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Review

Macular thickness and volume in the elderly: A systematic review

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ABSTRACT

Ageing leads to a number of changes in the body including the macula. Detailed imaging using optical coherence tomography have enabled *in vivo* studies of how macula changes with age. Here we systematically review 49 studies (9115 participants and 11,577 eyes) to provide an overview of how ageing manifests in the macula of the elderly focusing on clinical relevant measures that are thicknesses and volumes of different macular areas. Ageing seems to increase center point foveal thickness. Ageing does not seem to change the center subfield thickness significantly. Ageing decreases the inner and outer macular thickness, and the overall macular thickness and volume. Studies find that specific retinal layers at specific locations seem to be the contributor to these changes. These findings confirm that age-related changes suggested in histological studies are measurable *in vivo* on thickness and volume and differ depending on location. Studies are needed to explore reasons for the large variance in measurements and how ageing by itself contributes to development of macular disease.

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1. Introduction

The macula is an important tissue hypothesized to be the cornerstone of the evolutionary success of humans due to its contribution to development of a relatively large brain size (Kirk, 2006). A number of changes turned out to be a competitive advantage in the selection pressure: A higher visual acuity and a better binocular vision, achieved by a fovea entirely free of retinal vessels and rods and instead packed with cones, enabled more precise hand-eye coordination and metabolically economic navigation (Veilleux and Kirk, 2014; Williams et al., 2010). The densely packed avascular foveal tissue comes at a price: an extremely high metabolic turnover compared to its volume (Lange and Bainbridge, 2012) that is managed well in young adults, but perhaps not in the aged since becoming 60 years old or more is quite new in an evolutionary perspective and has not been a selection pressure. Understanding normal age-related changes is crucial for mapping pathogenesis of age-related macular diseases: what constitutes normal ageing and what is the abnormal part of the story? These are important questions to answer as demographic projections forecast more and more elderly leading to a steadily increasing prevalence of diseases such as the age-related macular degeneration (Lindekleiv and Erke, 2013; Wong et al., 2014).

Detailed imaging of the macula using optical coherence tomography (OCT) have enabled *in vivo* studies of structural details. Measures of thickness and volumes are used to understand the retina and its layers in relationships to health and disease, and to evaluate treatment response for medical and surgical interventions. Interestingly, ageing also influences these measures, which is important to understand and distinguish from disease. In this systematic review, we aim to provide an overview of *in vivo* OCT manifestations of normal macular ageing in humans focusing on thickness and volume measures.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews (Moher et al., 2009).

2.1. Eligibility criteria

Eligible studies had to evaluate macular thickness using OCT on aged (defined as being >50 years old) healthy individuals. We expected that the majority of studies would be of observational and cross-sectional nature, but we did not restrict on study design apart from case studies and publications without original data which were excluded. All eligible studies regardless of study design had to correlate age (i.e. using correlation statistics, regression analyses, or by comparing aged with young individuals) with available OCT data. We also included studies having participants with retinal diseases if they had a healthy control group with isolated OCT and age correlations, but limited data extraction from these studies to only that of healthy participants. We did not restrict on gender, ethnicity, or study settings (e.g. hospital based or population study). Eligible studies had healthy study participants at least as a subgroup of study participants, and healthy was defined as not having an intraocular disease or a systemic disease with a retinal component. We did not restrict on OCT technology, scan protocol, definition of macular structures, or measured macular thicknesses. Physiological studies of OCT changes during temporary settings (e.g. sitting, exercising, drug-infusion, or pregnancy) were not included. Eligibility was restricted to studies of human subjects and studies written on English.

2.2. Search strategy and study selection

We searched the bibliographic databases PubMed, the Cochrane Library, EMBASE, and the Web of Science using the following search terms: *("optical coherence tomography" OR "OCT") AND ("macula" OR "retina") AND ("ageing" OR "ageing" OR "elderly" OR "age") AND ("healthy").* The search was performed on October 2nd, 2015. Search results were imported to EndNote X7.4 (Thomson Reuters, New York, NY, USA) to manage records, and exclude duplicates and obviously irrelevant References

One author (Y.S.) removed duplicates and excluded references that were obviously irrelevant by screening title and abstract. Two authors (Y.S. and T.F.) independently read all potentially eligible studies in full-text. Disagreement on whether a study was eligible was resolved by discussion. One author (Y.S.) reviewed reference lists of all studies read in full-text to find additional eligible studies.

2.3. Data extraction, risk of bias assessment, and data synthesis

We extracted data on study design, participant eligibility criteria, study population characteristics (number of participants, number of eyes, age, sex, and country), type of OCT and OCT protocol, results on how ageing correlated with macular thickness in different macular areas, and factors adjusted in the analyses. Study quality was assessed using the Agency for Healthcare Research and Quality checklist for cross-sectional studies (Zeng et al., 2015) in items 1–8. We judged that items 9–11 (9: If applicable, explains how missing data were handled in the analysis; 10: Summarizes patient response rates and completeness of data collection; 11: Clarifies what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.) were irrelevant for the type of studies included in this review. Two authors (Y.S. and T.F.) extracted data from the eligible studies, and disagreements between authors were discussed in the author group until consensus was reached. Due to significant differences in the included studies in demographic characteristics, OCT used for data collection, definition of macular fields, and factors adjusted in analyses (including potential unit of analysis issues such as eyes from same participant treated as independent values), we refrained from pooling extracted data into a meta-analysis and instead present extracted data in a qualitative analysis to provide an overview of the field. Since measurements from different OCT brands and systems may be subject to significant differences, we supplemented change over time data with change in standard deviation (SD) over time where possible to provide more comparable values.

3. Results

3.1. Study selection

Our search yielded 1245 records, of which 485 were duplicates. We screened title and abstract of 760 records of which 101 were found potentially eligible and read in full-text. We excluded 67 of these because 34 studies had no age-correlation of data, 17 studies had data on choroid only, 11 studies had OCT of structures outside the area of interest (e.g. papillary OCT), four studies did not have participants 50+ years old, and one had no original data. We found 15 additional eligible studies by hand searching reference lists of all studies read in full-text. In total, 49 studies were found to be eligible and included in our review (Fig. 1).

3.2. Study characteristics, methods, and population

All studies were cross-sectional (Table 1, see supplementary data). Recruitment was described in 17 studies, of which four were