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The 100 most-cited papers on age-related macular degeneration: a bibliographic perspective

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ABSTRACT

The 100 most-cited papers on age-related macular degeneration (AMD) were analysed using a bibliographic study. The bibliographic databases of the Institute for Scientific Information Web of Knowledge were searched, limited to research articles published between 1965 and 2020 in peer-reviewed journals. The papers were ranked in order of number of citations since publication. Five of the top 10 (and 3 of the top 4) papers reported randomised clinical trial results for either anti-vascular endothelial growth factor agents or nutritional supplements. Four of the top 10 papers reported genotype-phenotype associations between AMD and variants in *Complement Factor H*. This bibliographic study provides perspective and insight into many of the most influential contributions in the understanding and management of AMD and its evolution over time.

Age-related macular degeneration (AMD) remains the leading cause of irreversible visual loss among the elderly in industrialised nations.[1] Despite substantial progress in the diagnosis and treatment of AMD over the past 20 years, there are many unmet clinical needs.[2] AMD is the subject of extensive basic science, translational and clinical research efforts, resulting in thousands of peer-reviewed publications.

Historically, AMD was first described in the second half of the 19th century, after the invention and introduction of the ophthalmoscope. The disorder was known under different names, and these names might have varied between languages. In the first half of the 20th century, it was called among other names, disciform macular degeneration, retinal circinate degeneration (Fuchs' circinate retinitis), external exudative retinitis, tumour-like tissue proliferation in the macula lutea, senile exudative macular retinitis, senile macular degeneration, central senile chorioretinitis, and serous and haemorrhagic disciform detachment of the macula. In the second half of the 20th century, most researchers used either senile macular degeneration or AMD, although other terms could be found, including senile exudative maculopathy, disciform detachment of the neuroepithelium, senile disciform macular detachment, senile macular choroidal degeneration, age-related maculopathy, age-dependent macular degeneration, age-related macular disease and ageing macular disease/disorder.[3–5] This evolution demonstrates the importance of using a unified terminology for knowledge dissemination and development.

Over the past 30 or so years, the primary diagnostic modality for AMD has evolved from fluorescein angiography to optical coherence tomography (OCT) and OCT angiography, and the primary therapeutic modality for patients with neovascular AMD has evolved from no therapy, to thermal photocoagulation,[6] to photodynamic therapy (PDT),[7] to antivascular endothelial growth factor (anti-VEGF) agents, including chronologically pegaptanib (Macugen),[8] bevacizumab (Avastin),[9] ranibizumab (Lucentis)[10 11] and Eylea (aflibercept) with different treatment protocols.[12] Most patients with at least intermediate AMD are offered nutritional supplementation per the Age-Related Eye Disease Study (AREDS).[13] And there is a growing understanding of the complex genetic risk factors affecting the pathogenesis of the disease.[14–17]

One approach to evaluate the impact of an individual scientific article is by the number of subsequent citations.[18 19] Our group has used this approach to report the 100 most-cited papers on vitrectomy,[20] intravitreal injections[21] and retinal detachment.[22] Other investigators have used similar techniques in other areas of ophthalmology.[23–26]

In this study, we identified the 100 most-cited articles on AMD over the past 55 years, in order to provide a bibliographic-historic perspective on the evolution of the understanding and management of this disease.

METHODS

The bibliographic databases of the Institute for Scientific Information (ISI) Web of

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Knowledge databases were searched with the assistance of an expert medical librarian. The search was performed using the keyword combinations of 'AMD' and 'senile macular degeneration' that had to appear in the title of the manuscripts. The search included all publications in peer-reviewed journals from 1965 (the earliest year archived in the ISI Web of Knowledge databases) through the date of the search (31 December 2020). The search included all types of publications (original articles, reviews, meta-analyses, case reports, etc) and all available journals and sources, not only those specific to the field of ophthalmology.

The papers were then ranked by the number of total citations since publication. Each paper was reviewed and excluded if not relevant to the topic of AMD. After the list of the 100 most-cited papers was finalised, the following details were recorded for each paper: overall number of citations, mean citations per year since publication, journal name, year of publication, names of first and last authors, number of authors, country of origin (determined by the corresponding author), type of study, number of patients included, and the theme of its main topic. In some cases, the authors listed on the papers in the databases conflicted with the authors listed on the original publications; in these instances, the authors listed in the original publications were used for the present analysis.

Values of the results are presented as mean±SD. Correlations between year of publication and total number of citations and between the year of publication and mean number of citations per year were analysed using Pearson's correlation coefficient, with a p value of 0.05 used to determine statistical significance. Data was analysed using SPSS for Windows V.20.

RESULTS

Overall, the search yielded 7755 articles. Most of these were published in ophthalmology journals (68.7%), and the rest in fields related to other major fields such as genetics, pharmacology, general medicine and biology. The most common countries of origin were the USA (35.5%), Germany (8.3%), United Kingdom (8.1%), Australia (6.1%), France (4.9%), China (4.7%) and Japan (4.5%).

Research interest in AMD has risen greatly in the past two decades. When looking at the total number of publications per year, an increase from about 200–300 to about 500 has occurred in 2004, and then again to over 1000 in 2013. This is presented in the figure 1.

The 100 most-cited papers on AMD, according to this methodology, are presented in the online supplemental table. The mean number of total citations was 754±585, with a median of 543 citations and a range of 343 to 3919. Sixty-one of the 100 most-cited papers on AMD were published in ophthalmology journals, and 39 were published in journals from other fields of research.

The ophthalmology journals, in order of number of papers from the list, were *Ophthalmology* (n=17), *Archives of Ophthalmology* (n=11), *American Journal of Ophthalmology* (n=8), *Survey of Ophthalmology* (n=7), *Investigative Ophthalmology and Visual Science* (n=4), *Retina* (n=4), *Progress in Retinal and Eye Research* (n=3), *Experimental Eye Research* (n=3), *BMC Ophthalmology* (n=1), *Molecular Vision* (n=1), *Eye* (n=1) and *Ophthalmic Surgery, Lasers and Imaging* (n=1). More than half (36) of these papers were published in three leading journals in ophthalmology-*Ophthalmology, Archives of Ophthalmology, and American Journal of Ophthalmology*. Of note is that more than half of the papers published in other journals (22/38) were published in the most prestigious scientific journals-*Science* (n=6), *New England Journal of Medicine* (n=6), *Lancet* (n=4) and *Nature/Nature Genetics* (n=7). All papers in the top 100 were published in English.

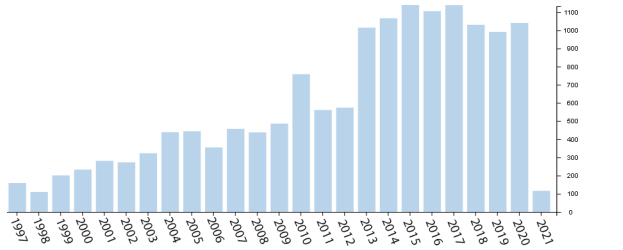

Figure 1 Distribution of total publications related to AMD by year of publication. AMD, age-related macular degeneration.

The 100 most-cited papers on AMD included 75 original articles, 24 reviews and one case report.[9] Of the original articles, 27 (36%) were basic science or animal studies, and 48 (64%) were human studies. These included 30 prospective, 15 retrospective and 3 observational studies. Twenty-two of the articles reported the results of multicentre studies, corresponding with 29.3% of the original articles and 45.8% of the human clinical studies.

The top 100 papers were also analysed for the themes of their main topics. The most common topic was treatment of AMD (n=30), followed by genetics (n=23) and pathology and pathogenesis (n=21). Additional topics included AMD risk factors (n=8), epidemiology (n=7), classifications (n=4), general reviews (n=4), natural history (n=2) and imaging (n=1). Since treatment was the leading topic, the top 100 papers were also analysed for the various treatment methods mentioned. These included: ranibizumab (n=12), bevacizumab (n=5), aflibercept (n=2), pegaptanib (n=2), PDT (n=7), triamcinolone (n=1), and AREDS supplementation (n=5).

The 100 most-cited papers on AMD were published between 1983 and 2016. When further divided by decades, there were 18 papers published up to 1999, 61 papers published between 2000 and 2009, and 21 papers published after 2010. There was no correlation between year of publication and total number of citations (p=0.42), but a significant correlation was found between the year of publication and mean number of citations per year (p<0.001), with later publications on average had significantly higher citations per year.

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DISCUSSION

The 100 most-cited papers in AMD illustrate the evolution of the diagnosis and treatment of the disease over the past three decades. In addition, they reflect the growing understanding of the role of genetics in the pathogenesis of the disease.

The #1, #3, #7, and #15 papers report, respectively, phase III randomised clinical trial (RCT) results for the anti-VEGF agents ranibizumab (Lucentis),[10 11] pegaptanib (Macugen),[8] and aflibercept (Eylea).[12] The #2, #5, #6, and #10 papers are the four original reports that variants in *Complement Factor H* (*CFH*) associate with clinical AMD.[14–17] The #4 paper reports the RCT for the original AREDS supplements.[13] The #8 paper is the Comparison of AMD Treatments Trials (CATT) report of an RCT comparing ranibizumab to bevacizumab (Avastin).[27] The #9, #11, and #14 papers are landmark epidemiological reports.[1 28 29] The #12 paper reviewed oxidative stress in disease pathogenesis.[30] The #13 paper is the initial RCT for PDT.[7] Collectively, these top 15 papers illustrate most of the major advances in AMD diagnosis, treatment, and understanding in the past 30 years. Interestingly, only 6 of these 15 papers (and only 2 of the top 10) were published in ophthalmology journals.

Bevacizumab, an off-label medication which never underwent a major phase III RCT, appears to be underrepresented in the top 15 papers. The first report of bevacizumab was in a single patient; this was the #29 paper and the only case report in the top 100 list.[9] Subsequent retrospective series, such as the #20 and #49 papers,[31 32] are also included on the list.

When viewed chronologically, there were about 200–300 papers published per year from 1997 through 2003. There is a modest but appreciable increase starting in 2004, the year pegaptanib received US Food and Drug Administration (FDA) approval. Similarly, there is a more substantial increase in 2013, the year aflibercept received US FDA approval.

The 100 most-cited AMD papers include nine papers authored by a study group with no individual authors named, plus two papers in which the study group is named as the first author, followed by individual investigators. These include the AREDS Research Group (#4 and #46),[13 33] the CATT Research Group (#8),[27] the Treatment of AMD With PDT Study Group (#13 and #18),[7 34] the Verteporfin in Photodynamic Therapy Study Group (#28),[35] the AREDS 2 Research Group (#51),[36] the Eye Disease Case-Control Study Group (#62),[37] and the Macular Photocoagulation Study Group (#68).[6] The two papers which listed the study group first, followed by individual investigators, were authored by the CATT Research Group (#16)[38] and the UK Inhibition of VEGF in Age-Related Choroidal Neovascularization Study Group (#55).[39]

In terms of nomenclature, 98 of the top 100 papers exclusively used the term 'AMD'. The only exceptions were the #66 paper (published in 1983, which used 'senile macular degeneration')[40] and the #11 paper (published in 1995, which used both 'age-related maculopathy' and 'AMD').[29]

The limitations of this study are similar to the limitations of previous works using this methodology. The most-cited papers are not necessarily the most scientifically important or clinically relevant. For example, papers #1,[10] #3,[11] #4,[13] and #8[27] report RCT results for, respectively, ranibizumab, AREDS supplements, and bevacizumab; these interventions remain highly clinically relevant. Papers #2,[14] #5,[15] #6[16] and #10[17] report the genotype–phenotype association with variants in *CFH*; this is scientifically important and has stimulated much further research but as yet has no clinical applicability. On the other hand, paper #7[8] reports the RCT results for pegaptanib, which is no longer available in the USA; and paper #9[28] reports prevalence rates from 2004 which are now outdated.

Regardless of these limitations, these 100 papers are among the most infuential in this field of study.

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