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Original article

MACULAR THICKNESS CHANGES EVALUATED BY OPTICAL COHERENCE TOMOGRAPHY IN CORRELATION WITH GLUCOSE AND HBA1C PARAMETERS AFTER SWITCHING DIABETES TREATMENT FROM ORAL HYPOGLYCEMICS TO INSULIN THERAPY IN PATIENTS WITH TYPE 2 DIABETES

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Abstract

Introduction: To assess the impact of insulin therapy in the initial period on central macular thickness evaluated by optical coherence tomography (OCT) in patients with type 2 diabetes.

Materials and methods: A prospective observational study including 12 patients (24 eyes) with type 2 diabetes with or without DME was conducted. Patients had been treated only with oral hypoglycemics before inclusion in the study, and all of them were prescribed additional insulin therapy at the time of enrollment in the study. The main outcome parameters were changes in visual acuity (BCVA) and changes in central subfield thickness (CST) measured by optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). Additional variables analyzed included 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 initiation of diabetes treatment with insulin.

Results: In all 12 subjects (24 eyes studied), no change in BCVA was observed. The laboratory parameters for glucose and HbA1c were analyzed, and at each follow-up showed a satisfactory reduction and stabilization of the results. From an anatomical point of view, CST showed minimal deterioration in 20 examined eyes - 209.3 μm to 240.21 μm ($p<0.001$). The mean HbA1c levels showed better results after insulin therapy.

Conclusion: This study suggests that in the initial phase of insulin therapy compared to oral antidiabetic agents, no decrease in visual acuity was observed, but changes in the anatomical structure of the macular region and macular volume occurred.

Keywords: type 2 diabetes, diabetic retinopathy, diabetic maculopathy, oral hypoglycemics, insulin

Introduction

Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the most common and most significant chronic complications of diabetes mellitus. DME is an important cause of severe vision loss in patients with type 2 diabetes. Diabetic macular edema (DME) is manifested as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers[1]. It is believed to be the result of hyperpermeability of the retinal vascular network. DME can be present at any level of diabetic retinopathy Diabetic

retinopathy is a chronic, microvascular complication of diabetes mellitus. It results from a set of metabolic, endocrine and hemodynamic factors with mutual interaction, where basically, the key factor is the high concentration of blood glucose which initiates the other processes, such as disruption of the blood-ocular barrier, and changes in retinal microcirculation. Hyperpermeability of the retinal blood vessels and the subsequent formation of edema and hard exudates are the key clinical features. In general, diabetic retinopathy is classified into stages: non-proliferative diabetic retinopathy, with or without diabetic maculopathy affecting the macular region (yellow spot), and proliferative diabetic retinopathy.

Main risk factors for the occurrence of diabetic retinopathy are: hyperglycemia, hypertension, duration of diabetes, obesity, smoking, pregnancy and cataract surgery[2].

Diabetic retinopathy usually does not give specific symptoms until the advanced stage of the disease occurs. It is often discovered only after a complete vision loss has already occurred. In general, patients subjectively complain of blurring in the eyes (result of changes in the vitreous body), loss of part of the visual field (result of hemorrhage), weakening of central vision as a result of changes in the macula (diabetic maculopathy), or complete loss of vision as a result of massive hemorrhage in the vitreous body or retinal detachment[3,4]. Nowadays, modern medicine offers a large number of diagnostic tools for controlling and monitoring the condition of the posterior segment of the eye. Determination of the best-corrected visual acuity (BCVA) and examination of the posterior segment of the eye with a wide pupil are the basic diagnostic methods that should be performed in each patient. Additional diagnostic tools for a more detailed examination of eye and vision condition include ultrasonography, optical coherence tomography with/without angiography (OCT/OCTA), and fundus fluorescein angiography (FFA). Optical coherence tomography (OCT) is a modern non-contact non-invasive diagnostic method in ophthalmology, which is based on layered laser imaging of the retina and optic nerve, which allows viewing cross-sections of the internal eye structures. Due to its performance and unlimited number of repetitions, the method is a significant aid not only in the diagnosis of diseases of the retina and optic nerve, but also in monitoring pathological changes in the macula. According to numerous clinical trials, strict metabolic control still remains the standard of care for the prevention of DR, which in many cases is achieved only with intensive insulin therapy. Good glucose control is better achieved with insulin therapy compared to oral hypoglycemic agents as reported in large trials. On the other hand, switching from oral hypoglycemic agents to insulin therapy in the treatment of diabetes is associated with a paradoxical worsening of diabetic retinopathy and worsening of diabetic macular edema in the initial phase. However, the mechanism of this paradoxical association is not well understood. In the literature, there are several theories explaining this condition[5].

Regarding the treatment of DME, intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) with or without laser photocoagulation have become the gold standard for reducing macular edema and improving visual acuity.

Materials and methods

A prospective observational study involving 12 patients (24 eyes) with type 2 diabetes with or without DME was conducted. The study was realized at the Eye Department of the City General Hospital “8th September” - Skopje. Patients had been treated only with oral hypoglycemic agents prior to their enrollment in the study, and all of them were prescribed additional insulin therapy at the time of inclusion in the study. This study was approved by the Ethics Committee for Research on Humans, at the Faculty of Medicine - Skopje, at its XVIII session held on 13.06.2023, no. 03-2633/7, and all participants signed informed consent to be part of this study.

Inclusion criteria:

- Age over 50 years
- Gender - male and female
- Diabetes mellitus type 2
- Duration of diabetes over 5 years
- Change of diabetes control therapy from oral hypoglycemics to standard insulin treatment in the initial period of the study

Exclusion criteria:

- Age-related macular degeneration (dry and wet form)
- Macular dystrophies
- Patients with previously applied anti-VEGF therapy
- Patients with previous laser photocoagulation (LPK)
- Patients with retinal vein occlusions
- Patients with central serous choroidopathy.

The main outcome measures were changes in visual acuity (BCVA) and changes in central subfield thickness (CST) measured by optical coherence tomography (OCT) and optical coherence tomography with 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 diabetes treatment with insulin.

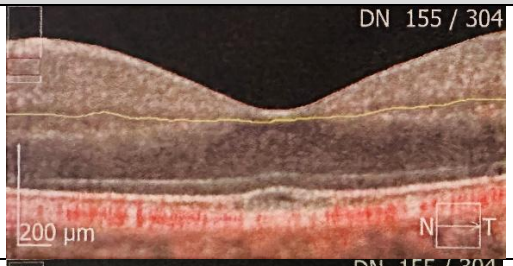
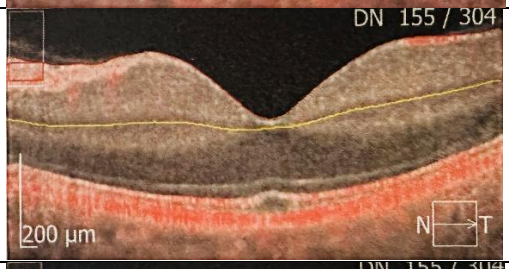
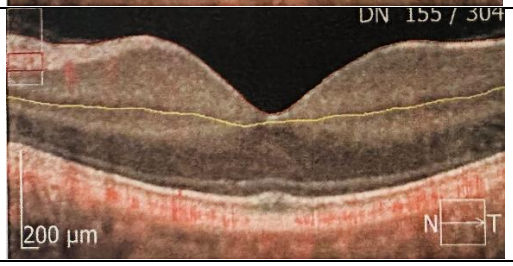
Statistical analysis of data was performed using the SPSS Windows software. For the series of numerical characteristics for BCVA, the values of laboratory parameters for Glu, HbA1c, LDL, Tg, as well as macular thickness (SD-CST), descriptive statistics was used. The analysis of OCT parameters was conducted 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. The data are presented in tables and figures.

Results

All 12 subjects (24 eyes examined) had no change in BCVA. Laboratory parameters for glucose and HbA1c were analyzed at each follow-up, and they showed satisfactory reduction and stabilization of the results. In the first 6 months after initiation of insulin therapy, glucose levels decreased from 7.64 mmol/L to 7.44 mmol/L and 6.91 mmol/L, in the first, third and sixth months, respectively. The average glucose level was around 7.33 mmol/L. Also, the HbA1c level gave positive results, with average ranging from 8.9%, to 7.98%, or 7% in the first, third, and sixth month, respectively (Table 1). The average HbA1c levels showed better results after starting insulin therapy (7.96%).

Our field of interest was the effect of a rapid decline in glycemic levels on parameters in the macular area examined with OCT (optical coherence tomography). From an anatomical point of view, CST showed minimal deterioration in 20 examined eyes - 209.3 μm to 240.21 μm or 253.4 μm ($p<0.001$), in the follow-up period of 6 months[6,7].

Table 1. Correlation between macular central subfield thickness (measured by OCT) and laboratory parameters for HbA1c in mild/moderate NPDR when switching type 2 diabetes treatment from oral hypoglycemics to insulin.

	OCT image	Central subfield thickness (CST) µm	HbA1c(%)
1st month		209.3µm	8.9%
3rd month		240.21µm	7.98%
6th month		253.4 µm	7%

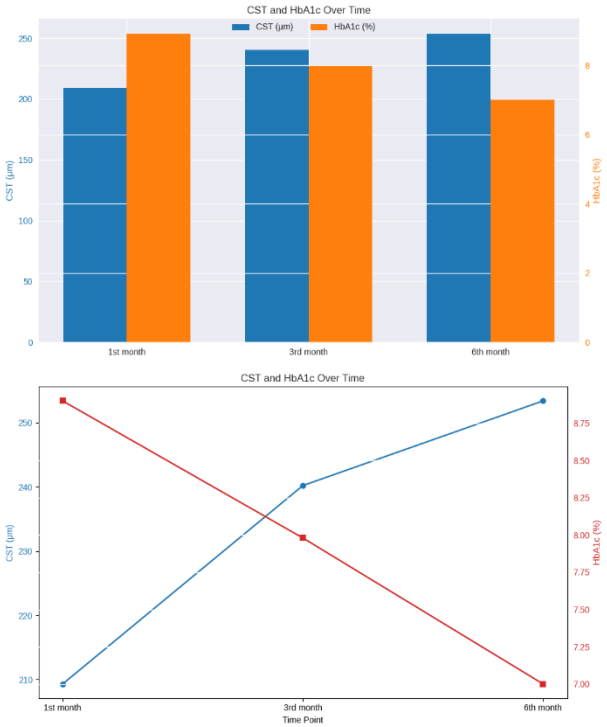


Fig. 1. Correlation between macular central subfield thickness (measured by OCT) and laboratory parameters for HbA1c

Discussion

As reported in the literature, up to 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 underlying physiological defect that causes leakage of retinal vascular tissue is still unknown. Chronic hyperglycemia remains the most well-known risk factor for DME[8]. Hyperglycemia leads to the accumulation of free radicals and advanced angiogenic end products (AGEs). In addition, upregulation of VEGF, prostaglandins, and other cytokines alter the structure and function of the BRB. Other systemic risk factors include hypertension, nephropathy, anemia, sleep apnea, and pregnancy. Good glucose regulation is better achieved with insulin therapy compared to oral hypoglycemic agents as reported in large trials. However, insulin use may also increase the risk of DR and DME in certain patients. Poulaki *et al.,* reported that acute, intensive insulin treatment in diabetic rats causes BRB to decompose through increased VEGF expression. Henrikson *et al.* reported a 100% increased risk of DME with insulin treatment compared to oral drugs in more than three hundred patients treated with insulin. In addition, Zapata *et al*., found that people with type 2 diabetes, who received insulin therapy, had increased macular thickness compared to the control group that were on oral hypoglycemic treatment. Possible mechanisms of action include regulation of VEFG expression and the vasoactive effects of insulin itself and the rapid effect of glycemic control that further compromises the already damaged BRB. In addition, a recent study has shown that insulin could disrupt the tight junctions in the retinal pigment epithelial cells that regulate the external blood-retinal barrier[8,9].

Good glucose regulation is better achieved with insulin therapy compared to oral hypoglycemic agents as reported in large trials. Insulin as an anabolic hormone undoubtedly gives excellent results in the regulation of serum glucose levels, with an extremely fast response. On the other hand, changing diabetes treatment from oral hypoglycemic agents to insulin therapy is associated with a paradoxical deterioration of diabetic retinopathy and deterioration of diabetic macular edema in the initial phase. However, the mechanism of this paradoxical association is not well understood. In the literature, there are several theories explaining this condition[10,11].

One of them is the so-called osmotic force theory, according to which the rapid fall in plasma glucose concentration with intensive and aggressive glucose-lowering agents reduces intravascular osmotic pressure. This creates an osmotic gradient between the extracellular and intravascular compartments in favor of the interstitium. The water shifts from higher osmotic pressure (interstitium) into lower osmotic pressure in the blood vessels. This is more characteristic of the small retinal blood vessels, which are more sensitive to water retention[12,13].

The synergistic effect hypothesis is based on the simultaneous action of insulin and vascular endothelial growth factor (VEGF) on retinal blood vessels. According to this, high doses of exogenous insulin may act synergistically with VEGF expressed by retinal ischemia to cause vascular proliferation and deterioration of diabetic retinopathy. This is based on evidence from basic science, epidemiological and interventional studies in diabetes and could have important therapeutic implications[14,15].

Insulin is known as the anabolic hormone essential 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 VEGF levels. This may explain deterioration of the degree of diabetic retinopathy and maculopathy by formation of new blood vessels (neovascular network) during the initiation of treatment with insulin, unlike with oral hypoglycemic agents. This hypothesis has potential therapeutic implications for the benefit of patients with diabetes and regardless of their visual status[16,17].

Regarding the treatment of DME, intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) with or without laser photocoagulation have become the gold

standard for reducing macular edema. Considering the prevalence of people with diabetes and the growing trend, regular ophthalmological examinations play a key role in preventing the onset and progression of diabetic retinopathy, combined with good metabolic control, normal cholesterol and triglyceride levels, stable arterial blood pressure and smoking cessation.[18] Even when ophthalmological examination shows normal findings, without changes in the fundus, patients should continue maintain metabolic control, adhere to a healthy lifestyle, and undergo regular control examinations every 6-12 months. One of the goals of our study was to emphasize the benefits of introducing a protocol for examination of the posterior segment of the eye in all patients whose diabetes treatment was changed from oral hypoglycemics to insulin therapy. Timely diagnosis and therapeutic treatment can prevent vision loss in most cases and, above all, lead to stabilization of macular edema and improvement in visual acuity [19-21].

Conclusion

Although our study included a smaller number of subjects, the results obtained are in line with those in the literature, and suggest that in the initial phase of insulin therapy compared to oral antidiabetic agents, no decrease in visual acuity was observed, but changes in the anatomical structure of the macular region and macular volume occurred. This research is a pilot study that analyzed data from subjects included in a larger observational study. The aim was to evaluate the effects of the rapid hypoglycemic action of insulin, as well as the direct effect of insulin itself on changes in the macular area in patients with type 2 diabetes, in the first 6 months after the initiation of insulin treatment.

Conflict of interest statement. None declared.

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