

# An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia

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## ABSTRACT.

The available evidence suggests that both genes and environment play a crucial role in the development of juvenile-onset myopia. When the human visual system is examined from an evolutionary perspective, it becomes apparent that humans, living in the original environmental niche for which our species is genetically adapted (as hunter-gatherers), are either slightly hypermetropic or emmetropic and rarely develop myopia. Myopia occurs when novel environmental conditions associated with modern civilization are introduced into the hunter-gatherer lifestyle. The excessive near work of reading is most frequently cited as the main environmental stressor underlying the development of myopia. In this review we point out how a previously unrecognized diet-related malady (chronic hyperinsulinaemia) may play a key role in the pathogenesis of juvenile-onset myopia because of its interaction with hormonal regulation of vitreal chamber growth.

**Key words:** myopia – form deprivation – insulin resistance – retinoic acid (RA) – retinoic acid receptors (RAR) – retinoid X receptors (RXR) – hunter gatherers – insulin like growth factor 1 (IGF-1) – insulin like growth factor binding protein 3 (IGFBP-3)

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Within the visual science community there is emerging consensus that the aetiology of juvenile-onset myopia involves both genetic and environmental elements (Wallman 1994; Mutti et al. 1996). However, the exact manner by which these two components interact to cause refractive errors remains elusive. Numerous studies have demonstrated that near work is related to myopia (Goldschmidt 1968; Angle & Wissmann 1980; Adams & McBrien 1992; Zylber-

mann et al. 1993), and a prospective study of microscopists, whose occupation requires excessive near work, has demonstrated that former emmetropes develop a progressive myopic shift during the course of their work (McBrien & Adams 1997). Further, animal studies verify that refractive errors can be induced through form deprivation and lens-induced defocus (Raviola & Wiesel 1985; Troilo & Wallman 1991; Norton & Siegart 1995). Hence, excessive near work represents the

single most frequently cited environmental factor associated with the development of juvenile-onset myopia.

Virtually all literate people in industrialized countries must do regular near work during childhood education, yet only a certain percentage (~25–35% of the US population) ultimately develop myopia (Angle & Wissmann 1980; Sperduto et al. 1983; Wingert 1995). Therefore, the development of juvenile-onset myopia must also involve genetic susceptibility to excessive near work, and/or another unrecognized environmental stressor or stressors must operate either synergistically with, or independently of, excessive near work to elicit the phenotypic expression of juvenile-onset myopia.

Previous aetiologic analyses of myopia have almost always evaluated proximate mechanisms and have not considered evolutionary or ultimate explanations for this refractive malady. The intent of the present analysis is to review the available literature on the aetiology and pathogenesis of myopia from an evolutionary perspective in order to facilitate an understanding of how environmental factors may interact with genetic factors to cause refractive errors. Furthermore, we point out how a previously unrecognized dietary factor may play a key role in the pathogenesis of juvenile-onset myopia via interaction with hormonally mediated regulation of vitreal chamber growth.

## The evolutionary perspective

There is little doubt that the development of myopia, in virtually all free-living wild vertebrates, represents a severe defect that in most cases would result in an early death. Except for certain species of non-visually dependent wild animals or domesticated animals, clear distance vision is required for escape from predators, location of food, recognition of other species members and awareness of environmental dangers and benefits. Consequently, any gene or genes that would elicit myopia would be lethal and rapidly eliminated by natural selection. Virtually all mammalian and bird eyes are usually slightly hyperopic at birth and move towards emmetropization during growth and development (Wallman 1990). The failure to appropriately match the focal length of the eye's optics with its axial length during growth and development produces myopia and, except for recent evidence with domesticated dogs (Mutti et al. 1999), appears to be unique to the human species.

The first members of the human genus (*Homo*) appeared in East Africa approximately 2.33 million years ago, and for all but the past 10,000 years (500 generations) since the advent of the agricultural revolution, all human ancestors have occupied the hunter-gatherer niche (Eaton & Konner 1984), a niche in which accurate distance vision was essential for survival (Nesse & Williams 1994). Despite the enormous selective pressures that would tend to eliminate myopic genes in humans living in a preagricultural, pretechnological society, myopia is extremely prevalent, affecting 25–35% of European descent populations (Angle & Wissmann 1980; Sperduto et al. 1983; Wingert 1995) and up to 50% or more of Asian descent populations (Au Eong et al. 1993). It has been suggested that, as primitive human societies acculturate, a relaxation of the selective pressures which would normally eliminate the gene or genes that evoke myopia has been responsible for its increased prevalence (Post 1962). It is certainly plausible that the natural selection pressures that had previously strongly selected against myopia in hunter-gatherers may have been slightly reduced with the advent of organized society. Moreover, these selective pressures would have been almost completely eliminated with the wide-scale availability of spectacle lenses in the 200

years since the industrial revolution. However, a number of lines of evidence strongly reject the notion that this recent (in evolutionary terms) relaxation of natural selection pressures could be responsible for the high incidence of myopia in modern, technological societies.

### Visual acuity in hunter-gatherers

Most human populations worldwide abandoned the hunter-gatherer mode of subsistence long before the advent of modern visual refractive procedures. However, a few isolated hunter-gatherer societies persisted into the early 20th century and, fortunately, were refracted by frontier physicians, optometrists and ophthalmologists. These data provide important glimpses into the natural status of the primordial human visual system before our species' recent departure from the environmental niche to which we are genetically adapted.

Using a retinoscope and cycloplegia, Holm (1937) refracted 2364 members (aged 20–65 years) of several hunter-gatherer tribes in Gabon (formerly French Equatorial Africa) in 1936. Of the 3624 eyes examined, only 14 were classified as myopic (nine eyes from  $-0.50$  to  $1.00$  D; five eyes from  $-3.00$  to  $-9.00$  D), thereby yielding a myopia incidence rate of 0.4%. Similar low rates for myopia were reported by Skeller (1954), who refracted the eyes of 775 Angmagssalik Eskimos as part of a comprehensive anthropological study carried out in 1954. Retinoscopy in conjunction with cycloplegia demonstrated that of the 1123 eyes examined, only 13 (1.2%) were classified as myopic (nine eyes =  $-1.00$  D; four eyes =  $-1.25$  D). The now classic and often cited work by Young et al. (1969) demonstrated that the rate of myopia in 508 recently acculturated Eskimos in Barrow, Alaska was largely a function of age. The right eyes of 131 subjects over 41 years of age yielded only two myopic eyes (1.5%), whereas examination of the right eyes of 284 subjects aged between 11 and 40 years indicated a 51.4% rate of myopia of at least  $-0.25$  D. It was suggested that this astounding difference in incidence rates of myopia between younger and older subjects may have resulted from the influence of increasing acculturation. Most of the older adults had grown up and lived most of their early lives in isolated communities in the traditional aboriginal Eskimo mode and consequently had little or no schooling, whereas many of their children and grandchildren grew up in

Barrow and had compulsory American style schooling. Young et al. (1969) concluded that the aetiology of myopia was largely due to environmental factors, specifically the excessive near work of reading that had only recently (within 2–3 generations) been introduced into this formerly traditional society of hunters and fishermen.

In a comparable study of 3677 recently acculturated Eskimos and Indians living in the Yukon and North West territories, Morgan & Munro (1973) demonstrated a similar age-dependent reduction in myopia to that of the Alaskan Eskimos. Figure 1 shows that the prevalence of myopia (~25–35%) in the younger subjects (aged 10–20 years) is similar to rates found in fully westernized countries, whereas the incidence of myopia (2–7%) in the older subjects (aged 30–60 years) more closely resembles rates of myopia among hunter-gatherers. This dramatic and rapid increase in the prevalence of myopia in a single generation (> 30 years versus < 20 years) occurred much too rapidly to reflect a sudden reduction in natural selection pressures. These data and that supplied by Young et al. (1969) fully support the notion that recently introduced, novel environmental stressors, perhaps interacting with previously latent myopia susceptibility genes, induce the phenotypic expression of refractive errors in distance vision. Morgan & Munro (1973), like Young et al. (1969) before them, suggested that increased schooling and hence increased near work in the younger subjects represented a novel environmental stressor that may have produced the dramatically higher rates of myopia in the younger subjects relative to their elders. Morgan & Munro (1973) hypothesized that dietary changes, especially increases in carbohydrate intake, might affect the structure of a growing eye. Cass (1966, 1973) has likewise reported low incidence rates of myopia in Eskimo adults when compared to those in children and suggested that increasing westernization, particularly the availability of store-bought food that is high in sugars and carbohydrate, may have been associated with the rapid increase of myopia noted in these aboriginal people.

Taken together, the few studies carried out in existing hunter-gatherer societies and in recently westernized hunter-gatherer groups indicate that the prevalence of myopia normally occurs in 0–2% of the population, and most refractive errors are less than  $-1.00$  D. Moderate

to high myopia ( $-3.00$  to  $-9.00$  D) is either non-existent or occurs in about one person out of a thousand. The available literature suggests that either emmetropia or a slight hypermetropia represent the normal human refractive state under the environmental conditions for which our current genes were selected. When the novel environmental conditions associated with modern civilizations are introduced into the hunter-gatherer lifestyle, these people rapidly develop (within a single generation) incidence rates for myopia that equal or exceed those in western societies. There is substantial evidence to show that increased near work brought on by civilization's requirement for literacy, perhaps interacting with latent myopia susceptibility genes, may sometimes induce myopia. However, modern civilization brings with it not only literacy, reading and increased near work, but other environmental factors that may have the potential to disrupt the emmetropization process during growth and development.

#### Refractive status in partially westernized populations

When the remnant hunter-gatherer societies of the far Northern Arctic westernized in the 20th century, the process was immediate, rapid and virtually all-inclusive. Many groups literally progressed from a Stone Age to a Space Age way of life in one or two generations. They rapidly adopted most of the trappings of fully modern societies with few or no intermediate steps (Schaefer 1977). In contrast, many of the less industrialized and less westernized societies that are still

present on the earth maintain traditional ways of life that are intermediate between fully modern western societies and hunter-gatherer societies. Quite often these less westernized societies have schools and formalized educational systems, and a majority of their populations are literate. Near work and reading are therefore requirements, yet the prevalence of myopia is frequently lower than in more industrialized countries and similar to rates found in hunter-gatherer societies. These studies suggest that other environmental factors in addition to near work may induce refractive errors in distance vision.

Garner et al. (1999) measured visual acuity in two groups of children of similar genetic background but with varying degrees of acculturation living in Nepal. Children ( $n=555$ ) residing in the urban environment of Kathmandu had a 21.7% prevalence of myopia, whereas Sherpa children ( $n=270$ ) living in the rural region of Solu Khumbu maintained a 2.9% rate of myopia. In the Sherpa children, the highest negative refractive error was  $-1.00$  D, while it was  $-6.50$  D in the Kathmandu population. Both groups of children had compulsory schooling. However, those in Kathmandu were thought, by the authors, to attend a more rigorous programme than those in Solu Khumbu and hence more demands may have been placed upon their near vision. It should be noted that Kathmandu is a large city in which all western-type goods, including modern, processed foodstuffs are available, whereas Khumjung is an isolated village without electric power, television and other urban

trappings. Consequently, Garner et al. (1999) suggested that other environmental factors besides excessive near work may have contributed towards the differences in the rates of myopia they observed. In an earlier study of 977 school children (6–17 years of age) on the remote South Pacific island of Vanuatu, Garner et al. (1985) found that only 1.3% of subjects had myopia greater than  $-0.25$  D, despite engaging in about 8 hrs of school work per day. These researchers concluded that genetic factors might have been responsible for the extremely low myopic rates in this group; however, they did not rule out environmental factors other than near work.

Lewallen et al. (1995) studied the prevalence of refractive errors in students ( $n=352$ ) attending a teacher's college in Malawi in sub-Saharan Africa. The students had originally come from rural areas where they had completed primary school and at least 2 years of secondary school, and all had engaged in regular reading. The prevalence of myopia was quite low, with only 4.1% of the population exhibiting mean spherical equivalents more negative or equal to  $-0.50$  D. Collectively, these studies indicate that, in rural populations, the near work of schooling does not elicit myopia incidence rates much beyond rates found in hunter-gatherer societies. It may be that the quantity and intensity of near work brought on by rural schooling is less than with urban schooling and hence produces lower rates of myopia. It could also be argued that additional environmental factors in urban areas, which are not present in rural areas, may influence the development of myopia.

In contrast to literate populations raised or living in rural areas, a number of studies have reported the incidence of myopia in illiterate populations living in both urban and rural areas. The percentage of myopes among urban illiterates in Cairo, Egypt has been reported as ranging from 11 to 39% in four groups totaling 1173 subjects (Post 1962). More recently, Wong et al. (1993) demonstrated an 18.4% rate of myopia among urban Hong Kong fishermen ( $n=152$ ) who had never attended school. In contrast to illiterate urban populations, the rate of myopia (2.4%) in illiterate rural groups (Lewallen et al. 1995) is similar to the rates found in hunter-gatherer societies (Holm 1937; Skeller 1954; Cass 1966; Young et al. 1969; Cass 1973; Morgan & Munro 1973). It is certainly possible that illiter-

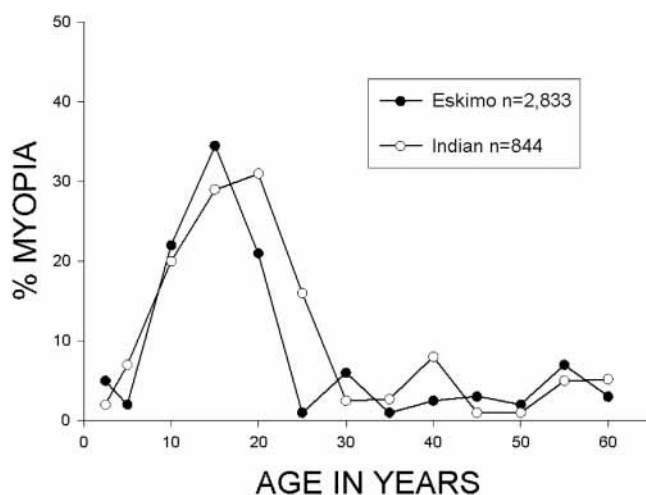


Fig. 1. Moderate myopia (1.00–5.00 D) by age in Indians and Eskimos of the Yukon and North West territories. Adapted from Morgan et al. (1973).

ate urban workers may engage in other near work besides reading that could potentially evoke myopia. However, anthropological studies of hunter-gatherers, particularly Eskimos, have shown that while both women and men may engage in near work (sewing, tool making, artwork) for hours on end in dimly lit snow houses during the long arctic winter (Stefansson 1919), they do not develop myopia (Skeller 1954; Cass 1966; Young et al. 1969; Cass 1973; Morgan & Munro 1973). Furthermore, because three peculiarities of the printed page (a narrow range of luminance, achromaticity of text, and high spatial frequency of text) reduce the activity of non-foveal retinal neurons during reading, it has been argued that the near work of reading is a more potent inducer of form deprivation and hence the development of myopia than other types of near work (Chew & Balakrishnan 1992). These studies of the incidence rates of myopia among illiterate groups again suggest that environmental factors as well as excessive near work play a part in the aetiology of myopia.

## Dietary induced hyperinsulinaemia and myopia

### Dietary carbohydrates in hunter-gatherers

When hunter-gatherer societies of the 20th century left their Stone Age existence behind, they not only became literate and began reading within one or two generations, but they characteristically altered the type of food they had previously consumed (Schaefer 1971; Schaefer 1977). In their study of 229 hunter-gatherer societies, Cordain et al. (2000) found that although refined cereals and sugars were rarely if ever consumed by groups living in their traditional manner, these foods quickly became dietary staples following western contact. Schaefer (1971; 1977) has shown that, in two Eskimo groups undergoing western acculturation, the per capita consumption of sugar in all forms increased from 11.8 kg in 1959 to 47.4 kg in 1967. The same groups' per capita consumption of cereals and flour products increased from 71.0 kg in 1959 to 80.0 kg in 1967. Prior to western contact, neither of these carbohydrates was ever consumed (Stefansson 1919).

Hunter-gatherer diets are typically characterized by high levels of protein,

moderate levels of fat and low levels of carbohydrate when compared to modern western diets (Cordain et al. 1999). The carbohydrates present in hunter-gatherer diets are of a low glycaemic index: they are slowly absorbed and produce a gradual and minimal rise in plasma glucose and insulin levels when compared to the sugars and refined starches in western diets (Thorburn et al. 1987a; Thorburn et al. 1987b). The glycaemic index is influenced by the particle size, processing technique, and relative fibre, protein and fat content of the carbohydrate food. The glycaemic index of mixed meals is determined by multiplying the percentage of total meal carbohydrate by its glycaemic index and summing these values for all foods (Wolever et al. 1991). The total glycaemic load is the (glycaemic index  $\times$  carbohydrate content) of each food.

The addition of high glycaemic load carbohydrates to the diet represented a near universal change in the nutritional patterns of hunter-gatherer populations as they made the transition from forager to modern consumer in the 20th century (Brand & Colagiuri 1994; Eaton et al. 1997). Studies of recently acculturated hunter-gatherer populations that have adopted western dietary patterns frequently show high levels of hyperglycaemia, insulin resistance, hyperinsulinaemia and type II diabetes (Ebbesson et al. 1998; Daniel et al. 1999). Conversely, hunter-gatherer populations in their native environments rarely exhibit these symptoms (Schaefer 1969; Merimee et al. 1972; Spielman et al. 1982; O'Dea 1984).

### The secular increase in high glycaemic load foods in industrialized countries

Hunter-gatherer populations that adopted modern foods in the 20th century were subjected to an immediate change from low glycaemic to high glycaemic load carbohydrates that occurred shortly after western contact began. In industrialized countries, this dietary shift occurred more slowly over the 200 or so years since the advent of the industrial revolution as more and more refined sugars were gradually included in the diet along with increasingly greater levels of refined cereals. Although highly refined sugars and cereals are common elements of the modern urban diet, these carbohydrates were eaten sparingly or not at all by the average citizen in 17th and 18th century Europe and only started to become available to the masses after the in-

dustrial revolution (Teuteberg 1986). In England, the per capita consumption of sucrose has risen steadily from 6.8 kg in 1815 to 54.5 kg in 1970 (Cleave 1974). Although refined cereals represent the highest percentage of carbohydrate in the western diet, this has not always been the case (Cordain et al. 1999). Only with the widespread introduction of steel roller mills in the late 19th century (~1880) did fibre-depleted wheat flour of a low extraction ( $\leq 70\%$ ) become widely available (Cleave 1974). Hence, over the last 200–250 years the average glycaemic load of foods in urban areas of industrialized countries has risen steadily, primarily because of increasing consumption of refined cereals and sugars (Cleave 1974). Populations living in more rural areas of both industrialized and non-industrialized countries typically have limited access to processed foods, sugars and refined cereal products (Trowell 1985). Accordingly, their diets are usually comprised of locally grown, minimally processed foods, and hence the glycaemic load of these traditional foods is generally lower than highly processed and packaged foods typically available in urban markets (Foster-Powell & Brand Miller 1995). Table 1 shows the glycaemic index and glycaemic load of both traditional and processed foods.

### Hyperinsulinaemia and the consumption of high glycaemic load foods

Over the past 20 years, accumulating evidence has shown that the consumption of foods with a high glycaemic load, such as processed foods containing refined starches and sugars, promotes the development of both acute and chronic hyperinsulinaemia. Numerous studies have demonstrated that the addition of sucrose to the diet of both normal (Reiser et al. 1979; Coulston et al. 1983) and hyperinsulinaemic subjects (Reiser et al. 1981) causes an increase in postprandial insulin levels. Larger intakes of sucrose (35% total energy) have been shown to decrease insulin sensitivity (Beck-Nielsen et al. 1978), and impaired insulin binding also occurs from high fructose feedings (Beck-Nielsen et al. 1980; Dirlwanger et al. 2000). Further, dietary intervention studies using low glycaemic loads are known to improve insulin sensitivity (Frost et al. 1998), and low glycaemic loads reduce the risk of type II diabetes (Salmeron et al. 1997). In contrast, intervention studies manipulating dietary fatty acids have shown no beneficial ef-

fects upon insulin metabolism (Vessby 2000), nor have dietary interventions been able to show deleterious effects upon insulin sensitivity when total fat was increased from 20 to 40% energy (Riccardi & Rivellese 2000). When dietary manipulations lead to weight loss, insulin sensitivity is generally improved (Klein 2001). Collectively, these studies show that increasing consumption of high levels of refined carbohydrates, particularly under hyper caloric conditions, is partially responsible for the worsening of glycaemic control, which may in turn promote insulin resistance and compensatory hyperinsulinaemia (Reaven 1994).

**Hyperinsulinaemia and insulin like growth factor (IGF) and IGF binding proteins**

The metabolic ramifications of dietary induced perturbations of insulin action are diverse and complex. It has recently been demonstrated that the compensatory hyperinsulinaemia that characterizes adolescent obesity chronically suppresses hepatic synthesis of insulin like growth factor binding protein-1 (IGFBP-1), which in turn serves to increase free insu-

lin like growth factor-1 (IGF-1), the biologically active part of circulating IGF-1 (Nam et al. 1997; Attia et al. 1998). Circulating levels of insulin and IGFBP-1 vary inversely throughout the day, and the suppression of IGFBP-1 by insulin (Brismar et al. 1994), and hence elevation of free IGF-1, may be maximal when insulin levels exceed 70–90 pmol/L (Holly 1991). Additionally, growth hormone (GH) levels fall via negative feedback of free IGF-1 on GH secretion, resulting in reductions in IGFBP-3 (Attia et al. 1998). These experiments show that both acute (Attia et al. 1998) and chronic (Nam et al. 1997; Attia et al. 1998; Wong et al. 1999) elevations of insulin result in increased circulating levels of free IGF-1, a potent stimulator of growth in all tissues. Because consumption of refined sugars and starches promotes both acute and chronic hyperinsulinaemia, these common foods in the western diet have the potential to elevate free IGF-1 and lower IGFBP-3 in all peripheral tissues, including scleral chondrocytes and fibroblasts.

The reductions in IGFBP-3 stimulated by elevated serum insulin levels (Nam et al. 1997; Attia et al. 1998) or by acute ingestion of high glycaemic carbo-

hydrates (Liu 2000) may also contribute to unregulated cell proliferation in scleral tissue. Insulin like growth factor binding protein-3 has been shown to act as a growth inhibitory factor in murine knockout cells lacking the IGF receptor (Valentinis et al. 1995). Accordingly, in this capacity IGFBP-3 is inhibitory to growth by preventing IGF-1 binding to its receptor. Consequently, enhanced scleral growth may result synergistically from both elevations in free IGF-1 and reductions in IGFBP-3.

**Hyperinsulinaemia and retinoid receptors**

Retinoids are natural and synthetic analogues of vitamin A that inhibit cell proliferation and promote apoptosis (programmed cell death) (Evans & Kay 1999). The body's natural retinoids (trans retinoic acid and 9 cis retinoic acid) act by binding two families of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Retinoid receptors, in turn, activate gene transcription by binding as RAR/RXR heterodimers or RXR homodimers to retinoic acid response elements located in the promoter regions of target genes whose function is to limit growth in many cell types (Yang et al. 2001). It has recently been es-

**Table 1.** Glycaemic indices and loads (glycaemic index × carbohydrate content in 10 g portions) of refined western foods and unrefined traditional foods (glucose as reference standard = 100), adapted from Foster-Powell & Brand Miller (1995).

Food	Western refined foods		Food	Unrefined traditional foods	
	Glycaemic index	Glycaemic load		Glycaemic index	Glycaemic load
Rice crispie cereal	88	77.3	Parsnips	97	19.5
Jelly beans	80	74.5	Baked potato	85	18.4
Cornflakes	84	72.7	Boiled millet	71	16.8
Lifesavers	70	67.9	Boiled broad beans	79	15.5
Rice cakes	82	66.9	Boiled couscous	65	15.1
Table sugar (sucrose)	65	64.9	Boiled sweet potato	54	13.1
Shredded wheat cereal	69	57.0	Boiled brown rice	55	12.6
Graham crackers	74	56.8	Banana	53	12.1
Grapenuts cereal	67	54.3	Boiled yam	51	11.5
Cheerio cereal	74	54.2	Boiled garbanzo beans	33	9.0
Rye crispbread	65	53.4	Pineapple	66	8.2
Vanilla wafers	77	49.7	Grapes	43	7.7
Corn chips	73	46.3	Kiwi fruit	52	7.4
Mars bar	68	42.2	Carrots	71	7.2
Stone wheat thins	67	41.9	Boiled peas	48	6.8
Shortbread cookies	64	41.9	Boiled beets	64	6.3
Granola bar	61	39.3	Boiled kidney beans	27	6.2
Angel food cake	67	38.7	Apple	39	6.0
Bagel	72	38.4	Boiled lentils	29	5.8
Doughnuts	76	37.8	Pear	36	5.4
White bread	70	34.7	Watermelon	72	5.2
All bran cereal	42	32.5	Cherries	22	3.7
Whole wheat bread	69	31.8	Peach	28	3.1
Croissant	67	31.2	Peanuts	14	2.6

tablished that IGFBP-3 is a ligand for the RXR alpha nuclear receptor and that IGFBP-3 enhances RXR-RXR homodimer mediated signaling (Liu et al. 2000). Studies in knockout rodents show that the RXR alpha gene is required for actions of the two endogenous retinoic acid ligands (trans retinoic acid and cis 9 retinoic acid) (Chiba et al. 1997; Wendling et al. 1999), and both RXR alpha agonists and IGFBP-3 are growth inhibitory in many cell lines (Grimberg & Cohen 2000).

Additionally, RXR alpha receptors are preferentially found in periocular mesenchyme (Mori et al. 2001) and scleral chondrocytes (Fischer et al. 1999). Consequently, low plasma levels of IGFBP-3 induced by hyperinsulinaemia may reduce the effectiveness of the body's natural retinoids in activating genes that would normally limit scleral cell proliferation.

**Proposed model of juvenile-onset myopia**

Numerous studies have conclusively demonstrated that, in juvenile-onset myopia, abnormal axial elongation of the eyeball is the major structural change that causes refractive errors in distance vision (Zadnik et al. 1993; Lin et al. 1996; Lam et al. 1999). Both animal (Raviola & Wiesel 1985; Troilo & Wallman 1991; Norton & Siegwart 1995) and human (Meyer et al. 1999) studies suggest that the absence of a clear retinal image during critical periods of postnatal development triggers an axial elongation of the vitreal chamber producing a so-called form deprivation myopia. Furthermore, in animal models of form deprivation myopia, there is a characteristic active remodelling and differentiation of scleral cartilage brought about by proliferation of both scleral chondrocytes and fibroblasts that causes the axial elongation of experimental myopia (Seko et al. 1995; Kusakari et al. 1997; Gentle and McBrien 1999).

The chemical messenger linking retinal image clarity to appropriate growth rates in scleral tissue has recently been shown to be retinoic acid synthesized by both the retina and choroid (Bitzer et al. 2000; Mertz & Wallman 2000). Reduced choroidal synthesis of retinoic acid increases scleral growth, whereas increased synthesis of retinoic acid slows growth (Mertz & Wallman 2000). Consequently, excessive near work may induce myopia because form deprivation causes the choroid to produce too little retinoic acid.

Compensatory hyperinsulinaemia, via

its lowering of plasma IGFBP-3 and subsequent reduction in RXR homodimer signaling, may augment scleral tissue growth by attenuating the ability of endogenous retinoids to activate genes that would normally limit scleral cell proliferation. Additionally, diet-induced hyperinsulinaemia chronically elevates IGF-1, which may operate synergistically with plasma reductions in IGFBP-3 to accelerate scleral tissue growth. Figure 2 schematically represents our model of juvenile-onset myopia.

**Corroborative evidence**

The recent realised fact that hyperinsulinaemia elicits an abnormal increase in circulating levels of free IGF-1 has ramifications that extend beyond the accelerated growth of scleral tissue and the development of myopia. Free IGF-1 is a potent mitogen for virtually all of the body's tissues (Ferry et al. 1999), as well as a stimulant for increased growth velocity during puberty (Juul et al. 1995). Numerous studies have confirmed that low levels of IGF-1 are associated with reduced stature (Blum et al. 1993; Lindgren et al. 1996) and conversely high levels are known to result in increased stature (Gourmelen et al. 1984; Binoux & Gourmelen 1987; Blum et al. 1993). Human recombinant IGF-1 therapy has also been shown to improve linear growth (Camacho-Hubner et al. 1999). Further, hyperinsulinaemic subjects with elevated levels

of free IGF-1 are more sexually mature than subjects with superior insulin sensitivity (Travers et al. 1998; Wong et al. 1999), and recombinant IGF-1 therapy has been shown to accelerate the tempo of puberty in a primate model (Wilson 1998). Recently, Wong et al. (1999) provided metabolic evidence showing that black American girls were more advanced in their pubertal development and taller than a comparable group of white American girls. Further, circulating levels of IGFBP-1 were lower in the black group than in the white group, while circulating levels of insulin and free IGF-I were higher in the black group than in the white group. This suggests that the metabolic cascade (insulin resistance – hyperinsulinaemia – decrease in hepatic IGFBP-I production – increase in circulating free IGF-I – accelerated growth) may take place. Collectively, this evidence supports the view that increased levels of IGF-1 act systemically to cause increased stature and an earlier onset of puberty.

As consumption of refined carbohydrates has the capacity to acutely and chronically elevate insulin levels, which in turn increase circulating levels of free IGF-1, it might be assumed that epidemiological studies would indicate a relationship between the consumption of high glycaemic foods and increased stature and earlier onset of puberty. Further, it might be expected that myopes would tend to consume foods of a higher glyca-

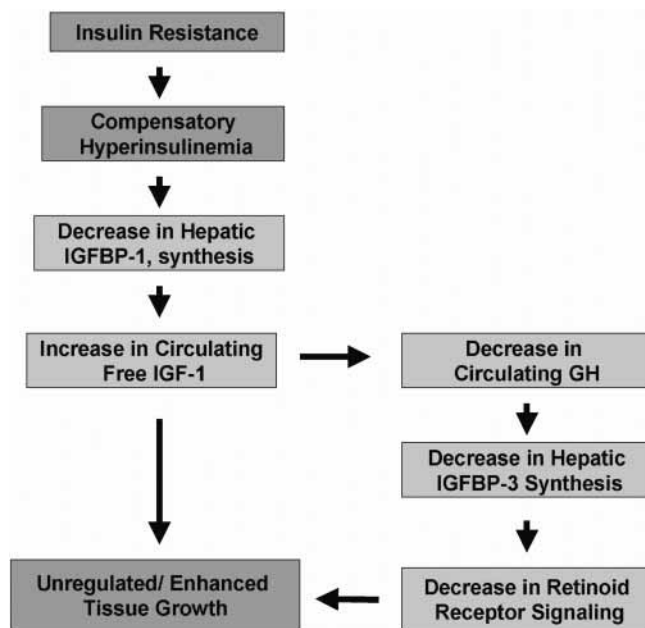


Fig. 2. Schematic diagram depicting how compensatory hyperinsulinaemia facilitates unregulated scleral tissue growth via increases in IGF-1 and attenuation of the retinoic acid signal.

emic index, be taller, have an earlier pubertal age and present more frequently with type II diabetes than non-myopes.

Industrialized countries have witnessed a steady and progressive secular increase in stature and reduction in pubertal age over the 200–250 years since the advent of the industrial revolution (Malina 1990). The standard explanation for this trend has been that improvements in nutrition, particularly increases in protein and fat from animal sources, and improvements in hygiene operate to increase stature (Roche 1979). In contrast to this explanation, Ziegler (1967, 1969) has demonstrated that the secular increase in stature correlates highly with sucrose consumption in the UK, Japan, Netherlands, Sweden, Norway, Denmark, the USA and New Zealand. In support of Ziegler's hypothesis, Schaefer's (1970) data on recently acculturated Eskimos shows that during the 30-year period (1938–68) when a several fold increase in the consumption of sucrose and refined carbohydrates occurred, the group's average stature increased (by 4.6 cm in men and 2.9 cm in women), while its average age of onset of puberty (by –2.0 years). Moreover, animal protein intake during the period declined by 60%. Since then, a study examining the relationship of dietary fibre to the age of menarche in girls from 46 countries has demonstrated a strong positive correlation ( $r = 0.84$ ) (Hughes & Jones 1985). Because dietary fibre is inversely related to the glycaemic index (Foster-Powell & Brand Miller 1995); Salmeron et al. 1997), this relationship supports the hypothesis that increasing consumption of refined carbohydrates may accelerate pubertal development. Further, multiple studies have demonstrated that hyperinsulinaemia and insulin resistance occurs more often in women with premature menarche than in compared to women with normal menarche (Loffer 1975; Ibanez et al. 1998). Taken together, these studies indicate that intakes of high glycaemic carbohydrates correlate well in time and space with the secular trends for increased stature and decreased pubertal age.

Many surveys of myopes have shown them to be taller than non-myopes (Johansen 1950; Gardiner 1954; Pendse & Bhave 1954; Gardiner 1955; Gardiner 1956a; Benoit 1958; Gardiner 1958; Douglas et al. 1967; Scholz 1970; Johnson et al. 1979; Krause et al. 1982; Teikari 1987; Teasdale & Goldschmidt 1988). However, not all surveys have shown my-

opes as taller (Young et al. 1954; Sorsby et al. 1961; Gawron 1981; Parssinen et al. 1985; Rosner et al. 1995). In a study examining the refractive errors in an isolated Labrador community of Eskimos, mixed Eskimo-Caucasians, and Caucasians, Johnson et al. (1979) demonstrated that the children of the Eskimos and mixed race population were taller than their parents, had greater axial eyeball lengths, and were more myopic. These researchers showed that the rise in the incidence of myopia, increased axial eyeball length and stature occurred coincidentally with the increasing volume of store foods (mainly in the form of carbohydrates) that had become available in the preceding 30 years. Gardiner (1955, 1956a, 1964) has extensively studied the growth patterns of myopes and has concluded that 'myopic children grow and mature faster than other children and that the more myopic they are, the more these trends are exhibited'. Figure 3 demonstrates differences in stature among 3–16 year-olds, comparing high and moderate myopes with a control group. Figure 4 shows that the body mass index in myopes is also higher than in non-myopes. Gardiner has not only shown that myopic children are taller than their non-myopic counterparts, but has presented both cross sectional (Gardiner 1954) and prospective (Gardiner 1964) evidence of an earlier age of menarche in female myopes. This evidence has been corroborated by two other large epidemiological studies (Douglas et al. 1967; Scholz 1970) showing that myopes were both taller and had an earlier age of menarche than non-myopes.

Gardiner (1964) suggested that accelerated growth patterns in myopes were linked to their refractive errors, and that diet may represent an underlying environmental factor common to both the development of myopia and generalized accelerated growth. In a number of studies, Gardiner (1956a, 1956b) indicated that myopes consumed significantly lower amounts of animal protein than non-myopes. Further, he was able to show that by increasing the level of animal protein in the diets of myopic children, the progression of their myopia slowed when compared to a control group receiving no dietary modification during a year long experiment (Gardiner 1958). Dietary protein generally results in lower rises in both plasma glucose and insulin when compared to carbohydrate (Brand Miller et al. 2000). Hence, it is possible that the increased animal protein levels in Gardiner's 1958 experiment may have attenuated postprandial and chronic insulin levels in his subjects, thereby reducing free IGF-1, elevating IGFBP-3 and enhancing RXR signaling which in turn slowed scleral axial growth and the progression of myopia. The benefits of reduced intake of carbohydrate and increased intake of animal protein on the progression of human myopia have also been reported elsewhere (Walkingshaw 1964).

Observations from Scandinavian studies (Fledelius 1983; Fledelius 1986; Fledelius et al. 1990) demonstrating increased incidence of myopia among type II adult diabetics compared to non-diabetics support the hormonal cascade linking insulin resistance to myopia. In

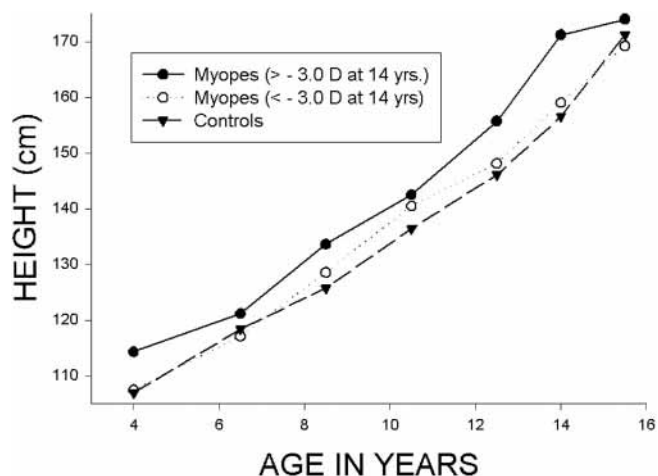


Fig. 3. Height from ages 3–16 years in myopes ( $> -3.0$  D at age 14 years;  $n = 74$ ), myopes ( $< -3.0$  D at age 14 years;  $n = 98$ ) and non-myopic controls ( $n = 277$ ). Adapted from Gardiner (1954).

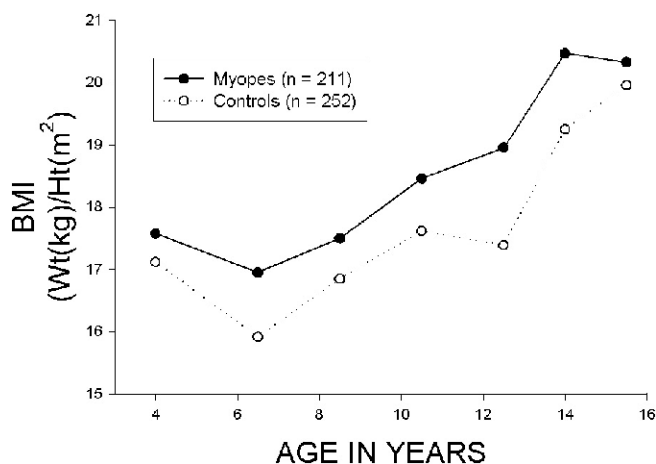


Fig. 4. Body mass index (BMI) from ages 3–16 years in myopes (myopia developed at any age) and non-myopic controls. Adapted from Gardiner (1954).

the diabetic group, 37.9% of the subjects were myopic compared to 27.5% in the non-diabetic group (Fledelius 1983).

Although diseases of insulin resistance including type II diabetes have an important environmental aetiological component, they also have a crucial genetic basis (Neel et al. 1998; Barroso et al. 1999). Population studies have demonstrated that people of Asian and Chinese descent tend to be more insulin resistant than people of European descent (Beischer et al. 1991; King & Rewers 1993). The prevalence of myopia is also higher in Asian populations than it is in European populations (Au Eong et al. 1993; McCarty et al. 1997); it is possible that the higher rates of myopia in Asian populations may, in part, be due to their increased genetic susceptibility to insulin resistance. Although some population studies have shown Asian groups to be shorter than people of European descent (Duignan et al. 1975; Chin et al. 1997), these data do not necessarily invalidate the presumed relationships between insulin resistance, myopia and height because of other known genetic determinants of adult stature, independent of insulin resistance, which vary between racial groups (Katzmarzyk & Leonard 1998). Hence, the comparison of stature between Asian myopes and non-myopes would represent a more logical and meaningful evaluation of the relationships between insulin resistance, adult stature and the development of myopia.

A number of human studies have shown that myopes have more dental caries than non-myopes (Goldstein et al. 1971; Hirsch & Levin 1973), and that the degree of myopia may be related to the caries inci-

dence (Hirsch & Levin 1973). Recently, it has been shown that progressive myopes have higher amounts of dental caries than stable myopes (Edwards & Chan 1995). The mechanistic nature of this relationship remains obscure. However, as we now know that high glycaemic load carbohydrates, such as sucrose and refined cereal products made with sucrose, may induce hyperinsulinaemia, and that hyperinsulinaemia increases free IGF-1, lowers IGFBP-3 and reduces RXR signaling, we may suppose that the causal mechanism probably involves sucrose's well known cariogenic effect and its hyperinsulinaemic effect.

High sucrose, low protein diets in both rabbits (Gardiner & MacDonald 1957) and rats (Bardiger & Stock 1972) have been shown to lower the degree of hypermetropia (i.e. produce refractive changes in a myopic direction); this had not proved possible with a sucrose free diet (Bardiger & Stock 1972). In summary, these studies suggest that high glycaemic load carbohydrate diets may induce permanent changes in the development and progression of refractive errors, particularly during periods of growth.

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