·Clinical Research·

Correlation of leaking microaneurysms with retinal thickening in diabetic retinopathy

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Abstract

• AIM: To investigate the contribution of fluorescein angiographic leaking microaneurysms (leak-MA) versus non-leaking microaneurysms (non-leak-MA) to retinal thickening in diabetic retinopathy.

• METHODS: A consecutive series of 38 eyes from 24 patients with diabetic retinopathy was included. Leak-MA and non-leak-MA in each eye were selected in pairs at corresponding topographic location. Leaking was defined by late phase fluorescein angiograms compared to early phase. Retinal thickness was measured with Heidelberg Spectralis OCT topographically aligned on early phase angiograms at the MA site and within a 1 mm circle.

• RESULTS: In all eyes, significant retinal thickening at the site of leaking compared to non-leaking microaneurysms was observed (356± 69μm *vs*318± 56μm, $P<0.001$), showing a mean increase in thickness in the areas of leak-MA *vs* non-leak-MA of 38 ± 39μm (95% confidence interval 25-51μm, $P<0.001$). All 1mm area measurements also showed significant ($P<0.001$) thickening of the leak-MA with average thickness of leak-MA *vs*non-leak-MA as 351± 67μm *vs* 319± 59μm; minimum thickness 311 ± 62μm *vs* 284 ± 60μm; maximum thickness 389± 78μm *vs* 352± 66μm; and retina volume 26.4± 6.0mm *vs* 23.6± 3.7mm^3, respectively.

• CONCLUSION: Leaking of microaneurysms on fluorescein angiography appears to cause focal thickening of retina, which can be measured with high-resolution OCT. Therefore, targeting leaking microaneursyms in diabetic retinopathy has the potential to reduce retinal thickening.

• KEYWORDS: diabetic retinopathy; microaneurysm; retinal thickness; OCT

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INTRODUCTION

Diabetic retinopathy is a leading cause of blindness in working population of industrialized countries [1]. Diabetic macular edema (DME) is a common complication of diabetic retinopathy and is known to be the most frequent cause for visual impairment. The pathophysiology of DME has not been completely understood yet. Biochemical changes, such as increased activity of protein kinase C, oxidative stress, accumulation of intracellular sorbitol and advanced glycosylation end products are supposed to cause a breakdown of the blood-retinal barrier, extravasation of fluids and plasma constituents and, subsequently, increase of retinal thickness and DME [2-4]. Several studies have documented consistent correlations among the findings of optical coherence tomography (OCT) and fluorescein angiography (FA) patterns, improving the understanding about pathophysiology and development of DME [2,5,6]. Microaneurysms (MA) as an early manifestation of diabetic retinopathy originate mainly but not exclusively from the retinal venous capillaries, are more numerous in the central retina, are localized predominantly in the inner nuclear layer and, therefore, in the deeper part of the inner retinal capillary plexus. OCT-diagnosed hyper-reflective foci are located within the walls of intraretinal MAs and seem to be correspondent to extravasated lipoproteins, representing a very early sign of subclinical barrier breakdown in DME [7]. Previously, we were able to demonstrate a moderate correlation between OCT retinal thickness and FA leakage in peripheral ETDRS fields in patients with diabetic retinopathy [6]. The aims of this study were to verify the correlation between focal retinal thickness and leaking MA (leak-MA) and, thus, to possibly identify leak-MA as source of focal retinal thickening in diabetic patients. Using the HRA-OCT (Heidelberg Engineering), which is the combination of fluorescein angiography and non invasive Spectral-Domain (SD) OCT-technology, we were able to

identify leaking and non-leaking microaneurysms (non-leak-MA) in patients with diabetic retinopathy and measure the exact retinal thickness at these vascular anomalies and the surrounding areas.

MATERIALS AND METHODS

Subjects A total of 38 eyes from 24 consecutive patients, mean patient age 64 years, ranged 32-77 years old, undergoing fluorescein angiography and Spectral-Domain OCT (HRA-OCT, Heidelberg engineering) at the same day for the evaluation of diabetic retinopathy at the Department of Ophthalmology, Ludwig-Maximilians-University, Munich were included in this study. All had known diabetes mellitus for at least 2 years, with the majority of patients (n=20) having non-proliferative diabetic retinopathy. Inclusion criteria were diagnosed diabetes and a mild to severe non-proliferative or proliferative diabetic retinopathy. Exclusion criteria were previous laser treatment in the scanned and analyzed field, degenerative disorders of the posterior pole and significant media opacities. In all patients, a full ophthalmological examination was performed and both fluorescein angiography and SD-OCT were carried out after informed consent. All research was conducted in accordance with institutional guidelines and board approval and conformed to the tenets of the World Medical Association Declaration of Helsinki.

Methods A commercially available Heidelberg Retina Angiograph-Optical Coherence Tomography (HRA-OCT) (Heidelberg engineering) was used for fluorescein angiography and Spectral-Domain optical coherence tomography (SD-OCT) examination. Wavelength of HRA and SD-OCT were 488nm and 870nm. Optical resolution was approximately 3.8μm axial and 6μm lateral (high resolution mode). Acquisition speed for OCT was approximately 40 000 A-scans per second, scan depth was 1.9mm. During fluorescein angiography for each eye, early- and middle-phase frames were obtained to determine the location of MA. The late-phase angiograms were employed to define leak-MA and non-leak-MA. A leak-MA was defined as a hyperfluorescent spot seen in the early phase of FA showing evident leakage in the late phases of the exam. MA showing no leakage in late-phase frames was defined as non-leak-MA. A matched pair of a leak-MA and non-leak-MA in each eye was chosen, both to be within major temporal retinal blood vessels and in corresponding topographic location, i.e. mirrored around a horizontal axis through the optic nerve. Hyperfluorescent scars due to laser photocoagulation close to selected MA or any other degenerative disorders of the posterior pole represented exclusion criteria.

A SD-OCT volume scan of the macula was performed for each eye to obtain measurements the retinal thickness in μm at each chosen leak-MA and non-leak-MA and the average, minimal and maximal retinal thickness in μm and the volume in mm^3 within 1 mm of each chosen MA.

Statistical Analysis Data were collected and analyzed using SPSS version 17.0. P <0.05 was considered as statistically significant. Univariate analyses were applied; paired testing and nonparametrical methods were chosen where appropriate.

RESULTS

Each studied eye showed leak-MA and corresponding non-leak-MA in fluorescein angiography. SD-OCT measurements of volume scans including these identified MA revealed a mean retinal thickness of 356 ±69μm at leaking and 318 ±56μm at non-leak-MA (P<0.001). The mean retinal thickening was 38 ±39μm with a 95% confidence interval from 25 to 51μm at the site of a leak-MA compared to non-leak-MA.

There was a significantly higher average retinal thickness around (<1 000μm) leaking compared to non-leaking MA (351±67μm *vs*319±59μm, P<0.001). Minimal and maximal retinal thicknes(minimal thickness: 311± 62μm *vs*284± 60 μm, P<0.001; maximal thickness: 389±78μm *vs*352±66μm, P< 0.001) and retinal volume (26.5±6.0mm^3 *vs*23.6±3.7mm^3, P< 0.001) around leak-MA were significantly increased.

Mean added retinal thickening around (<1000μm) leak-MA was 28 ±31μm (95% confidence interval 18 to 38μm) relating to minimal retinal thickness, 38 ±43μm (95% confidence interval 24 to 28μm) relating to maximal retinal thickness and 32 ±32μm (95% confidence interval 21 to 42μm) relating to average retinal thickness. The increase in retinal volume around leak-MA was 2.9 ±5.2mm^3 (95% confidence interval 1.2 to 4.6mm^3). Mean relative retinal thickening leak-MA/non-leak-MA is 112% measured at the site of the microaneurysm. Around (<1000μm) the microaneurysm, mean retinal thickening leak-MA/non-leak-MA is 110% regarding average retinal thickness, 110% regarding minimal retinal thickness and 111% regarding maximal retinal thickness. The mean relative increase of volume leak-MA/non-leak-MA was 112%.

DISCUSSION

In this study we were able to demonstrate a significant correlation between leak-MA seen in fluorescein angiography and retinal thickening measured with SD-OCT in diabetic patients. Retinal thickness and retinal volume at the site of and around the leak-MA were significantly higher than at and around non-leak-MA. These findings are in agreement with those of previous studies which showed an overall correlation of leakage with retinal thickness in eyes with diabetic retinopathy [2,8], whereas only few previously

published scientific articles have indicated a possible moderate topographic correlation between leakage and retinal thickening of peripheral macular ETDRS fields [6]. Microaneurysms as an early manifestation of diabetic retinopathy are localized predominantly in the inner nuclear layer and therefore in the deeper part of the inner retinal capillary plexus. Leaking microaneurysms result in an impaired inner blood-retina barrier and are thought to be a source for the extravasation of small molecules and therefore are one of the major factors causing retinal thickening and focal or diffuse macular edema respectively [9]. A correlation between leaking microaneurysms and localized thickening of the outer nuclear layer has been documented[10,11]. The spatial density of leaking microaneurysms seem to correlate with a variation in glycemic metabolic control even though the number of detected microaneurysms does not seem to correlate directly with glycosylated hemoglobin A(1c) levels or global retinal thickening [12]. On the other hand Sachdev *et al* [13]were able to demonstrate that a decrease in retinal thickness after focal or grid laser photocoagulation is highly correlated with the decrease in the number of leaking microaneurysms, though that observation was seen not till twelve weeks post treatment.

Limitations of our study include defining leaking microaneurysms as microaneurysms with clear leakage seen in fluorescein angiography-which was not further quantified by the amount of detectable leakage. In addition, we cannot rule out minimal leakage in microaneurysms classified as non-leaking in a thicker and therefore less transmissive retina. Despite careful manual realignment of scans and built-in tracking system of the used OCT/FA system, we also cannot rule out a minimal degree of misalignment between imaging modalities. Finally, edema of surrounding retina could alter the measurements of retinal thickness in the examined area-to minimize this possibility, we chose matching pairs of microaneurysms not located in edematous retina. In summary, we were able to show a significant correlation between leaking microaneurysms and corresponding focal retinal thickening in eyes with diabetic retinopathy.

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