Predictors of Retinal Vascular Calibre: A Review

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ABSTRACT

Retinal vascular calibre assessment offers a unique, non-invasive research tool to better understand the pathophysiology of the body's microvasculature and aid in the prediction of cardiovascular, cerebrovascular and metabolic related diseases. However, to fully understand the relationship between the microvascular alterations that occur in the retina and the role they play in human disease it is important to recognise the impact of genes, ethnicity, prenatal, perinatal and postnatal factors on retinal vascular calibre. This review highlights a range of genetic, ocular, systemic and birth parameters, most notably that of ethnicity and birth size, that appear to have a profound effect on retinal vascular calibre and therefore must be taken into account as a source of variation when determining the clinical significance systemic factors have on retinal vasculature.

Keywords: retinal vascular calibre, arteriolar calibre, venular calibre

WHAT IS RETINAL VASCULAR CALIBRE?

Retinal blood vessels are readily accessible via non-invasive retinal photography. Previous methods of measuring retinal vascular characteristics involved subjective clinical ophthalmoscopic examinations that proved to be variable and imprecise.[1] Objective measurement of retinal vascular changes can now be accurately assessed using computer-based imaging programs.[1] They provide a means to study the early structural changes that provide important information regarding the state of ocular microcirculation.[2] Retinal vascular calibre assessment involves measuring the diameter of retinal arterioles and venules and an overall value for each calculated via a specialised formula (normal range = 100-300 microns).[3] It has proven to be an effective tool in determining the clinical significance that systemic, environmental and genetic factors have on retinal vasculature. Furthermore, researchers have established that retinal vascular calibre assessment offers a unique, non-invasive research tool to better understand the pathophysiology of the body's microvasculature and aid in the prediction of cardiovascular, cerebrovascular and metabolic related diseases.[2] To fully understand the relationship between the microvascular alterations that occur in the retina and the role they play in human disease, it is important to recognise the impact that genes, ethnicity and pre-, peri- and post-natal factors have on retinal vascular calibre.

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ETHNICITY

Increasing evidence suggests retinal vascular calibre varies significantly between different ethnic groups.[2,4-6] The Singapore Cohort Study of the Risk Factors for Myopia (SCORM) examined retinal vascular calibre in 768 children from Chinese, Indian and Malaysian backgrounds.[2] Findings were such that retinal venules and arterioles were narrower in Chinese children compared to Malay and Indian children.[2] Wong et al further highlighted the presence of ethnic variations in retinal microvasculature when they found that both retinal arteriolar and venular calibre were significantly larger in Black and Hispanic participants compared to Chinese and Caucasian participants.[6] A later Australian study by Rochtchina et al found that retinal vascular calibre was wider in children of East Asian appearance compared to Caucasians. This difference however, could be principally explained by darker iris colour which approximated to darker retinal pigmentation.[4] They suggested that a higher level of pigmentation in those darker races reduces the contrast between background and retinal vessels, making the vessel's edge harder to detect by the specialised semi-automated computer program, leading to the erroneous overestimation of retinal vascular calibre.[4] This implies that retinal pigmentation may affect comparisons of retinal vascular calibre between subjects with different ethnic backgrounds. Despite these findings the precise reasons for these differences still remain largely unclear. Ethnic differences in calibre may reflect the susceptibility to vascular risk factors, ocular biometry measures, variations in retinal background colour and/or genetic factors.[2,4-6]

GENETIC DETERMINANTS

The Beaver Dam Eye Study was the first to investigate the genetic basis of retinal vascular calibre, focussing on familial aggregation initially and then building on this research using genome-wide linkage in a subsequent study.[7-8] When investigating correlations among family members they found that retinal vascular calibre measurements were more strongly correlated between relatives compared to unrelated individuals and these correlations were likely the result of shared genes. This novel finding provided the first evidence for a genetic influence on retinal vascular calibre.[7] A later study by Xing et al utilised data from the Beaver Dam Eye Study to assess genome wide linkage. Findings were such that retinal arteriolar and venular calibre were linked to multiple genetic loci, some unique to only arterioles and some unique to only venules.[8] This finding further highlighted that structural changes in retinal microcirculation may have genetic determinants as some distinct genes are likely to play a part in determining the size of arteriolar and venular calibre.[8] Taarnhoj et al went on to examine the heritability of retinal vascular calibre, recruiting 55 monozygotic and 50 dizygotic twins to assess the relative influence of genetic and environmental factors on vascular calibre.[9] Retinal vascular calibre was found to be significantly influenced by genetic factors as it accounted for 70% of variance in arteriole diameters and 83% variance in venule diameters.[9] The results from these three studies suggest that retinal vascular calibres and the associated variations in risk of systemic disease may be a primary genetic characteristic. Despite this, further research is required to aid in the understanding of genetic associations on vascular calibre in various systemic diseases.[10]

BIRTH PARAMETERS

The impact of early life factors on retinal vascular calibre still remains largely unclear. Children have been a popular choice as participants in these studies as they are generally free of potentially confounding systemic and environmental factors and therefore provide an ideal study population.[11-12] Several studies have examined the relationship between birth weight and retinal vascular calibre and have shown a possible association between the two.[3,10,13-15] It has been suggested that low birth weight and shorter birth length may impact the body's microcirculatory structure possibly leading to the development of various cardiovascular and systemic disorders.[3] Cheung et al was one of the first studies to assess the relationship between birth factors and retinal vascular calibre in children.[2] They found that there was no association between vascular calibre and the birth factors of gestational age and birth weight. These results do not support the growing body of evidence that suggests a person's risk of hypertension, diabetes and coronary heart disease begins in early life.[10,14] Cheung et al must be commended for their large sample size (n = 768), however the school-based design may not have been truly representative of the entire community.[2]

Conversely, later studies by Sun et al and Mitchell et al, who also assessed the relationship between birth parameters and retinal vascular calibre, found a consistent association between smaller birth size and narrower retinal arterioles.[10,14] Mitchell et al also added that children with a smaller birth length and head circumference also displayed significantly narrower retinal arterioles.[14] These findings support the concept that poor in utero growth may have an adverse influence on microvascular structure.[10,14] Mitchell et al utilised a large population-based sample (n = 1369), however they did not account for genetic or socioeconomic factors that could confound associations between retinal vascular calibre and birth weight.[14] On the other hand, despite a small sample size (n = 266), Sun et al's twin study accounted for any vascular determinants that would be constant across twin pairs (maternal nutrition, environmental factors, gestational diabetes, socioeconomic factors) suggesting that arteriolar changes are likely related to individual specific factors such as different foetal nutrient supplies.[10] These findings are consistent with those in adult populations.[3] Liew et al examined the association between birth weight and retinal arteriolar calibre in 3,800 persons aged between 51 and 72 years.[3] Similarly, they found that lower birth weight was associated with narrower retinal arteriolar calibre. Findings from Liew, Mitchell and Sun imply that intrauterine influences of low birth weight may result in structural circulatory changes.[3,10,14]

OCULAR PREDICTORS

Myopia

There is still much debate surrounding the relationship between retinal vascular calibre and an individual's refractive state. Wong et al was one of the first studies to assess this relationship and found that smaller retinal arteriolar and venular calibres were associated with a myopic refraction and the opposite was noted in hyperopic participants.[1] It remained uncertain however, whether the variations noted were related to biological or pathological processes in eyes of different refraction or whether the variation in ocular magnification between myopic and hyperopic eyes was the source of this variation.[1] The effect of ocular magnification is such that as the ocular dimensions of the eye increase the retinal blood vessel diameters as measured from fundus photographs decrease.[16-17] A later study conducted by Wong et al went on to examine this relationship further.[18] Similarly to their previous study, they found that participants with myopic refractive errors displayed significantly narrower retinal arteriolar and venular calibres compared to their hyperopic counterparts.[18] Despite this, they noted that refraction had no effect on the association between blood pressure and retinal vascular diameter. This suggests that correcting for ocular magnification in myopia may only be necessary when quantifying and comparing precise retinal vascular measurements between participants but not so important when looking at associations within participants, for example in research surrounding retinal microvasculature parameters and systemic conditions such as hypertension.[18] Assuming that these differences between hyperopic and myopic participants are a direct result of ocular magnification, various formulae have been developed to counter this issue.[18] These assume however, that myopia is only associated with longer axial length and do not account for the effect that other ocular dimensions such as corneal curvature have on refractive errors. Findings from Shimada et al and Nemeth et al support the theory that biological processes are responsible for these retinal vascular alterations. They found that myopes displayed narrower retinal vessel diameter with associated decreased retinal blood flow.[19-21] Shimada et al further suggested that these findings may be related to the development of chorioretinopathy in high myopia.[19] These results highlight that there is still conjecture surrounding the mechanisms responsible for the variations in retinal vascular calibre in myopia and hyperopia. Furthermore, additional research is required to evaluate whether these variations are significant enough to consider in future calibre studies.

Axial Length

Like myopia, there are currently varying opinions in the literature as to the relationship between retinal vascular calibre and axial length. Patton et al was one of the first studies to assess this relationship and found a significant association between narrow retinal vessels and longer axial length in pseudophakic eyes of older adults.[22] However, as this study was conducted in an older adult population the results may be biased by the presence of concurrent systemic disease.[11,23] Furthermore, there was no correction for ocular magnification. The effect of ocular refraction and ocular dimension on the image size of retinal photographs has been postulated previously.[16-17] A later study by Cheung et al sought to rectify previous limitations examining this relationship in children aged seven to nine years old.[24] They found that there was no association between axial length and retinal vascular calibre after correcting for ocular magnification. This highlights the possibility that previously reported associations between axial length and vascular calibre could be related to differences in ocular magnification.[24] Despite this, more research needs to be conducted to determine the clinical significance of these findings.

Intraocular Pressure and Optic Disc Diameter

To develop an understanding of the physiological and anatomical determinants of retinal vascular calibre, several researchers have assessed the affect that intraocular pressure (IOP) and optic disc diameter have on the retinal microvasculature.[25-28] Previous studies in adult populations have reported conflicting associations between IOP and retinal vascular calibre. Results from Klein et al and Shin et al suggested that IOP was related to retinal vascular calibre changes in adults with glaucoma and diabetes.[29,30] Mitchell et al and Ikram et al on the other hand, found that no relationship existed between the two variables in adult participants with glaucoma.[11,28] As stated previously, this inconsistency may be related to ocular and systemic diseases that are common in adult populations which could bias the results. Cheung et al was the first study to examine the relationship between IOP and retinal vascular calibre in children.[25] They found that both arteriolar and venular calibre were similar across the distribution of IOP, suggesting that IOP does not influence retinal vascular calibre. Based on these findings it may not be crucial to control for an association between IOP and retinal vascular calibre in future studies conducted on children. However, evidence surrounding this association in adults is inconclusive and further research is warrented.[25]

Very few studies have examined the relationship between retinal vascular calibre and optic disc parameters. Findings in adult populations have been inconsistent in describing the association between retinal vascular calibre and optic disc size. Klein et al and Ikram et al reported no relationship between retinal vessel diameters and cup to disc ratio or incident optic disc changes, suggesting that retinal vascular calibre plays an insignificant role in the pathogenesis of glaucoma.[27,28] Cheung et al were the first researchers to explicitly examine this relationship in children.[25] They found a statistically significant association between smaller vertical optic disc diameter and narrower retinal arteriolar and venular calibres. Despite the fact that the detected differences in vascular calibre were quite small, similar associations have also been found in adult populations[11] suggesting that a possible anatomic relationship may exists between optic disc dimensions and retinal vascular calibre.[11,25] However, as limited research concerning this relationship has been conducted in the child population, further research is required before any significant conclusions can be drawn.

BODY MASS INDEX (BMI) AND BLOOD PRESSURE

Childhood obesity is a significant public health issue in today's society with 10% of children worldwide being classed as obese.[31-33] The relationship between obesity and microvascular disease remains largely unknown. Cheung et al examined the association of BMI and weight with retinal vascular calibre in children.[34] They found that greater BMI and weight were associated with larger retinal venular calibre. These findings are consistent with those in adult populations that also found that larger venular calibre was associated with higher BMI, increased waist circumference, and higher waist to hip ratios.[35-37] Mechanisms surrounding retinal venular dilation have been related to metabolic risk factors and inflammation.[38] Retinal arteriolar alterations on the other hand, have been more strongly associated with blood pressure.[39] Evidence suggests that retinal arteriolar narrowing is a result of prolonged hypertension and is associated with cardiovascular related deaths in adult populations.[40] Mitchell et al set out to determine the effect of blood pressure on retinal arteriolar calibre in children.[39] Similarly to those studies on adult populations,[23,41-45] they too found that blood pressure was associated with retinal arteriolar narrowing suggesting that the effects of raised blood pressure may manifest earlier in life. These novel findings in child populations may shed light on the microvascular alterations that result from a high BMI and blood pressure. Further research in this area is required to replicate these findings and investigate mechanisms by which these microvascular alterations occur.

CONCLUSION

Due to the limited research into the effects of ocular parameters, BMI and blood pressure on retinal vascular calibre measurements, it remains relatively contentious whether these factors influence retinal microvascular particularly in children. However, this review highlights that a range of genetic and birth parameters, most notably that of ethnicity and birth size, appear to have a considerable effect on retinal arteriolar and venular calibre. This emerging evidence suggests that the well-established systemic factors that influence retinal microvasculature, such as blood pressure and blood glucose levels, may not be solely responsible for the variations noted in retinal vascular calibre and that birth factors may also contribute to the variation. Further research is required to determine the clinical importance of the specific predictors of retinal vascular calibre and how they relate to the pathogenesis of cardiovascular, cerebrovascular and metabolic related diseases.

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