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Is myopia another clinical manifestation of insulin resistance?

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ABSTRACT

Myopia is a multifactorial visual refraction disease, in which the light rays from distant objects are focused in front of retina, causing blurry vision. Myopic eyes are characterized by an increased corneal curvature and/or ocular axial length. The prevalence of myopia has increased in recent decades, a trend that cannot be attributed exclusively to genetic factors. Low and middle income countries have a higher burden of refractive error, which we propose could be a consequence of a shorter exposure time to a westernized lifestyle, a phenomenon that may also explain the rapid increase in cardiometabolic diseases, such as diabetes, among those populations. We suggest that interactions between genetic, epigenetic and a rapidly changing environment are also involved in myopia onset and progression. Furthermore, we discuss several possible mechanisms by which insulin resistance may promote abnormal ocular growth and myopia to support the hypothesis that insulin resistance and hyperinsulinemia are involved in its pathogenesis, providing a link between trends in myopia and those of cardiometabolic diseases. There is evidence that insulin have direct ocular growth promoting effects as well an indirect effect via the induction of insulin-like growth factors leading to decreases insulin-like growth factor-binding protein, also implicated in ocular growth.

Introduction

Myopia is a multifactorial visual refraction disease that results in a number of problems, which significantly affect quality of life, self-esteem, ocular health and work capacity [1–3]. In myopia, parallel rays of light from distant objects does not converge properly toward a point in the retina, but in front of it, causing the image to be out of focus. Myopic patients present with blurry distance vision [4] and with eyes characterized by steeper corneal curvature and/or longer axial length compared to emmetropes [5]. These longer eyes, in cases of high myopia (usually defined as greater than −6.0 Diopters) are predisposed to a number of morbidities which can cause blindness such as choroidal atrophy, retinal detachments, macular hemorrhage, choroidal neovascularization, cataract and primary open-angle glaucoma [6–8]. Myopia development and progression is related to both genetic and environmental factors [6] but its precise etiology is largely unknown [8]. Genome-wide analysis has identified 21 loci associated with this disease [8]. Nonetheless, epidemiological studies from some areas of the world, specially from low and medium incomes countries, have shown significant increases in the prevalence of myopia during the last decades, particularly in the second to third decade of life [6,9], which cannot explained only by genetic factors. A similar epidemiological trend has also been described for cardio-metabolic diseases (CMDs) in low and medium incomes countries [10,11], where the rapid process of urbanization and associated changes in lifestyle are thought to underlie the increased prevalence of abdominal obesity, insulin resistance (IR), metabolic syndrome (MetS) and diabetes mellitus type 2 (DM2). MetS is a cluster of cardiovascular risk factors associated with IR, easily detectable but largely under-detected [11].

Abbreviations: CVD, cardiovascular disease; CMD, cardio-metabolic disease; MetS, metabolic syndrome; DM2, diabetes mellitus type 2; IR, insulin resistance; BMI, body mass index; GH, growth hormone; INSR, insulin receptor; IRS1, insulin receptor substrate 1; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; GAG, glycosaminoglycan; OGTT, oral glucose tolerance test; CI, confidence intervals.

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Regulation of gene expression by environmental factors, denoted as epigenetic alterations, refers to reversible changes in gene function that are mitotically and/or meiotically heritable but do not involve changes in DNA sequence [12,13]. Epigenetics have a key role in the pathogenesis of MetS, cardiovascular disease (CVD), and DM2 [14], and it has recently been proposed that epigenetics may also have an important role in progression of many eye diseases [15]. Various extrinsic and intrinsic factors are known to influence the risk of myopia and these are summarized in Fig. 1 [16,17].

The hypothesis

We argue that regional differences in the prevalence of myopia and its recent rapid increase in low-middle income countries, are like CMD [10,11] a consequence of a rapid socioeconomic transition in these countries interacting with epigenetic factors and an underlying genetic susceptibility. We suggest that both diseases are clinical manifestation of insulin resistance and hyperinsulinism, and a greater susceptibility to which in the populations of developing countries is driving the observed trends in these regions.

Evaluation of the evidence

Epidemiological evidence

In 2004, the World Health Organization estimated that uncorrected refractive errors affected 153 million people over 5 years old, accounting for 49% of visually impaired individuals, myopia being the most frequent refractive error [18]. In Latin America it was also reported that uncorrected refractive errors affected more than 48 million people, of which 35.4% were affected in one eye and 18.6% in both [19,20]. In 2006, approximately 25% of the world's population had myopia [21], and an increasing prevalence has been reported, particularly in low- and middle-income countries [22,23].

Changes in the prevalence of myopia over diverse periods of time and in different ethnicities (white, black, Hispanic and others) are well documented, with recent data showing progressive increases in myopia [24]. The National Eye Institute of the United States projected trends for myopia for the period between 2010 and 2050 indicate larger increases in prevalence among Hispanics (from 2.7 to 8.6 million), Blacks (from 2.2 to 3.3 million) and "other" ethnic groups (from 1.7 to 4.6 million) compared to Whites (from 27.3 to 27.7 million) (Fig. 2) [25]. In the United Kingdom in 1998/1999 the prevalence of myopia was 27% in 50–54 years old and 16% in 55–59 years old, while the corresponding values reported in 2008–2010 were higher: 34% and 32%, respectively [26]. In Colombian cities, a prevalence of 1.45% was reported in 1995 [22], and 11.45% in 2009 [23]. In Hong Kong in 2004, 36.7% of 6–12 year old children had myopia [27], and in 2012 the prevalence amongst 6–12 year old children reached 47.5% [28]. In Taiwan between 1983 and 2000 there was a 10% increase in prevalence in 16–18 year-old adolescents [29].

Fig. 3 shows that there are marked regional differences in myopia rates. Asian countries show the highest presence of myopia; for example, prevalences of 86.1% in Taiwanese 18–24 years old [30] and 96.54% in Korean 19 years old [31] have been reported. There also appears to be a pattern of a greater burden of myopia in low- to middle-, compared to high-income countries [16,32,33]. A prevalence of 36.5% was reported in South India [34]; 51% in Burma (Myanmar) [35] and 59.9% in Kenyans [36] while in the USA and Australia it was 16.8% [37] and 17% [38], respectively. These regional differences persist after adjusting for age and gender [6], with a similar epidemiological pattern described in children (Fig. 4) and Asian youth showing the highest rates of myopia.

In children there also appears to be an urban-rural patterning of myopia prevalence. For example, children in rural China and Nepal showed substantially lower rates of myopia than their age matched in urban counterparts [39–41], potentially related to differences in lifestyle factors and their consequences. These factors may also explain the higher prevalence of refractive error in Finland between those born in the second half of the 20th century (21–30%) compared to those born in the first half (10%) [42].

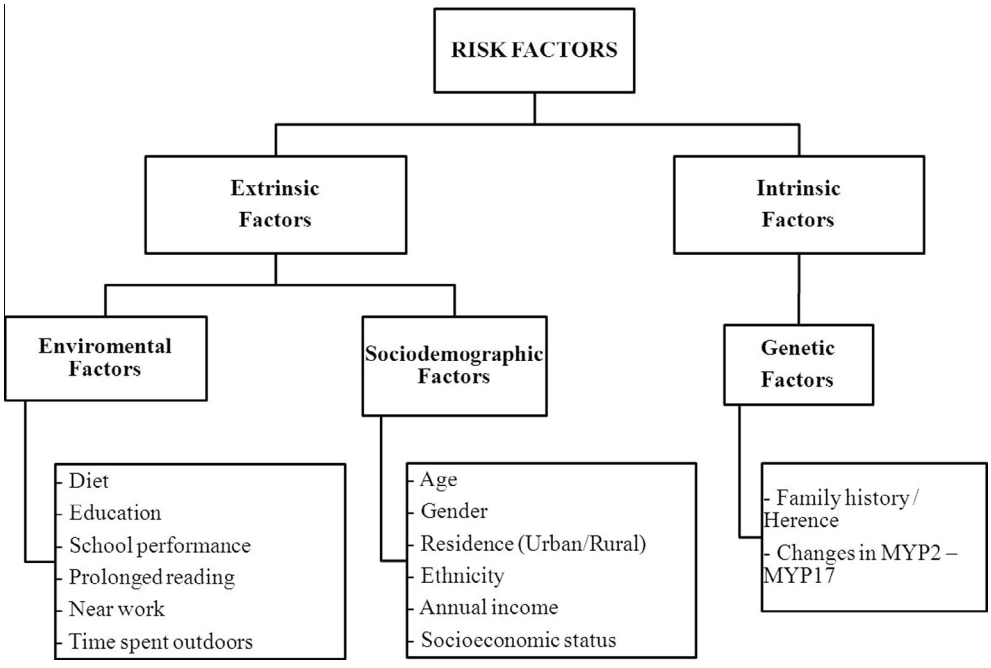

Fig. 1. Extrinsic and intrinsic factors related to myopia.