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Original article

ALTERATIONS OF MACULAR RETINAL MICROCIRCULATION EXAMINED WITH OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY AFTER SWITCHING FROM ORAL HYPOGLYCEMICS TO INSULIN THERAPY IN PATIENTS WITH TYPE 2 DIABETES

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Abstract

Introduction

Aim: To assess the impact of insulin therapy in the initial period on blood vessels density in the area of the macula lutea, evaluated with optical coherence angiography (OCTA) in patients with type 2 diabetes.

Materials and methods: A prospective observational study including 21 patients (42 eyes) with type 2 diabetes was conducted. In 4 examined eyes, a nonproliferative diabetic retinopathy (NPDR) form of diabetic retinopathy was present without diabetic macular edema, while the remaining examined eyes were without the presence of DR/DME. Patients had been treated only with oral hypoglycemic drugs before inclusion in the study, and all of them were prescribed insulin therapy at the time of enrollment in the study. The main investigated parameters were changes in the density of blood vessels in the superficial vascular plexus (SVP) and deep vascular plexus (DVP) in the macular area measured by optical coherence angiography (OCTA). Additional variables analyzed included changes in visual acuity (BCVA), HbA1c, serum glucose, blood pressure, triglycerides, and cholesterol and their correlation with clinical findings. The examinations were performed at 1, 3 and 6 months after diabetes treatment with insulin.

Results: In all 21 subjects (42 examined eyes) no change in BCVA was observed. The laboratory parameters for glucose and HbA1c were analyzed, and each control showed a satisfactory reduction and stabilization of the results. From an anatomical point of view, the density of blood vessels in the first month of starting insulin treatment showed a significant decrease, especially in the deep vascular plexus. Three months after the start of insulin therapy, a decrease in the blood vessels density in the superficial vascular plexus was noticed. All parameters showed a return to normal values after the sixth month. The average HBA1 levels showed better results after insulin therapy.

Conclusion: This study suggests that in the initial phase of insulin therapy compared to oral antidiabetic agents, changes in the density of the blood vascular network in the macular region were observed with no corresponding change in the visual acuity.

Keywords: type 2 diabetes, diabetic retinopathy, diabetic maculopathy, oral hypoglycemics, insulin, blood vessel density, OCTA

Introduction

Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the most common and most important chronic complications of diabetes mellitus. [1,2] DME is an important cause of serious vision loss in patients with type 2 diabetes. Glycemia, the existence of hypertension and hyperlipidemia[3,4].

Diabetic macular edema (DME) is manifested as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner (IPL) and outer plexiform layer (OPL). DME can be present at any level of diabetic retinopathy. Diabetic retinopathy is a chronic, microvascular complication of diabetes mellitus. It results from metabolic, endocrine and hemodynamic interaction factors, where basically, the key factor is the high concentration of blood glucose which initiates other processes. Disruption of the blood-retinal barrier (BRB) results in changes in retinal microcirculation[5,6]. Hyperpresence of retinal blood vessels and subsequent edema formation are key clinical features[7].

In principle, diabetic retinopathy is classified into stages: non-proliferative diabetic retinopathy, with or without diabetic maculopathy that affects the macular region (yellow stain), and proliferative diabetic retinopathy[8-10].

Main risk factors for the onset of diabetic retinopathy are: hyperglycemia, hypertension, duration of diabetes, obesity, smoking, pregnancy.

Diabetic retinopathy usually does not change BCVA until the advanced stage of the disease occurs. In principle, patients subjectively complain of blurring in the eyes (result of changes in the vitreous), loss of part of the field of vision (result of bleeding), weakening of central vision as a result of changes in macula (diabetic maculopathy or cystoid macular edema) [11,12]. Nowadays, modern medicine offers a number of diagnostic tools to control and monitor the condition of the back segment of the eye. Determining the best corrected visual acuity (BCVA) and fundus examination after pharmacological dilatation of the pupils are the basic diagnostic methods to be done in each patient. Additional standard diagnostic tools for more detailed eye and vision condition include optical coherent tomography with/without angiography (OCT/OCTA), fundus fluorescein angiography (FFA) and ultrasonography, which is particularly significant in non -transparent media[13-15]. Stereo-fundus photos also play a significant role.

Material and methods

A prospective observational study involving 21 patients (42 eyes) with type 2 diabetes was conducted. Four 4 tested eyes presented with a nonproliferative diabetic retinopathy (NPDR) and diabetic macular edema (DME), while the remaining tested eyes were without the presence of DME. Patients had been treated only with oral hypoglycemic agents prior to their enrollment in the study, and all were started on insulin therapy once included in the study. The main investigated parameters were changes in visual acuity (BCVA) and changes in the density of blood vessels in the surface vascular plexus (SVP) and deep vascular plexus (DVP) in the macular area measured by optical coherent angiography (OCTA). Additional analyzed variables included HBA1C, serum glucose, blood pressure, triglycerides and cholesterol, and their correlation with clinical findings. Examinations were performed at 1, 3 and 6 months after treatment of insulin diabetes. SPECTRAL DOMAIN OCT/OCTA, SLED Light Source, with an axial resolution of 5µm in tissue, obtained through the Optopol Revo NX, was used giving an image of morphological construction of the posterior segment (macula). OCT-A technology uses a reflection of laser light on the surface of movable red blood cells to accurately display blood vessels across different parts of the eye, eliminating the need to apply intravascular

contrasting colors. An OCTA scan of the patient's retina consists of multiple individual A-scans, which compiled into a B-scan, provide structural information on the cross-section. With OCT-A technology, the same tissue area is constantly scanned, and g the differences between scans over time allow detection of high-flow zones (with pronounced changes between scans) and slower or no-flow zones, which appear similar.

Statistical analysis was performed using the SPSS Windows software. For the series of numerical characteristics for BCVA, descriptive statistics was used evaluating values of laboratory parameters for Glu, HbA1c, LDL, Tg, as well as changes in the density of blood vessels in the surface vascular plexus (SVP) and deep vascular plexus (DVP) in the macular area measured by optical coherent angiography (OCTA). The analysis of OCTA parameters was performed using OCT Analyzer, which displayed progression curves for the examined intervals, while numerical values for the first, third, and sixth month were analyzed using Friedman ANOVA.

Results

All 21 participants (42 eyes tested) had no change in BCVA. Laboratory parameters for glucose and HBA1C were analyzed at each control, and they showed satisfactory reduction and stabilization of the results. From an anatomical point of view, the density of blood in the first month of insulin treatment showed a significant decrease, especially in the deep vascular plexus (Figure 1). In 67% of participants, the numerical values obtained with OCTA analysis showed an average decrease of 7.375% in blood vessel density in the deep vascular plexus. In 45% of these tests, the biggest decrease in the density occurred between the first and third months of insulin treatment. By sectors, the largest interception was observed in the upper macular sector. In the remaining 22% of participants, OCTA analysis showed an average 5.6% increase and all changes occurred within the first three months. By sectors, the biggest change was in the lower macular sector (Figure 2). In 11% of participants, the parameters analyzed did not show significant changes. Three months after insulin therapy, there was a decrease in the blood vessels density and in the superficial vascular plexus. In 72% of participants, OCTA analysis showed a decrease in the density in the surface vascular plexus by 4.375%, while in 18% of participants the analysis showed a 3.3% increase in density present after the first month of insulin treatment. The decrease in density was more pronounced in the lower sector. The remaining 10% of participants did not show a significant difference after starting the insulin treatment (Table 1). All parameters showed a return to normal values after the sixth month. The average HBA1C levels showed better results after starting the insulin therapy.

Table 1. OCTA analysis of blood vessel density changes

Blood vessel density	% of participants	p-value	Significance
Deep plexus density reduction	67%	0.126	✗
Superficial plexus density reduction	72%	0.05	✔ borderline
Deep plexus density increase	22%	0.016	✔
Superficial plexus density increase	18%	0.0045	✔✔
No change (overall)	10-11%	<0.001	✔✔✔

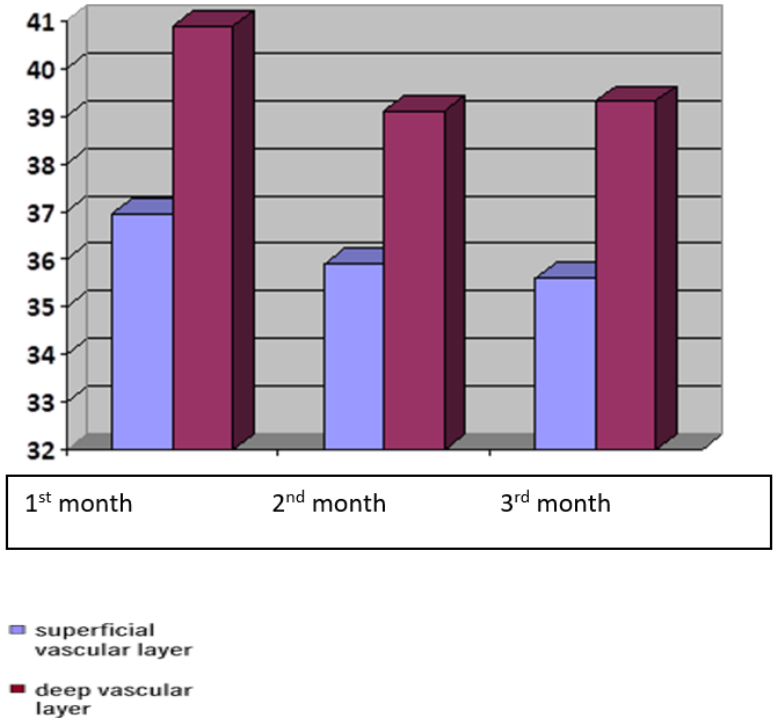
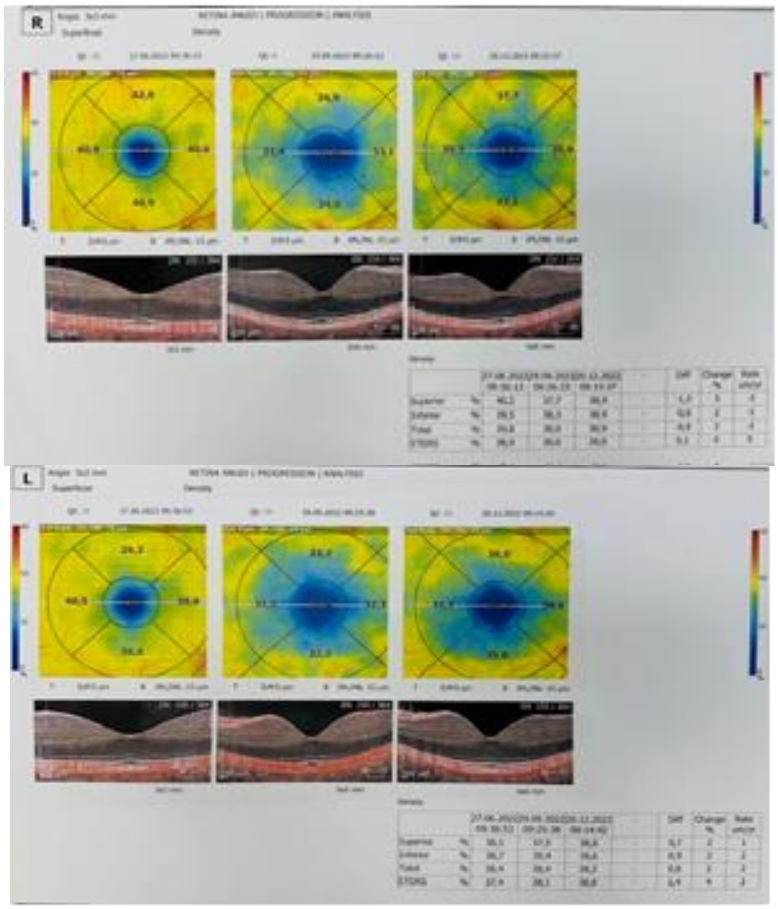


Fig. 1. Density of blood vessels in macular region in the first six months of starting insulin treatment in patients with type 2 diabetes



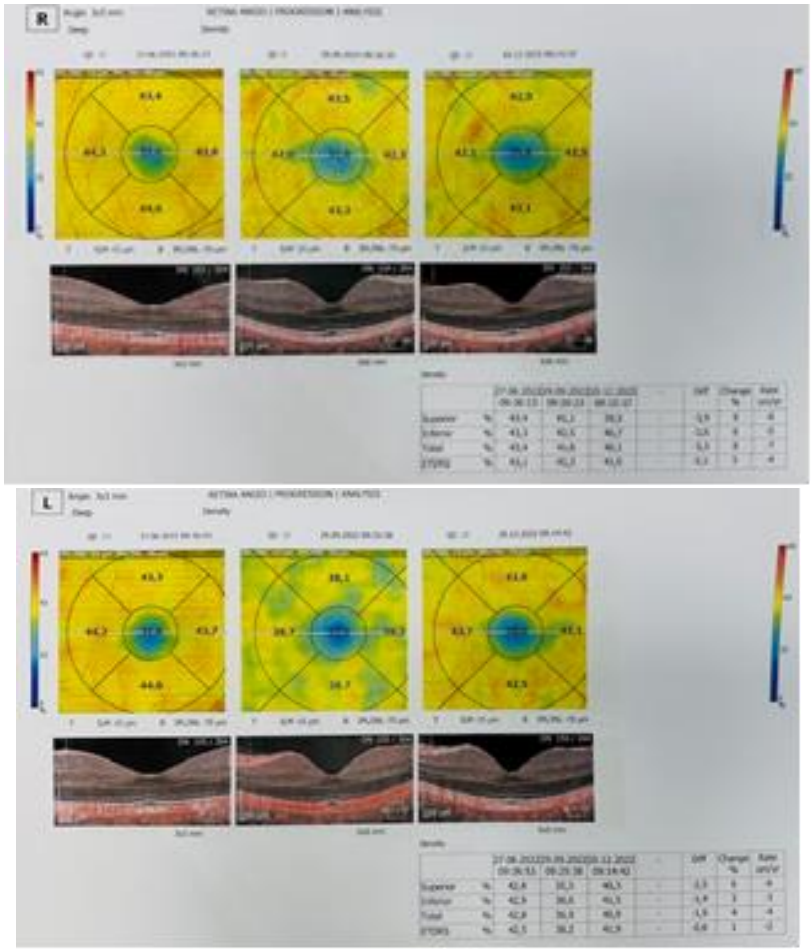


Fig. 2. Angiographic description of the change in blood vessel density in macula lutea in deep and superficial layers in the first six months of insulin treatment

Discusion

According to the literature, as many as 7% of all individuals with diabetes develop DME. Although the disruption of the blood-retinal barrier (BRB), which isolates the retina from the bloodstream, is an important feature of the DR, the basic physiological defect that causes changes in the vascular tissue of the retina is not yet known. Chronic hyperglycemia still remains the most common risk factor for DME[29,30]. Hyperglycemia leads to the accumulation of free radicals and end products of its metabolism (Age's). In addition, VEGF regulation, prostaglandins and other cytokines change the structure and function of BRB[31-33]. Other systemic risk factors include hypertension, nephropathy, anemia, sleep apnea and pregnancy. Good glucose regulation is better achieved by insulin therapy compared to oral hypoglycemic agents as reported in major tests. However, insulin use can also increase the risk of DR and DME in certain patients. Pollaki *et al.* reported that acute, intensive insulin treatment in diabetic rats causes BRB to decompose through increased VEGF expression. Henrikson *et al.* reported 100% increased risk of DME with insulin treatment compared to oral drugs in more than three hundred patients treated with insulin[34]. In addition, Zappa *et al.* found that people with type 2 diabetes, who received insulin therapy, had increased macula thickness compared to the control group that were on oral hypoglycemic treatment. Possible mechanisms of action include regulating VEFG expression and the vasoactive effects of the insulin itself and the rapid effect of glycemic control that further compromises the already damaged BRB[35,36]. In addition, a recent study found that insulin could disrupt the cell connection of the retinal pigment epithelium that regulates the external blood-retinal barrier.

Good glucose regulation is better achieved by insulin therapy compared to oral hypoglycemic agents as reported in major tests. On the other hand, the change in diabetes for oral hypoglycemic insulin therapy is associated with a paradoxical deterioration of diabetic retinopathy and deterioration of diabetic macular edema in the initial stage[37].

The deterioration of the DR in the initial period of initiation of insulin therapy in the literature is known as the so-called "early deterioration", a term related to the time frame of establishing a good glycemic control. This paradoxical deterioration phenomenon was first described in the 1980s and in patients with type 1 diabetes mellitus that were placed on continuous subcutaneous insulin therapy rather than conventional short/long-acting insulin treatment. The study reported that rapid and aggressive insulin treatment with Continuous Subcutaneous Insulin Infusion (CSII), is fast glycemic regulation is harmful to patients with pre-existing DR/DM. The most pronounced changes were observed during the period between 3 months and 3 years after therapy change[38].

However, the mechanism of this paradoxical association is not well understood. In the literature, there are several theories explaining this condition.

The osmotic force according to which the rapid drop in plasma glucose concentration with intense and aggressive glucose reduction reduces intravascular osmotic pressure. This creates an osmotic gradient between the extracellular and intravascular compartment in favor of interstitium. The fluid shifts from higher osmotic pressure (interstitium) into lower osmotic pressure in the blood vessels. This is more characteristic of small blood vessels of the retina, which are more sensitive to water retention[39,40].

The hypothesis for the synergistic default is based on the simultaneous effect of insulin and vascular endothelial growth factor (VEGF) of the retinal blood vessels. According to this, a high dose of exogenous insulin may act synergistically with VEGF expressed by ischemia of the retina that would cause vascular proliferation and deterioration of diabetic retinopathy. This is supported by evidence in basic sciences, epidemiological and interventional therapeutic studies on diabetes and could have important therapeutic implications[41].

Insulin is known as the anabolic hormone necessary for growth. Given that growth depends on blood supply, the role of insulin in growth implies the formation of new blood vessels by increasing the level of VEGF. This may explain deterioration of the degree of diabetic retinopathy and maculopathy by formation of new blood vessels (neovascular network) when insulin therapy is initiated, unlike with oral hypoglycemic agents. This hypothesis has potential therapeutic implications for the benefit of patients with diabetes. and regardless of vision[42,43].

Early deterioration of DR/DM, as a result of insulin treatment, suggests a mechanism of action associated with glycemia. However, other possible mechanisms to explain early deterioration in patients with diabetes should be taken into account[44].

The deterioration of DR/DM in the initial period of insulin treatment in type 2 diabetes mellitus may be due to a poor retinal circulation and, hence, reduced oxygen supply as a result of poor circulation. Thus, intensive insulin treatment leads to a rapid decrease in glycemia, which is the major source of energy of the retina. This can further lead to even greater hypoglycemia and increased VEGF expression as a compensatory mechanism[45-47].

Previous studies[53,54] showed a decrease in the density of retinal blood vessels in preclinical diabetic retinopathy. Some studies have also shown that damage to the retinal capillaries in early diabetic retinopathy does not form a fully prominent area without perfusion but is a reduced density of retinal blood vessels. Thus, OCTA is of great importance for monitoring the stage of diabetic retinopathy.

This study used OCTA to explore the effects of initial insulin therapy at various levels of retina in patients with type 2 diabetes. Quantitative monitoring was carried out to observe changes in vessel density in the macula area and macular parameters. To evaluate the degree

of damage to the retina blood vessels, it is necessary to detect changes in the microvascular structure before and after insulin treatment. We have also noticed that the reduction in DCP-VD is associated with thickening of the macula.

In our study, we found that initiation of insulin therapy caused a reduced blood vessel density in the macular area over the 6-month period of the change in oral insulin. therapy, Vessel density initially decreased during the first month, and significantly reduced by the third month. Three months after insulin treatment, SCP and DCP were significantly reduced and the differences were statistically significant. The results obtained showed that insulin therapy initially caused the most severe damage to the microcirculation system of the superficial and deep capillaries of the retina in the first three months of treatment, leading to ischemic changes [55]. The decrease in the density of the macular microvascular network was most pronounced in the first three months, and the causes and mechanisms need to be further studied.

Our findings revealed that the early stage of intense insulin therapy led to adverse effects on the macular microvascular structure, especially in the deep capillary plexus. One of the possible hypotheses for these ischemic changes in DCP is that DCP can be more sensitive to insulin treatment due to the relatively lower blood flow to the deep capillary plexus [56,57]. Histopathological studies have shown that diabetic micro-hemangiomas originate mainly from the deeper capillary network, which indirectly proves that deep tissue is more susceptible to hypoxia. The SCP has been shown with less hypoxic damage because it is directly linked to retinal arterioles, which have higher perfusion pressure and oxygen supply. These results are consistent with those of previous studies [58].

From the perspective of longitudinal research, we found that retina microcirculation was extensively affected after initial insulin treatment. It can be argued that rapid decrease in blood glucose levels results in a transient reduction in retina microcirculation. However, there are studies suggesting that the decrease in vessel density is not due to fluctuations in blood glucose levels. Previous studies have shown that an insulin-like growth factor (IGF-1) may affect the function of retinal angiogenesis, which plays a vital role in the appearance and development of DR[59,60].

Given the prevalence of people with diabetes and the growing trend, regular ophthalmic examinations play a key role in preventing the occurrence and progression of diabetic retinopathy, in correlation with good metabolic control, good cholesterol and triglyceride values. Even when ophthalmic examination shows normal findings, without changes in the eye, patients should maintain metabolic control, adhere to a healthy lifestyle, and undergo regular control examinations every 6-12 months. According to numerous clinical trials, a strict metabolic control remains a standard care for DR prevention, which in many cases is only achieved by intense insulin therapy. Good glucose regulation is better achieved by insulin therapy compared to oral hypoglycemic agents as reported in major tests. On the other hand, switching from oral hypoglycemic insulin therapy to insulin is associated with paradoxical deterioration. However, the mechanism of this paradoxical association is not fully clarified. In the literature, there are several theories explaining this condition. In terms of treatment with DME, intravitreal injections with anti-VEGF preparations have become a gold standard for reducing macular edema and improving visual acuity[61].

Conclusion

Although our study included a smaller number of participants, the results obtained correlate with those published in the literature, even though the mechanism of decreased density at the level of macular microvasculature is not yet fully understood. This research represents a pilot analysis of data from a subset of participants involved in a larger observational study aimed at evaluating the effects of rapid hypoglycemic effect of insulin, as well as the direct effect of insulin itself on changes in macular areas.

Conflict of interest statement. None declared

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