Review article

Retinal microvascular changes in low-birth-weight babies have a link to future health

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Abstract

Background: *In utero* insults that result in low-birth-weight (LBW) infants are now recognized risk factors for the development of vascular-related diseases in adulthood. Microcirculatory pathologies are believed to form a mechanistic link between fetal insult and the manifestation of illness in adulthood.

Objectives: The challenge has been to investigate microcirculatory changes *in vivo*. The objective of this review is to determine whether LBW infants and individuals undergo abnormal microvascular changes and, if so, whether these changes can be objectively identified and measured by investigating retinal vessels.

Methods: An online publication search was carried out using the following keywords to identify and review relevant articles: retinal microvasculature, retinal vessels, small for gestation age, growth restriction, and intrauterine growth restriction. Articles published from 1980 to 2011 were considered.

Conclusions: The ability of retinal imaging technology to assess and measure retinal microvasculature makes it a valuable assessment tool. The current tool is, however, unsuitable for

non-invasive assessment in infants and young children. Once this hurdle has been overcome, a longitudinal study of LBW individuals from infancy to adulthood, with regular retinal microvascular assessments, would help prove the mechanistic link between LBW and cardiovascular disease in adulthood.

Keywords: Low birth weight; microcirculation; microvascular; retina; retinal vessels.

Introduction

Globally, more than 20 million low-birth-weight (LBW) infants are born each year [33]. The World Health Organization has defined LBW as a birth weight of <2500 g (5.5 lb) [22]. This is based on epidemiological observations that infants weighing <2500 g are approximately 20-fold more likely to die than heavier babies [33]. More common in developing than developed countries, a birth weight <2500 g contributes to a range of poor health outcomes. LBW defines a heterogeneous group of infants: some are born early, some are born growth-restricted (weight below the 10th percentile for their gestational age) and others are born both early and growth-restricted. It is generally acknowledged that LBW is a disadvantage for the baby. It is now recognized that the *in utero* insults that result in LBW are risk factors that contribute to the development of vascular-related diseases in adulthood [2–6]. The exact mechanism of this phenomenon is yet to be fully understood, but there is increasing evidence to suggest that microcirculatory pathology forms the mechanistic link between fetal insult and the manifestation of illness in adulthood [26, 28, 30, 35, 39].

The ability to investigate microvascular structure and function is important for improving our understanding of the mechanism of cardiovascular disease. The challenge has been to investigate microcirculatory changes *in vivo*. Various techniques are emerging for the investigation of different aspects of microcirculation in animals and humans [1]. Understanding the changes that occur in microcirculation may allow the identification of paths for early intervention in order to prevent adverse long-term consequences. Screening procedures that assess microcirculation may also allow the early identification of individuals at a high-risk of cardiovascular and renal disease, thereby enabling early intervention to mitigate the effects of microvascular changes on long-term health.

The objectives of this review are to determine whether LBW infants and individuals experience abnormal microvascular

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changes and whether these changes can be objectively identified and measured by investigating the retinal vessels.

Methods

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Results

The human retina and microcirculation

The human retina has long been recognized as a site where human microcirculation can be visualized and assessed. In 1851, Hermann von Helmholtz presented his now famous and classic monograph *Augenspiegel*, which made the technology for the visualization of retinal microcirculation available to all [37]. Approximately 40 years later, in 1892, Marcus Gunn [18] first described the changes in retinal vessels that occur in hypertension. It was thus recognized that the human retina provides a window for the *in vivo* investigation of human microcirculation. The availability of digital photography and the technology to store, retrieve and transmit these data have made retinal imaging an important clinical tool [27].

The value of retinal imaging has been further enhanced by the availability of software to for automated analysis [21]. Retinal vascular analysis is currently used in two broad areas of cardiovascular research [27]. First, it is a non-invasive research tool for investigating the pathophysiology and role of the microvasculature, typically defined as vessels between 100 and 300 μm in size, in the development of clinical cardiovascular pathologies. Second, retinal vascular imaging is being explored in clinical settings as a risk stratification tool for helping clinicians identify patients with microvascular signs who are at a high-risk of future clinical cerebrovascular and cardiovascular disease [27].

Automated diagnosis using digital image analysis of retinal images offers huge potential benefits in terms of the accuracy and speed of analysis [27, 39, 48]. There are various methods for image analysis. In a commonly used method, image analysis software identifies the retinal vessels that completely pass through the region between 0.5 and 1 disc in diameter from the optic disc margin (zone B). It denotes the edges of the vessels using the pixel density histogram technique [10, 21, 27]. The analysis is usually performed on a sequence of complete trees, generally from a single eye but continuing with the other eye if necessary in order to achieve the required number of vessel segments and bifurcations. The cross-sectional diameters of retinal arterioles and venules are repeatedly measured, and these measurements summarized using mathematical formulae in order to obtain values representing the mean arteriolar and venular caliber of that particular eye. Other programmes, such as ROPtool [43], Retinal Image Multiscale Analysis [42] and computer-

aided image analysis of the retina [45], use different techniques for the semi-automatic measurement of retinal vessel dilatation and tortuosity.

Blood flow in vessels is not a random occurrence but follows the principles of fluid mechanics in order to ensure it adheres to optimality principles. This was elegantly described approximately 85 years ago by Murray [32]. A vascular network can be defined in terms of bifurcation angles and junction exponents (a measure of the relative diameters of the parent and daughter branch vessels) at branching points. These parameters have implications on circulatory energy costs [53] and the efficiency of space filling by vascular networks [24]. Various types of circulation processes in humans conform to optimal health patterns, including the retinal microvascular architecture [24, 52]. In adults, aging and possibly hypertension are associated with disadvantageous branching geometry, such as narrower bifurcation angles and smaller vessel diameters in the human retinal vasculature [38]. These findings imply increased power costs for blood transport and the uneven distribution of shear forces throughout the microvascular tree [32].

Retinal microvascular changes in LBW adults and children

Do LBW patients undergo microcirculatory changes and, if so, can these changes be detected through assessment of the retinal microvasculature? Chapman et al. [9] investigated the association between LBW and alterations in the retinal microvasculature. In their study, a random sample of 100 men aged 64–74 years was selected from a cohort of men whose birth weights were known. The men were stratified by birth weight (low ≤ 3200 g or high ≥ 3700 g) and systolic blood pressure (low ≤ 140 mm Hg or high ≥ 160 mm Hg) into four groups:

- LBW and low blood pressure;
- LBW and high blood pressure;
- high birth weight and low blood pressure; and
- high birth weight and high blood pressure.

Retinal photographic images were taken for each adult patient by an investigator who was blinded to the birth weight and clinical status of each participant. These photographs were converted into digital images using a special camera (Micro-Nikkor 60 mm f/2.8D lens, SWK-21-CCd camera, Nikon, Tokyo, Japan) and a personal computer (Viglen, Alpertown, Middlesex, UK). The images were measured and vessel diameters and branching angles calculated using the commercially available software Java (Jandel Scientific, Corte Madera, CA, USA) and Mathcad (MathSoft Inc., Cambridge, MA, USA).

The investigators found that the LBW groups had significantly narrower arteriole bifurcation angles than the high-birth-weight groups. The investigators postulated that narrower arteriole bifurcation angles are associated with increased circulatory energy costs and that this may be related to a lower than normal microvascular density. They concluded that differences in retinal microvascular architecture might reflect a persistent alteration in the vascular architecture as

a result of an impairment during fetal development and suggested that this could provide a mechanistic link between LBW and increased cardiovascular risk.

In another study, retinal vessel morphology was evaluated in 21 young adults who were born small for gestational age (SGA) [19]. Digital images taken of these adults were compared with those taken from a group of 23 individuals born at an appropriate gestational age (AGA). The investigators found that SGA adults had significantly less retinal vascularization, as evidenced by the lower number of vascular branching points (median: 26; range: 20–31) compared with AGA adults (median: 28; range: 26–32, Figure 1). They concluded that intrauterine growth restriction is associated with abnormal retinal vascular morphology in young adult life. They proposed that this finding may not be restricted to the retina and might represent a more global effect of vascular growth within the body.

Liew et al. [26] examined the association between birth weight and retinal arteriolar caliber in 3800 subjects aged 51–72 years in four USA communities. Participants born at full term with known birth weights underwent retinal photography. Retinal arteriolar and venular calibers were measured from digitized retinal photographs using a validated computer-assisted method. The investigators found that a lower birth weight was associated with narrower retinal arteriolar calibers, because each kilogram decrease in birth weight was associated with a 2.4 μm (95% confidence interval (CI), 1.3–3.5; $P < 0.001$) narrowing of retinal arteriolar calibers after controlling for age, gender, race, education, smoking, alcohol consumption, adult body mass index and height.

There is evidence that retinal microvascular changes are detectable from childhood in LBW individuals. Mitchell et al. [31] examined the relationship between birth parameters and the retinal microvasculature in 1369 six-year-old children in Sydney, Australia. The children's birth weight, birth

Figure 1 Number of retinal branching points in people with intra-uterine-growth restriction (IUGR) ($n=21$; •) and in subjects who were born average for gestational age ($n=23$; ○) in relation to a healthy reference (control) group. The upper dotted line depicts the 5th centile, the lower dotted line depicts the 95th centile range, and the solid centerline indicates the median in relation to percentage birth weight deviates from the mean of the normal population (reproduced with permission from [19]).

length and head circumference were obtained from parental records. Retinal arteriolar and venular calibers were measured from digitized retinal photographs using a previously published protocol [47]. The investigators found that lower birth weight, shorter birth length and smaller head circumference were associated with narrower retinal arteriolar calibers (Figure 2). Each kilogram decrease in birth weight was associated with a 2.3 μm (95% CI, 0.6–3.9; $P < 0.01$) narrowing of retinal arteriolar calibers after controlling for age, gender, ethnicity, height, body mass index, axial length, mean arterial blood pressure and prematurity. Similar associations with narrower retinal arteriolar calibers were observed for shorter birth length and smaller head circumference. The authors concluded that children who had lower birth weights, shorter birth lengths and smaller head circumferences had narrower retinal arteriolar calibers.

In another study of the relationship between retinal microvasculature and birth weight, 263 children were systematically screened in their 12th year of follow-up [41]. Complete data were available for 166 children with gestations of

Figure 2 Relationship between birth weight and retinal arteriolar/venular caliber (reproduced with permission from [31]).

≥37 weeks. The children were divided into three groups based on their birth weights (<3.2 kg, 3.2–3.6 kg and >3.6 kg). Retinal circulatory measures were evaluated, including retinal microvascular tortuosity and bifurcation optimality deviance. The relationship between the arteriolar diameters at a bifurcation is due to fluid power losses and endothelial function [32]. This relationship can be quantified by calculating an optimality ratio and the optimality deviation, the latter measuring the extent to which the optimality ratio deviates from the theoretically predicted optimum [32, 46]. The optimality ratio is the sum of the “daughter” arteriolar diameters divided by the “parent” arteriolar diameter. For a theoretically optimal bifurcation, the optimality ratio has a value of 0.79 [46]. Departures from the theoretically predicted optimum are associated with increased power losses at bifurcations and are indicative of endothelial dysfunction [32, 41, 46]. Linear regression modeling was used to assess the association between retinal microvasculature measures and birth weight. The investigators found that optimality deviance (an indicator of endothelial dysfunction) and retinal tortuosity were higher among LBW children.

An Australian study also reported an association between smaller birth size and narrower retinal vascular calibers [40]. In total, 266 twins (49 monozygotic and 84 dizygotic pairs; mean age 9.3 years) underwent ophthalmic examinations including the use of retinal photography [20]. The investigators used linear regression models to determine the association between birth parameters and retinal vessel diameter and found that each kilogram decrease in mean birth weight was associated with a 4.53 μm narrowing of mean retinal arteriolar calibers. Furthermore, a 5 cm decrease in mean birth length was associated with a 4.79 μm narrowing of mean retinal arteriolar calibers and each 2 cm decrease in head circumference at birth was associated with a 2.68 μm narrowing of the mean retinal arteriolar calibers. However, there were no overall statistically significant associations between these birth parameters and retinal venular calibers.

Retinal microcirculation and systemic disease

Does an abnormal retinal microvasculature increase cardiovascular risk? McGeechan et al. [29] published a systematic review of the studies that have investigated the relationship between retinal vessel calibers and the coronary artery, while adjusting for traditional risk factors. A total of 21,428 participants who underwent retinal assessments were followed over time (median follow-up period: 4.9–14.5 years) and monitored for cardiovascular disease events. Retinal photographs (film or digital) were taken of one or both eyes, centered on the optic disc and macula. These photographs were then viewed by trained graders, who were blind to participant characteristics. The graders measured the diameters of all of the arterioles and venules. The investigators demonstrated that variations in retinal vessel calibers (both wider retinal venules and narrower retinal arterioles) were associated with an increased risk of incident cardiovascular disease. The risk associated with changes in retinal vessel calibers was higher among women without diabetes or hypertension.

Other studies have demonstrated an association between retinal microvascular changes and stroke/neurological function [14, 16, 25, 44, 51], renal diseases [7, 13, 17, 49], and diabetes mellitus [34, 49, 50].

Role of perinatologists and neonatologists: should screening begin in infancy?

Do LBW infants have abnormal retinal microvasculatures from infancy? The answer to this question is not yet fully understood. Normal retinal microvasculature measurements in term infants have only recently become available [23]. Although the retinal microvasculatures of premature infants are routinely assessed to detect and treat retinopathy of prematurity (ROP) [36], LBW infants, particularly SGA term infants, rarely fulfill the ROP screening criteria (i.e., infants <1500 g, gestation >32 weeks) and thereby they do not routinely undergo eye assessments. These infants do not receive regular follow-ups, unlike premature infants [8]. Moreover, there is no consensus on following up to assess the neurodevelopmental outcomes for SGA infants.

It is important that physicians who care for SGA infants appreciate that this group of individuals has a higher risk of developing cardiovascular-related diseases. A long-term follow-up, similar to that recommended for ex-premature infants, would be helpful for monitoring the health statuses of these infants as they grow. Once such follow-ups become available, the option of having infants undergo serial retinal vascular assessments can be seriously considered. However, technology hurdles have to be overcome before serial retinal assessments can become standard practice in follow-up clinics.

The retinal cameras that are currently used on neonates are unsuitable for older infants. The ability of infants to keep their eyes still only briefly while undergoing eye assessments also makes this a challenging procedure [23]. Another possible difficulty in assessing the retinal microvasculature is our inability to account for refractive errors that could influence measurements [12]. In adults' and children's eyes, corrections can be applied to compensate for inaccuracies in the measurement of the retinal structure that occur because of refractive errors; these corrections require ocular biometric measurements, including axial length, anterior chamber depth, lens thickness, vitreous chamber depth and keratometry (measurements of the curvature of the anterior surface of the cornea) [15]. These calculations are more challenging in infants, however, because of the continued growth of their eyes [15]. Newer and more portable technology for retinal imaging is becoming increasingly available, and it is likely in the near future that such devices will be used to capture retinal images in young infants [11].

Conclusion

Retinal microvascular changes in LBW infants can be used as a risk stratification tool for future cardiovascular disease. Current research has proven that LBW individuals have abnormal retinal microvasculatures compared with the average

population. There is sufficient evidence to show the association between changes in the retinal microvasculature and cardiovascular disease. Future research could take the form of a longitudinal study of LBW individuals from infancy, with regular retinal microvascular assessments using new technology to demonstrate the mechanistic link between LBW and cardiovascular disease in adulthood. Such a study, which would non-invasively detect early microvascular changes through the serial assessments of retinal microvasculatures in LBW individuals, could improve our understanding and perhaps even explain Barker's hypothesis.

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The authors stated that there are no conflicts of interest regarding the publication of this article.

Received August 26, 2011. Revised September 17, 2011. Accepted September 23, 2011. Previously published online December 13, 2011.