of resistin in patients with the proliferative diabetic retinopathy (PDR) and to compare those with age-matched control subjects.

Methods: The study included 45 eyes with PDR (group 1) and a control group of 22 (group 2). All eyes underwent vitrectomy surgery. The lipid profile, fasting blood glucose (FBG), HbA1c and resistin levels were investigated in blood samples of all subjects. Complete ophthalmological examinations were evaluated. Vitreous samples were collected from both groups during vitrectomy surgery and resistin levels were investigated in those samples. The results were evaluated using SPSS 9.0 software.

Results: The demographic characteristics of the diabetic group and the control group were similar ($p > 0.05$). There was no significant difference between the groups in respect of mean visual acuity (VA), body mass index (BMI) values, or lipid profiles ($p > 0.05$). There was no measurable value of resistin in the vitreous samples of all the eyes. The mean blood resistin level was 367 ng/ml in the control group and 387 ng/ml in the study group and the difference was not statistically significant ($p > 0.05$).

Conclusions: In the light of the findings of this study, it can be assumed that resistin did not pass through the vitreous at measurable levels. However, the serum resistin levels of the diabetic patients were higher than those of the control group although not statistically significant. Therefore, it can be considered that resistin does not play a major role in retinal neovascularization.

1. Introduction

One of the major causes of blindness in developed countries is diabetic retinopathy (DR). In eyes with DR, causes of visual loss are diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR) such as vitreous hemorrhage, tractional retinal detachment and neovascular glaucoma in advanced stages [1]. Hyperglycaemia leads to capillary obstruction resulting in vascular leakage and then capillary occlusion results in retinal ischemia and increased vascular

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endothelial growth factor (VEGF) levels, which are responsible for the development of neovascularization and the proliferative phase of diabetic retinopathy.

In the etiopathogenesis of DR, biochemical changes have been identified such as oxidative stress, activation of protein kinase C, and the formation of advanced glycation end products [2,3]. In recent years, strong evidence has shown that immunological factors and inflammation may play a major role in the pathogenesis of DR. In many animal models, increased leukocyte adhesion has been observed in the diabetic retina [4]. Therefore, DR has been described as a low-grade inflammatory disease [5]. There has been a limited number of studies showing increased inflammatory mediators in vitreous fluid and serum samples of patients with DR [6–8].

The recently-discovered resistin is an adipocyte that is thought to have a role in obesity and cardiovascular diseases. Resistin was identified during research into the mechanisms of the anti-diabetic drug, thiazolidinedione (TZD). TZD is an anti-diabetic that increases fat intake into the cell and reduces the amount of plasma free fatty acid, thereby increasing insulin sensitivity [9]. Studies have shown that resistin provided angiogenesis in coronary, lung and placental endothelial cells. Resistin has been determined to lead to vascular endothelial growth factor receptor 1 (VEGFR1) and vascular endothelial growth factor receptor 2 (VEGFR2) up-regulation through mRNA expression in human coronary and lung endothelial cells. It is thought that as a result of this, matrix metallo proteinase 1 (MMP1) and matrix metallo proteinase 2 (MMP2) activation provides endothelial cell migration in the capillaries and tube formation in the cells [10].

Based on the idea that resistin may contribute to the development of PDR, the aim of this study was to investigate the vitreous and blood resistin levels in patients with PDR and to compare these results with those of non-diabetic subjects.

2. Material method

67 eyes of 67 patients who underwent pars plana vitrectomy (PPV) surgery were included. The patients were divided into two groups; group 1 comprised 22 eyes of 22 subjects without DM and group 2 comprised 45 eyes of 45 subjects with PDR. Surgery was applied those 45 eyes for complications of PDR and 22 eyes for non-diabetic retinal disease. The study protocol was approved by the Ethics Committee of the Hospital and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients included in the study.

Vitrectomy indications for non-diabetic patients were vitreous hemorrhage, macular hole, idiopathic epiretinal membrane and regmatogenous retinal detachment. Exclusion criteria were a history of ocular surgery and ocular trauma, loss of vision for other reasons, a history of long-term use of systemic drugs such as thiazolidinedione or ocular therapy, and systemic disease.

For all patients with indications for vitrectomy, a record was made of systemic diseases, use of systemic drugs, and the duration of diabetes if present. From all patients with surgery indications, preoperative blood samples were withdrawn into a biochemical tube for the resistin assay and for routine blood tests (lipid profile, fasting blood glucose (FBG) and HbA1c). The height and weight values of all patients were measured and body mass index (BMI) was calculated and noted.

All the eyes underwent comprehensive ophthalmic examinations including the best-corrected visual acuity (VA) using the Log MAR chart, intraocular pressure (IOP) measurement using applanation tonometry, a detailed biomicroscopic anterior segment examination and dilated fundus examination. Orbital USG was used in eyes where the fundus was not clear.

Vitreous specimens were obtained from all eyes before vitrectomy. The Dorc (Dutch Ophthalmic Research Center-Eckardt 23 Gauge vitrectomy System-Holland) vitrectomy device and the non-contact (Eibos) system were used for all operations by the same surgeons. 23-Gauge transconjunctival vitrectomy was planned for all patients. The operations were performed under local anesthesia. An average of 0.5–1 cc vitreous was obtained using a 23-G vitrectomy cutter while the infusion fluid closed, then the infusion fluid was opened and the vitrectomy was continued.

Preoperative lipid profile, FBG and HbA1c values were noted. Vitreous specimens were kept at −83 °C. ELISA kits were used for serum and vitreous resistin levels (Human resistin ELISA, Biovendor Laboratorni medicana a.s.). The ELISA plates were washed with an automatic washer (ELISA Washer, Clombus Plus, Tecan, Austria) and read at 450/620 nm with an ELISA reader (ELISA Reader, Sunries, Tecan, Austria).

Data obtained in the study was evaluated statistically using Statistical Package for Social Science for Windows (SPSS 9.0) software. The Shapiro Wilk test, the significance test of the difference between the two means, the Mann Whitney *U* test and the Chi-square test were applied during statistical analysis. A value of $p \leq 0.05$ was considered statistically significant.

3. Results

The patients in all groups comprised 32 (%47.7) males and 35 (%52.3) females. Group 1 comprised 22 eyes of 22 subjects and group 2, 45 eyes of 45 subjects. There was no statistically significant difference between the two groups in respect of mean age ($p > 0.05$) (Table 1).

The mean VA of the patients before surgery was 0.06 (log MAR) in group 1 and 0.1 (log MAR) in group 2, mean IOP was 13 mmHg in group 1 and 16 mmHg in group 2. There were no statistically significant differences between the groups in respect of VA or IOP ($p > 0.05$) The mean BMI of patients was 27.01 in group 1 and 28.98 in group 2, with no significant difference between the groups ($p > 0.05$) (Table 2).

Group 1 included 12 eyes (%54.5) with retinal detachment, 5 eyes (22.7) with macular hole, 3 eyes (13.6) with vitreous hemorrhage due to hypertensive retinopathy, 1 eye (4.5) with traumatic phaco donesis and 1 eye (4.5) with nucleus drop. All the patients were questioned regarding coronary artery disease (CAD), and 21 patients (95.5) reported no CAD and 1 patient (4.5) had CAD in group 1. In group 2, 34 patients (75.6) had no CAD and 11 patients (24.4) had CAD. The

Table 1 – Comparison of demographic data of groups.

	Group 1	Group 2
Number of patients	22	45
Gender (F/M)	10 F 12 M	25 F 20 M
Age (years) Mean ± SD	57.27 ± 13.6 (32–76)	61.55 ± 9.01 (43–82)

F: female, M: male, SD: standard deviation.

Table 2 – Comparison of clinical data of groups.

	Group 1	Group 2	P value
VA (mean) (min-max)	0.06 (0.001–0.5)	0.1 (0.001–0.63)	p > 0.05
IOP (mmHg) (min-max)	13 (5–21)	16 (7–29)	p > 0.05
BMI (mean) (min-max)	27.01 (19.53–32.76)	28.98 (20.06–37.10)	p > 0.05

BMI: body mass index, IOP: intra ocular pressure, VA: visual acuity.

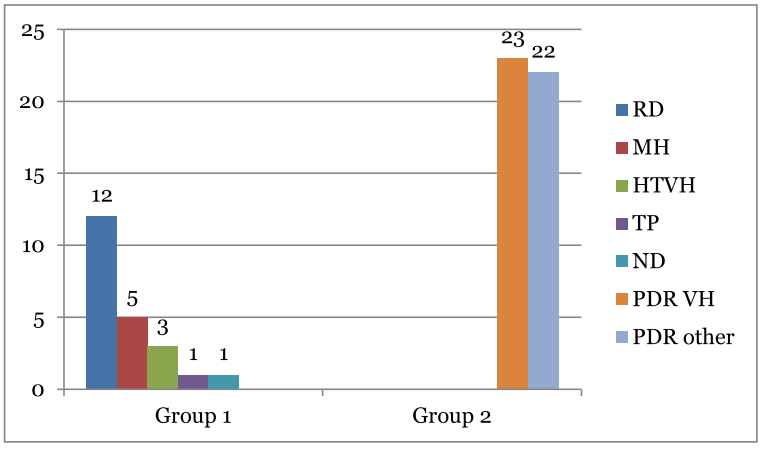
patients were questioned about hypertension. In group 1, 13 patients (59.1) had no hypertension and 9 patients (40.9) had hypertension. In group 2, 21 patients (46.7) had no hypertension and 24 patients (53.3) had hypertension (Figs. 1 and 2).

In group 2, the DM diagnosis had been made less than 5 years previously in 2 patients (%4.4), at 5–10 years in 14 (% 31.1) and more than 10 years in 29 (%64.4) Of the patients with DM, 6 (%13.3) were using oral antidiabetic drugs (OAD), 34 (% 75.6) were using insulin, and 5 (%11.1) were using both OAD and insulin (Fig. 3).

There was no measurable level of resistin in the vitreous specimens of all the patients. Therefore, only serum levels of resistin were compared in the study. The mean serum resistin level was 3.67 ng/ml in group 1 and 3.87 ng/ml in group 2, with no statistically significant difference between the groups in respect of serum resistin levels ($p > 0.05$). (Table 3) Mean FBG was 106.8 mg/ml in group 1, 185.27 mg/ml in group 2, and the difference between the groups was statistically significant ($p = 0.0001$). An HbA1C level >6 was not determined in any patient in group 1 and the levels group 2 were <6% in 1 (2.2) patient, between and %6.5 in 6 (13.3) patients, between %6.5 and %8.0 in 17 (37.8), and >%8.0 in 21 46.7).

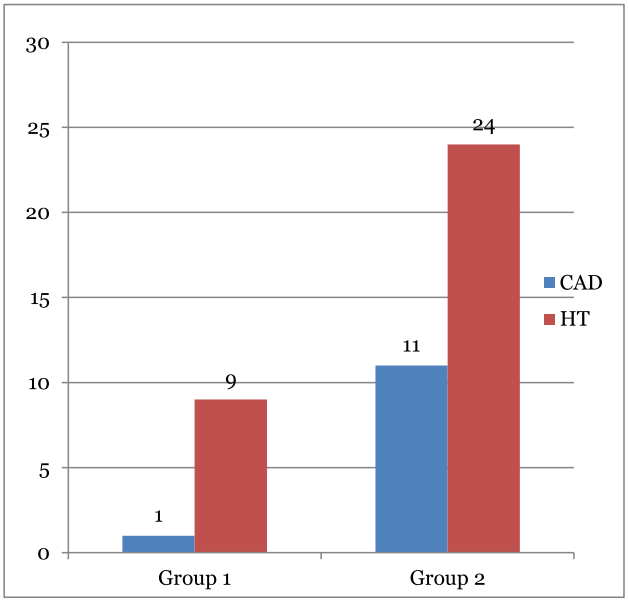
4. Discussion

It is thought that diabetic retinopathy (DR) will become more widespread in the future associated with the increase in the incidence of diabetes mellitus (DM) throughout the world. DR is a progressive state with microaneurysms and small haemorrhages leading to retina ischaemia, permeability and neovascularization [11]. For a long time, DR was not accepted as an inflammatory disease based on the retina being a tissue with separate immunity. In addition, typical DR findings such as oedema and neovascularisation are differentiating characteristics of inflammation. Although the retina has differenti-



HT VH: hypertensive vitreous hemorrhage, MH:macular hole, ND:nucleus drop, PDR VH: proliferative diabetic retinopathy vitreous hemorrhage, RD: retinal detachment, TP:traumatic phacodonesis

Fig. 1 – Patient diagnoses. HT VH: hypertensive vitreous hemorrhage, MH: macular hole, ND: nucleus drop, PDR VH: proliferative diabetic retinopathy vitreous hemorrhage, RD: retinal detachment, TP: traumatic phacodonesis.



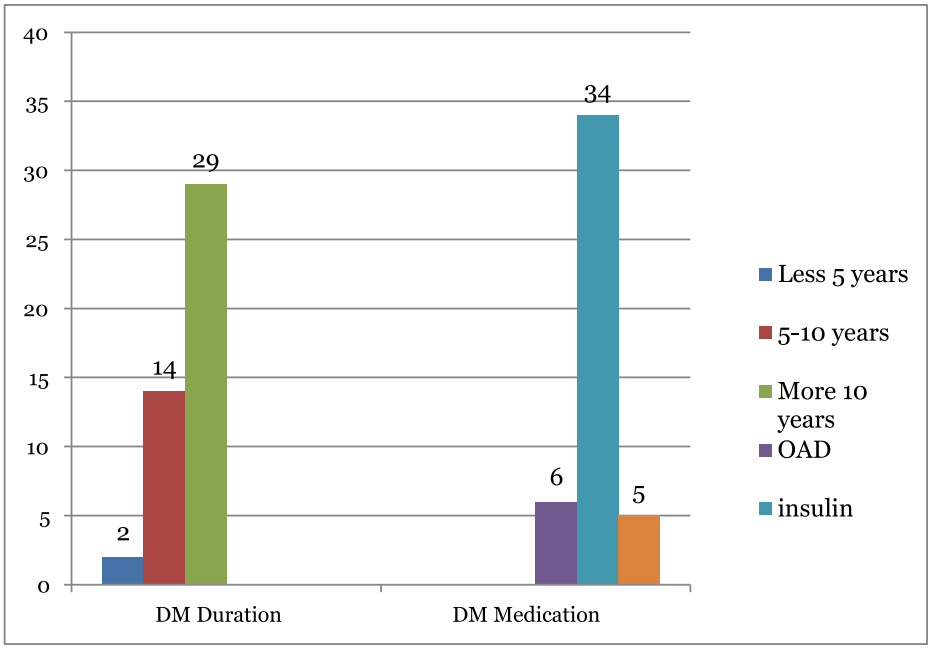
CAD:coronary artery disease, HT:hypertension

Fig. 2 – Patients systemic disease. CAD: coronary artery disease, HT: hypertension.

ated immunity, the up-regulation of ICAM (Intracellular Adhesion Molecule), caused by the VEGF signal pathway is a sign of the contribution of leukocytes in DR patients [12,13]. Therefore, the potential role of inflammatory mediators in DR has become a subject of research [14–17]. In a study by Tsai T. et al, measurements were taken of the levels of 3 inflammatory cytokines (IL-1, IL-6, IFN-γ), pleiotropic cytokines (IL-2, IL-4, IL-13) and VEGF, VEGF-A and platelet growth factor in DR patients. Up-regulation was determined in pro-inflammatory cytokines, and it was thought that this could be evidence of inflammation processes in the diabetic retina. The reaction against these immunomodulator cytokines was in the early stage and it was not seen to be strong until the processes could be corrected [18].

With the discovery of leptin, it was discovered that the central nervous system (CNS) is affected by several peripheral signalling molecules [19]. These are known as adipokines and are substances expressed from adipose tissue. Fat tissue, which is a mechanical barrier and an energy depot for the body, produces approximately 20 cytokines [20]. One of these cytokines is resistin, which is basically a 12.5-kDa weighted adipocytokine produced by macrophages in humans [21]. Resistin, which was first defined as an expressed protein which can induce insulin resistance in murine adipocytes [22], is a pro-inflammatory adipokine that induces TNFa and IL-6 secretion from various cell types, including peripheral blood mononuclear cells and pancreatic acinar cells [23,24]. Experimental rodent studies have shown that resistin contributes to hepatic insulin resistance and increases blood glucose levels. While the physiological role of resistin protects blood glucose levels when nutrition is insufficient, the pathological effects have been shown to be related to a deterioration in the use of glucose when there is excess body fat [25]. In contrast, suppression of resistin activity in rodents has been shown to impair adipogenesis and cause a subsequent increase in adipose tissue mass, followed by insulin sensitivity and an increase in glucose use [26].

Previous studies have shown that resistin provides angiogenesis in coronary, lung and placental endothelial cells. Mu et al demonstrated that resistin caused human coronary and lung endothelial mRNA expression and this led to up-



DM: Diabetes Mellitus OAD:Oral Antidiabetic Drug

Fig. 3 – DM: duration and medication. DM: diabetes mellitus. OAD: oral antidiabetic drug.

Table 3 – Comparison of serum and vitreous resistin levels of the groups.

	Group 1	Group 2	P value
Vitreus resistin level mean (ng/ml)	0.000 ng/ml	0.000 ng/ml	0
Serum resistin level mean (ng/ml)	3.67 ng/ml	3.87 ng/ml	p > 0.05
FBG mean (m/ml)	106.68 mg/ml	185.27 mg/ml	P = 0.0001

FBG: fasting blood glucose.

regulation of VEGFR1 and VEGFR2 receptors and activation of MMP1 and MMP2. It is thought that as a result of this, angiogenesis is obtained by capillary endothelial cell migration and tube formation in the cells [27].

Epidemiological studies have shown inflammatory markers with increased resistin in circulation and an increased risk of the development of type 2 diabetes (T2DM), atherosclerosis and myocardial infarct [21]. There has also been increasing interest recently in the role of resistin in the connection between insulin resistance and malignant diseases [28]. Data obtained from T2DM patients have shown increased serum resistin levels in patients with advanced DR [29]. However, there are conflicting results for T1DM patients. Some studies have shown a positive correlation between serum resistin levels and DR. Yazıcı et al compared serum adipokine levels and found higher resistin levels in type 1 DM compared to the control group [30]. These results were supported by the findings of a study by Geyikli et al [31]. In contrast to those studies, Majewska et al reported a negative correlation between Type 1 DM and serum resistin levels [32].

The majority of studies that have examined the correlation between resistin and DR have examined serum levels. In a study by Haruhiko et al, 238 T2DM patients in Japan were separated into 4 groups according to the retinopathy. DR was determined to be present in %61.2 of the patients, posterior plane DR in %19.2, pre-proliferative DR in %11.1 and proliferative DR in %8.5. A statistically significant positive correlation was determined between serum resistin levels and DR grade [33].

While most studies have found a positive correlation between resistin and DR, some studies have not found a correlation. In a study by Schaffer et al, the serum resistin levels were compared with the ELISA method in 216 healthy control subjects, 555 T2DM patients and 114 T1DM patients. The results of the study showed no significant relationship between serum resistin levels and retinopathy [34].

Naglaa Azab et al separated DM patients into 3 groups as those with no findings of DR, those with NPDR, and those with PDR, and a positive correlation was determined between DR grade and serum resistin [35].

Visfatin, which is a recently defined adipokine, is thought to have an angiogenic effect similar to resistin, and serum and vitreous levels have been examined. Visfatin serum and vitreous levels have been researched in PDR and NPDR patients, and a relationship has been found between the presence and severity of DR and visfatin serum and vitreous levels [36].

In the current study it was aimed to examine the serum and vitreous levels of resistin, which is an adipokine that plays a role in angiogenesis, in PDR patients. To the best of our knowledge, this is the first study to have examined vitreous levels of resistin in DR. No similar study could be found in literature. In the current study, no measurable level of resistin could be found in any of the vitreous samples. Although of a lower molecular weight than visfatin and despite the destruction of the blood-retina barrier, that resistin did not reach the measurable level of vitreous in the proliferative process suggested that resistin did not play a significant role in the development of PDR. When the serum resistin levels were examined, higher levels were determined in the PDR group than in the control group, but this difference was not at a statistically significant level. (p = 0.687).

5. Conclusions

Several factors in the development of PDR have been researched. These factors that have been researched may serve as new biomarkers in addition to traditional methods to evaluate the future risk of DR. Although serum levels of resistin may be a biomarker in DR, as it does not pass to the vitreous in the proliferative process, the role of resistin in the etiopathogenesis of PDR is debatable. There is a need for further more detailed, large-scale studies on this subject.

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Declaration of Competing Interest

None.

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Our study has not been published anywhere before and the authors declare it.

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