Contribution of optical coherence tomography angiography OCT-A in diabetic maculopathy

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ABSTRACT

Introduction: Diabetic retinopathy (DR) increases the risk of blindness by 25 times. Advanced researchs are justified for better management, leading to the role of Optical Coherence Tomography-Angiography (OCT-A), a new non-invasive imaging technique exploring retinal vascularization. Our purpose is to identify microvascular macular anomalies of DR on OCT-A with qualitative and quantitative evaluation of their impact on retinal vascularization.

Patients and methods: This is a descriptive cross-sectional study where 120 eyes of 66 diabetic patients were enrolled. All patients were diabetic and went through OCT-A imaging.

Results: Microanevrms were identified in both superficial capillary plexus (SCP) and deep capillary plexus (DCP) where they were more frequently visualized. Macular edema was present in 16.7% of cases in the SCP, and in 30% in DCP. Edema spaces were more frequently present in DCP (p < 0.05). Capillary nonperfusion areas were identified in 82.5% of cases in SCP and in 60% of cases in DCP. The main peri-foveal vascular density was 18,95 ± 5,37%. The main surface of foveal avascular zone (FAZ) in the SCP was 462,52 μm² and was 555,04 ± 329,11 μm² in the DCP where it was larger.

Conclusion: OCT-A is a modern imaging tool that could be used for the diagnosis and monitoring of DR as well as the understanding of its pathophysiology.
superficial plexus (6 × 6 mm images) and the calculation of the FAZ surface (on the 3 × 3 mm images) in the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) (by manual tracing).

Quantitative variables were expressed as averages ± standard deviation by specifying minimum and maximum values or medians. Qualitative variables were expressed by number and percentage. The VA was expressed in decimal VA and log MAR. In all statistical tests, the significance level was set at \( p = 0.05 \) between two groups being compared. The degree of correlation between two quantitative variables was assessed by the Pearson correlation coefficient \( r \). If \( | r | < 0.3 \) the correlation was considered low, and if \( | r | ≥ 0.5 \), the correlation was good. And in case of invalidity, the correlation coefficient of the Spearman ranks was determined. SPSS v23 was used for data analysis.

3. Results

120 eyes of 67 diabetic patients (44.8% female) were included in our study. The average age was 58.19 years (±9.46 years). The average duration of diabetes was 9.45 years.

The mean VA by far was 4.6/10 ± 0.27/10 (corresponding to log MAR ± 0.48), it varied from 0.05/10 to 10/10 (+2.3 to 0 log MAR) and was greater than 5/10 in 50.83% of eyes.

In structural OCT, the mean central macular thickness (CMT) was 288.29 ± 84.65 \( \mu \)m with extremes ranging from 187 to 547 \( \mu \)m.

We were able to visualize the basic lesions of DR with OCT-A, in both superficial and deep plexus. The results of these observations are noted in Table 1.

There were a total of 42 new vessels (NV) in SCP and 22 in DCP. Five NVs in DCP were also visible in the superficial plexus, and 17 were identifiable in the deep network only (Fig. 1).

In the group of patients with diabetic macular edema (DME) in OCT-A (Fig. 2), the mean number of microaneurysms (SCP = 6.72 ± 7.94 and DCP = 10.06 ± 8.37) was higher than in those with DR without edema (SCP = 3.69 ± 3.84 and DCP = 3.93 ± 5.11), especially in the DCP, with a statistically significant difference between the two groups in both plexuses (\( p = 0.013 \) in SCP and 0.001 in the DCP).

Among the eyes with edema spaces in the SCP, 19 eyes were associated with non perfusion area (95%), and for those with DME in the DCP, 35 eyes were associated with non perfusion area (97.22%).

On the other hand, the alteration of the normal vortex architecture of DCP was noted in 50 eyes (41.7%). In the patients with edema spaces in the DCP, 29 eyes (58%) had an altered vortex structure. The preservation of this structure was negatively correlated with the presence of edema with a significant difference (\( p < 0.05; r = -0.51 \)).

The FAZ was studied in the SCP in 113 eyes (94.17%). It was ruptured in 51 eyes (42.5%). The study was not possible for 7 eyes (5.83%) among which were noted: 4 cases of cystoid spaces. In the DCP: The FAZ was identifiable in 93 eyes (77.5%); of the remaining 27 eyes, 21 had central cystoid spaces (77%), the rest were the site of artifacts or significant architectural disorganization. The results of the FAZ measurement are detailed in Table 2.

In the group of patients with DME at OCT-A, the FAZ was wider compared to the DR group without edema in both the SCP (FAZ = 472.872 (edema group) vs. 399.779 \( \mu \)m² (no edema group)) and the DCP (571.262 (edema group) vs. 551.844 \( \mu \)m² (no edema group)) without a statistically significant difference (\( P = 0.24 \) in SCP and 0.8 in DCP). The FAZ in DCP was larger.

The VA was studied at the level of the superficial plexus. The measurements of the different VD territories are detailed in Table 2. In the group of patients with DME at the OCT-A, the perifoveolar VD of the SCP was lower (18 ± 4.69) than in the group with DR without edema (21.18 ± 6.22) with a statistically significant difference (\( P = 0.003 \)).

Concerning the clinical data, we found a correlation between the presence of OCT-A edema spaces in the SCP and the DCP with VA (\( p < 0.05 \)). The number of new vessels in SCP and DCP in our series was also correlated with lower VA (\( p = 0.04; r = -0.26 \) in both plexuses). On the other hand, the perifoveolar VD of SCP had a moderately positive correlation with VA (\( p = 0.009; r = 0.23 \)) and a moderately negative correlation with log MAR VA (\( p = 0.001; r = -0.31 \)). VA was also correlated with FAZ rupture (\( p = 0.001 \)), it was lower in patients with a larger FAZ in SCP and DCP (\( p = 0.014 \) and 0.001 respectively and \( r < 0 \) for both).

And about the relationship between the DR stage and the anomalies found at OCT-A, the results are detailed in Table 3. Microvascular abnormalities were significantly correlated with DR stage in both SCP and DCP.

### 3.1. MA: microaneurysm

The therapeutic modalities of DR and DME had not influenced the qualitative and quantitative data of OCT-A in either the SCP or DCP.

On the other hand, it was noted that ellipsoid rupture as well as alteration of the external retina in structural OCT was correlated with the presence of areas of vascular non-perfusion in DCP in OCT-A (\( p = 0.043 \) for both; \( r \) respectively = 0.186 and 0.185). Furthermore, among the microvascular lesions in DR, CMT was significantly correlated with the presence of microaneurysms in DCP (\( p = 0.023; r = 0.21 \)), but not in the superficial one (\( p = 0.6 \)). In addition, in our series the mean CMT in patients with altered DCP architecture (388 ± 138.59 \( \mu \)m) was higher than in those with DR without edema (357 ± 80.8 \( \mu \)m) with a statistically significant difference (\( P = 0.009 \)).

### Table 1

| SCP | Total number of lesions in all eyes (N) | Number of eyes (N) | Percent of eye (%) |
|-----|----------------------------------------|--------------------|--------------------|
| Microaneurysms | 538 | 90 | 75 |
| Superficial | 11 | 9,17 |
| Inferior | 2 | 1,67 |
| Nasal | 6 | 5 |
| Temporal | 3 | 2,5 |
| Supero-temporal | 2 | 1,67 |
| Infero-nasal | 1 | 0,83 |
| Supero-nasal | 1 | 0,83 |
| Infero-temporal | 3 | 2,5 |
| Perifoveolar | 19 | 15,83 |
| Edema spaces | 20 | 16,7 |
| Central edema | 8 | 6,67 |
| IRMA | 58 | 32 | 26,66 |
| New vessel | 42 | 20 | 16,7 |
| Non perfusion area | 99 | 82,5 |

| DCP | Total number of lesions in all eyes (N) | Number of eyes (N) | Percent of eye (%) |
|-----|----------------------------------------|--------------------|--------------------|
| | 754 | 95 | 79,16 |
| | | | 0.004 |

### P

- \( P = 0.004 \)
- \( < 0.05 \)
- \( < 0.005 \)

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A. Mahjoub et al.  
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than those with preserved architecture (287.34 ± 83.35 μm) with a statistically significant difference (p < 0.05). The FAZ study was more difficult for patients with a higher CMT, for whom the mean CMT was 381.7 ± 113.93 μm significantly higher than for patients with a studyable FAZ (259.65 ± 47.28 μm p < 0.05). CMT was also correlated with the rupture of the FAZ (p = 0.002). VD was, however, negatively correlated with CMT (p < 0.05, r = -0.38).
Anomaly of SCP and DCP depending on the stage of DR.

Table 3

| Anomaly of SCP and DCP depending on the stage of DR. | mild | Moderate | Severe | PDR |
|-----------------------------------------------------|------|----------|--------|-----|
| SCP in (n=17)                                       |      |          |        |     |
| FAZ in SCP (μm2)                                    | 462.52 ± 232.18 | <0,001 |         |     |
| (N=113)                                             | (128.82-1686.1)  |         |         |     |
| FAZ in DCP (μm2)                                    | 555.04 ± 329.11 |         |         |     |
| (N=91)                                              | (149.25-2404.67) |         |         |     |
| perifoveolar VD (mm -1)                             | 18.95 ± 5.37    |         |         |     |
| (N=118)                                             | (13.35-38.71)    |         |         |     |
| superior VD (mm -1)                                 | 43.7 ± 11.1     |         |         |     |
| (N=118)                                             | (10.52-29.29)    |         |         |     |
| inferior VD (mm -1)                                 | 42.96 ± 5.46    |         |         |     |
| (N=118)                                             | (13.98-37.35)    |         |         |     |
| nasal VD (mm -1)                                    | 42.43 ± 3.86    |         |         |     |
| (N=117)                                             | (31.16-51.54)    |         |         |     |
| temporal VD (mm -1)                                 | 43.67 ± 3.71    |         |         |     |
| (N=118)                                             | (35.62-53.04)    |         |         |     |

4. Discussion

4.1. Elementary lesions of DR

Microaneurysm, an early sign of DR, is a lesion that appears in OCT-A as a generally rounded, saccular signal [4-6]. According to our results, OCT-A has the advantage of locating these lesions at their exact intraretinal depths: microaneurysms were visible in both SCP and DCP. They were significantly more numerous in the latter (p = 0.004), in accordance with the literature [7-9]; this suggests that microaneurysms develop mainly in the deep capillary network, as already shown in histology [10]. Furthermore, we have noted that most microaneurysms are located at the edge of a non-perfused capillary zone as reported by the work of Ishibazawa, Peres and Hasegawa [7,9,11] and are therefore indirect signs of retinal ischemia. It was also described that these lesions sometimes surround the FAZ [7,12,13]. In our series, microaneurysms were predominant in the perifoveolar region in the majority of cases.

4.2. Visualization and quantification of macular ischemia

4.2.1. Areas of retinal non-perfusion

OCT-A finds a modification of both capillary networks. At the SCP level, DR causes a capillary depletion with non-perfusion zones, which can be visualized very well at the OCT-A level [17]. In DCP, these areas are less well delimited, and the DR induces an alteration of the normal capillary vortices [18].

In our series, in SCP, zones of vascular non-perfusion were identified in 99 eyes (82.5%). In DCP, they were present in 72 eyes (60%). The non-perfusion areas were mostly bordered by microvascular lesions according to the literature [7,9,11,15]. In Courtier’s series, these territories were present in all eyes in OCT-A inSCP; in DCP, they were present in only about 35% (7/20) of cases [8] with capillary vortex alteration in all eyes. The reason for such a discrepancy in the presentation of non-perfusion between SCP and DCP is not yet well explained.

IRMAs are complex, highly decorelated vascular structures that are visible near non-perfused areas. In our series, IRMAs were noted in both SCP and DCP, they were significantly predominant in SCP (53 in SCP vs 26 in DCP). Similar results were found by Ishibazawa and al [7] but Lupidi and al [14] found a predominance of IRMAs in DCP. Pan reported that IRMAs would have venous origin and drainage, and develop from the internal plexiform layer (boundary between SCP and DCP), the layer of ganglion cells, or optical fiber (SCP), which shows that these lesions can be identified in both plexuses. Perretinal new vessels are visible in OCT-A as hyper-reflective, high-flux lesions, with complex and disorganised architecture and variable calibre [15]. Pan had thus established a classification [16] in which the starting layer of NV type 1 was the most superficial, type 2 was the deepest, and type 3 was the intermediate. This distribution consolidates our results, and shows that NVs are visible in both plexuses, and that some can be identified in both at the same time.

Table 2

Quantitative anomalies in OCT A.

| Results | P |
|---------|---|
| FAZ in SCP (μm2) | 462.52 ± 232.18 | <0,001 |
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| (N=117)                                             | (31.16-51.54)    |         |         |     |
| temporal VD (mm -1)                                 | 43.67 ± 3.71    |         |         |     |
| (N=118)                                             | (35.62-53.04)    |         |         |     |
even histologically [7]. According to Bonnin, a disorganization of the deepplexus is systematic, and the normal vortex architecture is no longer respected [17], the vortices are hardly visible, and increasingly absent as the DR progresses. In our series, the normal vortex architecture was altered for 50 eyes (41.7%), with a strong negative correlation with the stage of DR (p < 0.05, r = −0.62) (Table 3).

Several studies on DR based on OCT-A suggest that DCP was affected more severely than SCP [7,8,12,19–21,27,36,45]. A correlation was found between the vascular changes observed in OCT-A, photoreceptor interruption and the severity of DR [22,23]. In our series, the presence of areas of vascular non-perfusion at DCP levels in OCT-A was correlated with ellipsoid rupture (p = 0.043; r = 0.186) and alteration of the external retina (p = 0.043; r = 0.185) in structural OCT. This would reflect the association of these anatomical lesions with capillary non-perfusion of the deep retina in ischemic maculopathy.

4.2. Vascular density (VD)

In our series, the VD was studied at the level of the SCP (Table 2). It was decreased in all territories in agreement with Agemy’s results [25]. In the literature, VD values were negatively correlated with the severity of diabetes [26–28] as well as in our series (p = 0.036) (Table 3). On the other hand, the results diverge regarding to the relationship between VD and VA. In Hwang’s series [30], no correlation was found between perifoveal and parafoveal VD and VA. On the other hand, in a larger study by Samara [29], a statistically significant negative correlation was found between log MAR (VA) and VD in SCP and DCP, however Durbin found a weak negative correlation between VD in SCP with VA [24], as did Attaallah who, on the other hand, found no correlation with VD in DCP [31]. In our series the perifoveal VD in SCP had a moderately positive correlation with VA (p = 0.009; r = 0.23) and a moderately negative correlation with log MAR (VA) (p = 0.001; r = −0.31). Adding a quantitative parameter to the current stage of DR makes the stage assessment a measurable parameter. This would make it possible to identify patients at risk, predict therapeutic efficacy and help in the follow-up of diabetic patients.

4.2.3. The central avascular zone (ZAC)

The underlying pathophysiology of FAZ enlargement in the DR is most likely related to microinfrastructures in the surrounding vascular arches [33,34] and loss of capillaries adjacent to the vessels [14].

Lupidi and al [14] as well as Attaallah and al [31] reported a statistically significant difference in the area of the FAZ between the superficial and deep plexus where it is wider. Similar results were found in our series with (p < 0.001 and r = 0.95). This was explained by the difference in vascular architecture which is terminal at the DCP as opposed to the SCP which has a continuous capillary ring around the FAZ.

The size of the FAZ (in SCP and DCP) has been reported in a few studies to be associated with function and visual acuity [35–38]. However, this correlation was not proven in another series [30]. In our series, both FAZ enlargement and FAZ disruption were correlated with visual acuity with a statistically significant difference (p respectively = 0.014 and 0.001). This is consistent with previous results based on clinical and angiographic findings [33,39].

However, the size of the FAZ in OCT-A is believed to play a limited role in predicting VA in eyes with DR, as inter-individual variation in the surface and morphology of the FAZ has been observed [40–43] and was attributed to a complex difference in foveal development with an increase in the length of its axis after the formation of the FAZ [44].

In addition, FAZ measures tended to increase with the progression of DR in most studies [12,28,36,46–48]. In our series, this widening in both SCP and DCP was proportional to the severity of diabetic retinopathy (p 0.002 and 0.016 respectively). The FAZ was wider in the advanced stages of DR (Table 3). These results confirm studies carried out with angiography several decades earlier [49] where microvascular changes and macular ischemia are pronounced in the advanced stages of DR [15].

4.3. Diabetic macular edema

DME appears in OCT-A as intraretinal space or hyporeflective cysts, devoid of signal, with rounded and smooth hyperreflective edges that do not follow the boundaries of neighboring capillaries [18].

In our series, microaneurysms are more numerous when associated with edema, in fact, the mean number of microaneurysms was higher in patients with DME compared to those with DR without DME, with a statistically significant difference between the two groups in the SCP and in the DCP. Microaneurysms associated with DME were also found to be more frequent in the DCP in congruence with the results of Peres [11]. CMT was also positively associated with the presence of microaneurysms in DCP in our series (P = 0.023; r = 0.21), in accordance with Hasegawa’s results [9].

Furthermore, Mané had suggested that for DME fluid would accumulate preferentially in areas of vascular depletion particularly in DCP [50]. In our series, it was noted that the presence of edema in OCT-A was associated with the presence of capillary non perfusion areas in 95% of cases in SCP and in 97% of cases in DCP.

Quantitatively, the VD of SCP was lower in the DR group with DME (18 ± 4.69) than in the group without edema territories (21.18 ± 6.22) with a statistically significant difference (P < 0.05) at the perifoveal level. The presence of edema spaces in the OCT-A would therefore be correlated with a lower VD. In agreement with the work of Kim and al [26] and Tang and al [51].

It should be noted that in our series a correlation between VD and CMT was found (P < 0.05 and r = 0.38) in conformity with Dimitrova’s results [32].

It was also reported in the Mané series, which included patients with DME, that the normal vortex vascular structure of DCP was altered in all patients [50]. In our series the impairment of this architecture was correlated with the mean CMT, which in patients with altered DCP architecture (388 ± 138.59 μm) was higher than in those with preserved architecture (287.34 ± 83.35 μm) with a statistically significant difference (p < 0.05). Vortex architecture was absent in 59% of patients with DME spaces in OCT-A, and the association of normal architecture with the cystoid spaces was negatively significant.

On the other hand, the distribution of cystoid spaces in our series was predominantly central, and this was a limitation to the estimation of the FAZ measurement especially in DCP where edema was predominant. It is important to note that the presence of DME influences the reproducibility and measurement efficiency of the FAZ in the SCP and the DCP [14,17,20,25,49].

Furthermore, we noted that the FAZ was wider in the DR group with DME compared to the DR group without DME both in the SCP (472,872 vs. 399,779 μm² respectively) and in the DCP (571,262 vs. 551,844 μm² respectively) without statistically significant difference. The FAZ in DCP was larger. Peres and al [11] and Di and al [47] also found that the DME was associated with a wider FAZ in both the superficial and deep plexus. Attaallah approved this result for the SCP only [31]. The angiography had already shown that the FAZ was wider in patients with DME compared to healthy controls [39,40]. As OCT-A is non-invasive and reproducible, it can identify retinal vascularization and microanatomy simultaneously and is able to visualize the capillary network in depth.

5. Conclusion

Our study showed that retinal microvascular abnormalities were observed in all stages of DR. It also showed that the presence of these abnormalities was proportional to the severity of DR and more pronounced in the presence of DME, and that DCP was more severely affected than SCP. In addition, the assessment of macular ischemia could be based on the identification of areas of vascular rarefaction, the quantitative assessment of VD and the qualitative and quantitative study of the FAZ.
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Ethical approval
Approval has been given.

Consent
Oral informed consent was obtained from the subjects to participate in this study.

Author contribution
Ahmed Mahjoub: Editing of the manuscript. Ines Cherni: Conceptualization, Data support, data collection, Editing of manuscript, investigation, writing original draft. Oumayma Khayrallah: Writing the paper. Nadia Ben Abdesslam: Examination and correction. Anis Mahjoub: Data collection. Anas Romdhane: Data collection. Mohamed Ghorbel: Manuscript correction, supervision of the manuscript. Hachemi Mahjoub: Supervision of the manuscript, manuscript correction. Leila Knani: Manuscript correction, supervision of the manuscript. Fathi Krifa: Study design.

Registration of research studies
1 Name of the registry: Research registry
2 Unique Identifying number or registration ID: 7057
3 Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6117a415d4bcc6001fe6fcd0/

Guarantor
Oumayma Khayrallah, Ines Cherni.

Declaration of competing interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jamsu.2021.102904.

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