An Evolutionary Analysis of the Etiology and Pathogenesis of Juvenile-Onset Myopia

By

Loren Cordain[1], Ph.D., S. Boyd Eaton[2], M.D., Jennie Brand Miller[3], Ph.D., Staffan Lindeberg[4], M.D., Ph.D., Clark Jensen[5], O.D.

[1]Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523; [2]Departments of Radiology and Anthropology, Emory University, Atlanta GA; [3]Department of Biochemistry, University of Sydney, New South Wales, Australia; [4]Department of Community Medicine, University of Lund, Sweden, [5]Jensen Optometrists, Grinnell, IA 50112

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 (hunter-gatherer) for which our species is genetically adapted, 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 hyperinsulinemia) may play a key role in the pathogenesis of juvenile-onset myopia because of its interaction with hormonal regulation of vitreal chamber growth.

Keywords: 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)

INTRODUCTION

Within the visual science community there is an emerging consensus that the etiology of juvenile-

onset myopia involves both genetic and environmental elements (Mutti et al. 1996, Wallman 1994). 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 (Adams & McBrien 1992, Angle & Wissmann, Goldschmidt 1968; Zylbermann 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 (Norton & Siegwart 1995; Raviola & Wiesel 1985; Troilo & Wallman 1991). 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 U.S. 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 etiologic 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 etiology 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. Further 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.

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 eyes' 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 pre-agricultural, pre-technological society, myopia persists in extremely high prevalence rates: 25-35% of European descent populations (Angle & Wissmann 1980, Sperduto et al. 1983, Wingert 1995) and up to 50% or more in Asian descent populations (Au Eong et al. 1993). It has been suggested that a relaxation of the selective pressures, that would normally eliminate the gene or genes that evoke myopia, is responsible for the increased prevalence of myopia as primitive human societies acculturate (Post 1962). It is certainly plausible that the natural selection pressures that previously had 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 past 200 years since the industrial revolution. However, there are a number of lines of evidence to strongly reject the notion that this recent (in evolutionary terms) relaxation of natural selection pressures could have been responsible for the high incidence of myopia now present in modern, technological societies.

Visual Acuity in Hunter-Gatherers

Most worldwide human populations abandoned the hunter-gatherer mode of subsistence long before the advent of modern visual refractive procedures, however a few isolated hunter-gather 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 2,364 members (aged 20-65 yr) of several hunter-gatherer tribes in Gabon (formerly French Equatorial Africa) in 1936. Of the 3,624 eyes examined, only 14 were classified as myopic (9 eyes from – 0.50 D to – 1.00 ; 5 eyes from –3.00 D 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 1,123 eyes examined only 13 (1.2%) were classified as myopic (9 eyes = – 1.00 D; 4 eyes = – 1.25 D). In the now classic and often cited work, Young et al. (1969) demonstrated that the rate of myopia in 508 recently acculturated Eskimos in Barrow, Alaska was largely a function of age. In the 131 right eyes of subjects greater than 41 years of age, there were only two myopic eyes (1.5%), whereas in the 284 subjects aged between 11 and 40 years, 51.4% showed

at least –0.25 D of myopia in the right eye. 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 etiology 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 3,677 recently acculturated Eskimos and Indians living in the Yukon and Northwest territories, Morgan and Munro (1973) demonstrated the same age dependent reduction in myopia that was also apparent in the Alaskan Eskimos (**Figure 1**). **Figure 1** shows that the prevalence of myopia (~25 – 35 %) in the younger subjects (aged 10 – 20 years) is similar to values found in fully westernized countries, whereas the incidence of myopia (2 – 7 %) in the older subjects (aged 30 – 60 years) more closely resembles values in hunter gatherers. This dramatic and rapid increase in the prevalence of myopia in a single generation (> 30 years vs. < 20 years) occurred much too rapidly to reflect a sudden reduction in natural selection pressures. This figure as well as Young et al.'s (1969) data 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 et al. (1973), like Young et al. (1969) before him, 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. Additionally, Morgan et al. (1973) hypothesized that dietary changes, especially increases in carbohydrate intake, might affect the structure of a growing eye. Cass

(1966, 1973) has also reported low incidence rates of myopia in Eskimo adults when compared to children and suggested that increasing westernization, particularly the availability of store food, 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 hunter-gatherer societies or in recently westernized hunter-gatherers 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 D 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 native environmental conditions for which our current genes were selected. When the novel environmental conditions associated with modern civilizations are introduced into the hunter-gather 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, it was immediate, rapid and virtually all-inclusive. Many of these people literally went from the Stone Age to the Space Age in 1-2 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 many 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 the population are literate – hence near work and reading are a requirement, yet the prevalence of myopia is frequently lower than in more industrialized countries and similar to values in hunter-gatherer societies. These studies are suggestive that other environmental factors in addition to near work may induce refractive errors in distance vision.

Garner et al. (1999) measured the 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 have a more rigorous program 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 trappings of more urban areas. Consequently, Garner et al. (1999) suggested that other environmental factors besides excessive near work may have been operative to produce the differences in the myopia rates they observed. In an earlier study of 977 school children (6 to 17 years of age) on the remote South Pacific island nation of Vanuatu, Garner et al. (1985) found that only 1.3 % of the subjects had myopia greater than – 0.25 D despite engaging in about 8 hours 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 two years of secondary school, and all had engaged in regular reading. The prevalence of myopia was quite low, and only 4.1 % of the population exhibited mean spherical equivalents that were 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 values found in hunter-gatherer societies. It could be argued that the amount and intensity of near work brought on by rural schooling is less than urban schooling and hence produces lower rates of myopia, or additional environmental factors in urban areas not present in rural areas may also 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 to range from 11 to 39 % in four groups totaling 1,173 subjects (Post 1962). More recently, Wong et al. (1993) demonstrated an 18.4 % rate of myopia in urban Hong Kong fishermen (n = 152) who had never attended school. In comparison to urban illiterates, the population rate of myopia (2.4 %) in rural illiterates (Lewallen et al. 1995) is similar to values found in hunter-gatherer societies (Cass 1966, Cass 1973, Holm 1937, Morgan & Munro 1973, Skeller 1954, Young et al 1969). It certainly is possible that illiterate 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 both women and men may engage in near work (sewing, tool making, artwork) for hours on end in dimly lighted snow houses during the long arctic winter (Stefansson 1919), yet do not develop myopia (Cass 1966, Cass 1973, Morgan & Munro 1973, Skeller 1954, Young et al 1969). Further, 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). Collectively these studies of myopia incidence rates in illiterates are again suggestive that environmental factors in addition to excessive near work may be operative in the etiology of myopia.

DIETARY INDUCED HYPERINSULINEMIA 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 1-2 generations, they characteristically altered the type of food they had previously consumed (Schaefer 1971, Schaefer 1977). Although refined cereals and sugars were rarely if ever consumed by 229 hunter-gather societies living in their traditional manner (Cordain et al. 2000), these foods quickly became dietary staples following western contact. Schaeffer (1971, 1977) has shown that the per capita consumption of sugar in all forms increased from 11.8 kg in 1959 to 47.4 kg in 1967 in two Eskimo groups undergoing western acculturation while the 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. 2000). The carbohydrates present in hunter-gatherer diets are of a low glycemic index – that is, 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 glycemic index is influenced by the particle size, processing technique, and relative fiber, protein and fat content of the carbohydrate food. The glycemic index of mixed meals is determined by multiplying the

carbohydrate content of each food by its glycemic index and summing these values for all foods (Wolever et al 1991), so that the more relevant total glycemic load (glycemic index x carbohydrate content) can be known.

The addition of high glycemic load carbohydrates to the diet represents 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 who have adopted western dietary patterns frequently show high levels of hyperglycemia, insulin resistance, hyperinsulinemia and type II diabetes (Daniel et al. 1999, Ebbesson et al. 1998), whereas hunter-gatherer populations in their native environments rarely exhibit these symptoms (Merimee et al. 1972, O'Dea 1984, Schaefer 1969, Spielman et al. 1982).

The Secular Increase in High Glycemic Load Foods in Industrialized Countries

In hunter-gatherer populations that adopted modern foods in the 20th century, there was an immediate change from low glycemic to high glycemic load carbohydrates that occurred shortly after western contact began. In industrialized countries this dietary shift occurred more slowly as more and more refined sugars were gradually included in the diet along with increasingly greater levels of refined cereals in the 200 or so years since the advent of the industrial revolution. Although highly refined sugars and cereals are common elements in 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 began to become available to the masses since the advent of the industrial revolution (Teuteberg 1986). In England the per capita consumption of sucrose has steadily risen from 6.8 kg in 1815 to 54.5 kg in 1970 (Cleave 1974). Although refined cereals comprise the highest percentage of carbohydrate in the western diet, this has not always been the case (Cordain et al. 2000). Only since the widespread introduction of steel roller mills in the late 19th century (~1880) did fiber-depleted wheat flour of a low extraction ($\leq$ 70%)

become widely available (Cleave 1974). Hence, in the past 200-250 years the average glycemic load of foods in urban areas of industrialized countries has steadily risen primarily because of the 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 glycemic 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 glycemic index and glycemic load of both traditional and processed foods.

Hyperinsulinemia and the Consumption of High Glycemic Load Foods

In the past 20 years accumulating evidence has shown that the consumption of foods with a high glycemic load, such as processed foods containing refined starches and sugars, promote the development of both acute and chronic hyperinsulinemia. Numerous studies have demonstrated that the addition of sucrose to the diet of both normal (Coulston et al. 1983, Reiser et al. 1979) and hyperinsulinemic subjects (Reiser et al. 1981) causes an increase in post-prandial 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, Dirlewanger et al. 2000). Further, dietary intervention studies using low glycemic loads are known to improve insulin sensitivity (Frost et al. 1998), and low glycemic loads reduce the risk for type II diabetes (Salmeron et al. 1997). In contrast, interventions studies manipulating dietary fatty acids have shown no beneficial effects 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 worsening of glycemic control, which in turn may promote insulin resistance and compensatory hyperinsulinemia (Reaven 1994).

Hyperinsulinemia and Insulin Like Growth Factor (IGF) and IGF Binding Proteins

The metabolic ramifications of dietary induced perturbations of insulin action are diverse and complex. Recently it has been demonstrated that the compensatory hyperinsulinemia that characterizes adolescent obesity chronically suppresses hepatic synthesis of insulin like binding protein-1 (IGFBP-1) which in turn serves to increase free insulin like growth factor-1 (IGF-1), the biologically active part of circulating IGF-1 (Attia et al. 1998, Nam et al. 1997). 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 to 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 (Attia et al. 1998, Nam et al. 1997, 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 hyperinsulinemia, 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 (Attia et al. 1998, Nam et al. 1997) or by acute ingestion of high glycemic carbohydrates (Liu 2000) also may contribute to unregulated cell proliferation in scleral tissue. IGFBP-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.

Hyperinsulinemia and Retinoid Receptors

Retinoids are natural and synthetic analogues of vitamin A that are inhibitors of cell proliferation and promoters of 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 (RXR). 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 established 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 hyperinsulinemia may reduce the effectiveness of the body's natural retinoids to activate genes that would normally limit scleral cell proliferation.

Proposed Model of Juvenile Onset Myopia

In juvenile onset myopia, numerous studies have conclusively demonstrated that abnormal axial

elongation of the eyeball is the major structural change causing refractive errors in distance vision (Lam et al. 1999, Lin et al. 1996, Zadnik et al. 1993). Both animal (Norton & Siegwart 1995; Raviola & Wiesel 1985; Troilo & Wallman 1991) 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. Further, in animal models of form deprivation myopia, there is a characteristic active remodeling and differentiation of scleral cartilage brought about by proliferation of both scleral chondrocytes and fibroblasts that causes the axial elongation of experimental myopia (Gentle & McBrien 1999, Kusakari et al. 1997, Seko et al. 1995).

The chemical messenger linking the retinal image clarity to appropriate growth rates in scleral tissue has been recently 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 hyperinsulinemia, via it's 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 hyperinsulinemia 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 realization that hyperinsulinemia 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 (Binoux & Gourmelen 1987, Blum et al. 1993, Gourmelen et al. 1984). Human recombinant IGF-1 therapy has also been shown to improve linear growth (Camacho-Hubner et al. 1999). Further, hyperinsulinemic 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 accelerates the tempo of puberty in a primate model (Wilson 1998). Recently, Wong et al. (1999) have provided metabolic evidence showing that Black American girls were more advanced in their pubertal development and taller than a comparable group of White girls. Further, circulating levels of IGFBP-1 were lower, and circulating insulin and free IGF-I were higher suggesting that the metabolic cascade (insulin resistance – hyperinsulinemia – 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 age of puberty.

Since consumption of refined carbohydrates has the capacity to acutely and chronically elevate insulin levels, which in turn increase circulating levels of free IGF-1, then it might be hypothesized that epidemiological studies would show that the consumption of high glycemic foods would be related to increased stature and an earlier pubertal age. Further, it might be expected that myopes would tend to consume foods of a higher glycemic index, be taller, have an earlier pubertal age and present more frequently with type 2 diabetes than non-myopes.

In industrialized countries, there has been a steady and progressive secular increase in stature

and reduction in pubertal age that has occurred in 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 England, Japan, the Netherlands, Sweden, Norway, Denmark, the United States and New Zealand. In support of Ziegler's hypothesis, Schaefer's (1970) data on recently acculturated Eskimos shows that stature increased (4.6 cm in men and 2.9 cm in women), and age of puberty decreased (-2.0 years) simultaneously during the 30 year period (1938-68) when a several fold increase in the consumption of sucrose and refined carbohydrates occurred. Moreover, animal protein intake declined by 60% as stature was increasing. In a study examining the relationship of dietary fiber to age of menarche in girls from 46 countries, a strong positive correlation ($r = 0.84$) was demonstrated (Hughes & Jones 1985). Because dietary fiber is inversely related to the glycemic index (Foster-Powell & Brand Miller, Salmeron et al. 1997), this relationship supports the hypothesis that increasing consumption of refined carbohydrates may accelerate pubertal development. Further, multiple studies have demonstrated hyperinsulinemia and insulin resistance occurs in women with premature menarche when compared to women with normal menarche (Ibanez et al. 1998, Loffer 1975). Taken together, these studies indicate that intakes of high glycemic carbohydrates correlate well in time and space with the secular trends for increased stature and decreased pubertal age.

Many (Benoit 1958, Douglas et al. 1967, Gardiner 1954, Gardiner 1955, Gardiner 1956, Gardiner 1958, Johansen 1950, Johnson et al. 1979, Krause et al. 1982, Pendse & Bhave 1954, Scholz 1970, Teasdale & Goldschmidt 1988, Teikari 1987), but not all (Gawron 1981, Parssinen et al. 1985, Rosner et al. 1995, Sorsby et al. 1961, Young et al. 1954) surveys of myopes have shown them

to be taller than non-myopes. 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 population were taller than their parents, and 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 advent of store foods (mainly in the form of carbohydrates) that had become available in the preceding 30 years. Gardiner (1955, 1956, 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 in high and moderate myopes compared to controls from ages 3 to 16 years. **Figure 4** shows that the body mass index in myopes is also higher than in controls. 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 the accelerated growth patterns in myopes was linked to their refractive errors, and that diet may have been 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 levels of animal protein in the diets of myopic children, their progression of myopia slowed when compared to a control group receiving no dietary modification during a year long experiment (Gardiner 1958). Dietary protein results in minimal 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 post-prandial 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. Others have reported benefits of reduced carbohydrate, increased animal protein diets in the progression of human myopia (Walkingshaw 1964).

In support of the hormonal cascade linking insulin resistance to myopia are observations from Scandinavian studies (Fledelius 1983, Fledelius 1986, Fledelius et al. 1990) demonstrating an increased incidence of myopia among type 2 adult diabetics compared to non-diabetics. In 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 etiologic component, they also have a crucial genetic basis (Barroso et al. 1999, Neel et al. 1998). 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). Asian populations also have a higher prevalence of myopia when contrasted to European populations (Au Eong et al. 1993, McCarty et al. 1997); consequently 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 Asians to be shorter than people of European descent (Chin et al. 1997, Duignan et al. 1975), these data do not necessarily invalidate the relationships among insulin resistance, myopia and height because there are other known genetic determinants of adult stature that vary among racial groups (Katzmarzyk & Leonard 1998) independent of insulin resistance. Hence, the comparison of stature between Asian myopes and non-myopes would represent a more logical and meaningful evaluation of the relationships among 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 incidence (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 has remained obscure. However with the realization that high glycemic load carbohydrates, such as sucrose and refined cereal products made with sucrose, may induce hyperinsulinemia, and that hyperinsulinemia increases free IGF-1, lowers IGFBP-3 and reduces RXR signaling, the causal mechanism likely involves sucrose's well known cariogenic effect and its hyperinsulinemic effect. High sucrose, low protein diets in both rabbits (Gardiner & MacDonald 1957) and rats (Bardinger & Stock 1972) have been shown to lower the amount of hypermetropia (i.e produce refractive changes in a myopic direction) that was not reversible upon a sucrose free diet (Bardinger & Stock). In summary, these experiments are suggestive that high glycemic load carbohydrate diets may induce permanent changes in the development and progression of refractive errors, particularly during periods of growth.

References

Adams DW & McBrien NA (1992): Prevalence of myopia and myopic progression in a population of clinical microscopists. Optom Vis Sci 69:467-473.

Angle J & Wissmann DA (1980): The epidemiology of myopia. Am J Epidemiol 111:220-228.

Attia N, Tamborlane WV, Heptulla R, Maggs D, Grozman A, Sherwin RS & Caprio S (1998): The metabolic syndrome and insulin-like growth factor I regulation in adolescent obesity. J Clin Endocrinol Metab 83:1467-1471.

Au Eong KG, Tay TH & Lim MK (1993): Race, culture and myopia in 110,236 young Singaporean males. Singapore Med J 34:29-32.

Bardiger M & Stock AL. The effects of sucrose-containing diets low in protein on ocular refraction in the rat. Proc Nutr Soc 1972;31:4A-5A.

Barroso I, Gurnell M & Crowley VE et al. (1999): Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension. Nature 402:880-883.

Beck-Nielsen H, Pedersen O & Lindskor HO (1980): Impaired cellular binding and insulin sensitivity induced by high-fructose feeding in normal subjects. Am J Clin Nutr 33:273-278.

Beck-Nielsen H, Pedersen O & Sorensen NS (1978): Effects of diet on cellular insulin binding and the insulin sensitivity in young healthy subjects. Diabetologia 15:289-296.

Beischer NA, Oats JN, Henry OA, Sheedy MT & Walstab JE (1991): Incidence and severity

of gestational diabetes mellitus according to country of birth in women living in Australia. Diabetes 40 (Suppl 2):35-38.

Benoit A (1958): Biotypologie de l'homme myope. Arch Opht (Paris) 18:734-752.

Binoux M & Gourmelen M (1987): Statural development parallels IGF I levels in subjects of constitutionally variant stature. Acta Endocrinol 114:524-530.

Bitzer M, Feldkaemper M & Schaeffel F (2000): Visually induced changes in components of the retinoic acid system in fundal layers of the chick. Exp Eye Res 70:97-106.

Blum WF, Albertsson-Wikland K, Rosberg S & Ranke MB (1993): Serum levels of insulin-like growth factor I (IGF-I) and IGF binding protein 3 reflect spontaneous growth hormone secretion. J Clin Endocrinol Metab 76:1610-1616.

Brand JC & Colagiuri S (1994): The carnivore connection: dietary carbohydrate in the evolution of NIDDM. Diabetologia 37:1280-1286.

Brand-Miller JC, Colagiuri S & Gan ST (2000): Insulin sensitivity predicts glycemia after a protein load. Metabolism 49:1-5.

Brismar K, Fernqvist-Forbes E, Wahren J & Hall K (1994): Effect of insulin on the hepatic production of insulin-like growth factor-binding protein-1 (IGFBP-1), IGFBP-3, and IGF-1 in insulin dependent diabetes. J Clin Endocrinol Metab 79:872-878.

Camacho-Hubner C, Woods KA, Miraki-Moud F, Clark A & Savage MO (1999): Effects of recombinant human insulin-like growth factor I (IGF-I) therapy on the growth hormone-IGF system of a patient with a partial IGF-I gene deletion. J Clin Endocrinol Metab 84:1611-1616.

Cass E (1973): A decade of northern ophthalmology. Can J Ophthalmol 8:210-217.

Cass E (1966): Ocular conditions amongst the Canadian western arctic Eskimo. In: Weigelin E (ed.) Proceedings of the XX International Congress of Ophthalmology. New York. Excerpta Medica

Foundation: 1041-1053.

Chew SJ & Balakrishnan V (1992): Myopia produced in young chicks by intermittent minimal form visual deprivation – can spectacles cause myopia. Singapore Med J 33:489-492.

Chiba H, Clifford J, Metzger D & Chambon P (1997): Distinct retinoid X receptor-retinoic acid receptor heterodimers are differentially involved in the control of expression of retinoid target genes in F9 embryonal carcinoma cells. Mol Cel Biol 17:3013-3020.

Chin K, Evans MC, Cornish J, Cundy T & Reid IR (1997): Differences in hip axis and femoral neck length in premenopausal women of Polynesian, Asian and European origin. Osteoporosis Int 7:344-347.

Cleave TL (1974): The Saccharine Disease. Bristol. John Wright & Sons Ltd.: 6-27.

Cordain L, Brand Miller J, Eaton SB, Mann N, Holt SH & Speth JD (2000): Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr71:682-692.

Cordain L (1999): Cereal grains: humanity's double-edged sword. World Rev Nutr Diet 84:19-73.

Coulston AM, Liu GC & Reaven GM (1983): Plasma glucose, insulin and lipid responses to high-carbohydrate low-fat diets in normal humans. Metabolism 32:52-56.

Daniel M, Rowley KG, McDermott R, Mylvaganam A & O'Dea K (1999): Diabetes incidence in an Australian aboriginal population. An 8-year follow-up study. Diabetes Care 22:1993-98.

Dirlewanger M, Schneiter P, Jequier E & Tappy L (2000): Effects of fructose on hepatic glucose metabolism in humans. Am J Physiol Endocrinol Metab 279:E907-E911.

Douglas JWB, Ross JM & Simpson HR (1967): The ability and attainment of short-sighted pupils. J Royal Stat Soc Series A (General) 130:479-504.

Duignan NM, Studd JW & Hughes AO (1975): Characteristics of normal labour in different racial groups. Br J Obstet Gynaecol 82:593-601.

Eaton SB, Eaton SB III & Konner MJ (1997): Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. Eur J Clin Nutr 51:207-216.

Eaton SB & Konner M (1984): Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 312:283-289.

Ebbesson SO, Schraer CD, Risica PM, Adler AI, Ebbesson L, Mayer AM, Shubnikof EV, Yeh J, Go OT & Robbins DC (1998): Diabetes and impaired glucose tolerance in three Alaskan Eskimo populations. The Alaska-Siberia project. Diabetes Care 21:563-569.

Edwards MH & Chan JCY (1995): Is there a difference in dental caries between myopic and nonmyopic children. Optom Vis Sci 72:573-576.

Evans TRJ & Kaye SB (1999): Retinoids: present role and future potential. Br J Cancer 80:1-8.

Ferry RJ, Cerri RW & Cohen P (1999): Insulin-like growth factor binding proteins: new proteins, new functions. Horm Res 51:53-67.

Fischer AJ, Wallman J, Mertz JR & Stell WK (1999): Localization of retinoid binding proteins, retinoid receptors, and retinaldehyde dehydrogenase in the chick eye. J Neurocytol 28:597-609.

Fledelius HC, Fuchs J & Reck A (1990): Refraction in diabetics during metabolic dysregulation, acute or chronic. With special reference to the diabetic myopia concept. Acta Ophthalmol 68:275-280.

Fledelius HC (1986): Myopia and diabetes mellitus with special reference to adult-onset myopia. Acta Ophthalmol 64:33-38.

Fledelius HC (1983): Is myopia getting more frequent? A cross sectional study of 1416 Danes aged 16 years+. Acta Ophthalmol 61:545-559.

Foster-Powell K & Brand Miller J (1995): International tables of glycemic index. Am J Clin Nutr 62:871S-893S.

Frost G, Leeds A, Trew G, Margara R & Dornhorst A (1998): Insulin sensitivity in women at risk of coronary heart disease and the effects of a low glycemic diet. Metabolism 47:1245-51.

Gardiner PA & MacDonald I (1957): Relationship between refraction of the eye and nutrition. Clin Sci 16:435-442.

Gardiner PA (1954): The relation of myopia to growth. Lancet 1:476-479.

Gardiner PA (1955): Physical growth and the progress of myopia. Lancet 2:952-953.

Gardiner PA (1956a): Observations on the food habits of myopic children. Br Med J 2:699-700.

Gardiner PA (1956b): The diet of growing myopes. Trans Ophthalmol Soc 76:171-180.

Gardiner PA (1958): Dietary treatment of myopia in children. Lancet 1:1152-1155.

Gardiner PA (1964):. Factors associated with the development of myopia in the growing child. In: The First International Conference on Myopia. Chicago. The Professional Press, Inc.:29-32.

Garner LF, Kinnear RF, Klinger JD & McKellar MJ (1985): Prevalence of myopia in school children in Vanuatu. Acta Ophthalmol 63:323-326.

Garner LF, Owens H, Kinnear RF & Frith MJ (1999): Prevalence of myopia in Sherpa and Tibetan children in Nepal. Optom Vis Sci 76:282-285.

Gawron VJ (1981): Differences among myopes, emmetropes and hyperopes. Am J Optom Physiol Opt 58: 753-760.

Gentle A & McBrien NA (1999): Modulation of scleral DNA synthesis in development of and recovery from induced axial myopia in the tree shrew. Exp Eye Res 68:155-163.

Goldschmidt E (1968): On the etiology of myopia: an epidemiologic study. Acta Ophthalmol

98(suppl):1-172.

Goldstein JH, Vukcevich WM, Kaplan D, Paolino J & Diamond HS (1971): Myopia and dental caries. JAMA 218:1572-1573.

Gourmelen M, Le Bouc Y, Girard F & Binoux M (1984): Serum levels of insulin-like growth factor (IGF) and IGF binding proteins in constitutionally tall children and adolescents. J Clin Endocrinol Metab 59:1197-1203.

Grimberg A & Cohen P (2000): Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. J Cell Physiol 18:1-9.

Hirsch MJ & Levin JM (1973): Myopia and dental caries. Am J Optom Arch Am Acad Optom 50:484-488.

Holly JMP (1991): The physiological role of IGFBP-1. Acta Endocrinol 124:55-62.

Holm S (1937): The ocular refraction state of the Palae-Negroids in Gabon, French Equatorial Africa. Acta Ophthalmol 13(suppl):1-299.

Hughes RE & Jones E (1985): Intake of dietary fibre and age of menarche. Ann Hum Biol 12:325-332.

Ibanez L, Potau N, Chacon P, Pascual C & Carrascosa A (1998): Hyperinsulinaemia, dyslipaemia and cardiovascular risk in girls with a history of premature pubarche. Diabetologia 41:1057-1063.

Johansen EV (1950): Simple myopia in schoolboys in relation to body height and weight. Acta Ophthalmol 111:220-228.

Johnson GJ, Matthews A & Perkins ES (1979): Survey of ophthalmic conditions in a Labrador community. I. Refractive errors. Br J Ophthamol 63:440-448.

Juul A, Scheike T, Nielsen CT, Krabbe S, Muller J & Skakkebaek NE (1995): Serum insulin-

like growth factor I (IGF-1) and IGF-binding protein 3 levels are increased in central precocious puberty: effects of two different treatment regimens with gonadotropin-relating hormone agonists, without or in combination with an antiandrogen (cyproterone acetate). J Clin Endocrinol Metab 80:3059-3067.

Katzmarzyk PT & Leonard WR (1998):. Climatic influences on human body size and proportions: ecological adaptations and secular trends. Am J Phys Anthropol 106:483-503.

King H & Rewers M (1993): Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. Diabetes Care 16:157-177.

Klein S (2001): Outcome success in obesity. Obes Res 9 (suppl 5):S354-S358.

Krause U, Krause K & Rantakallio P (1982): Sex differences in refraction errors up to the age of 15. Acta Ophthalmol 60:917-926.

Kusakari T, Sato T & Tokoro T (1997): Regional scleral changes in form-deprivation myopia in chicks. Exp Eye Res 64:465-476.

Lam CS, Edwards M, Millodot M & Goh WS (1999): A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. Optom Vis Sci 76:370-380.

Lewallen S, Lowdon R, Courtright P & Mehl GL (1995): A population-based survey of the prevalence of refractive error in Malawi. Ophthalmic Epidemiol 2:1 45-149.

Lin LL, Shih YF, Lee YC, Hung PT & Hou PK (1996): Changes in ocular refraction and its components among medical students—a 5-year longitudinal study. Optom Vis Sci 73:495-498.

Lindgren BF, Segovia B, Lassarre C, Binoux M & Gourmelen M (1996): Growth retardation in constitutionally short children is related both to low serum levels of insulin-like growth factor-I and to its reduced bioavailability. Growth Regul 6:158-164.

Liu B, Lee HY, Weinzimer SA, Powell DR, Clifford JL, Kurie JM, Cohen P (2000): Direct functional interaction between insulin-like growth factor-binding protein-3 and retionoid X receptor-alpha regulate transcriptional signaling and apoptosis. J Biol Chem 275:33607-33613.

Liu VR (2000): The glycaemic index and the insulin-like growth factor system. Honours Thesis. Human Nutrition Unit, Department of Biochemistry, University of Sydney, Sydney, Australia.

Loffer FD (1975): Decreased carbohydrate tolerance in pregnant patients with an early menarche. Am J Obstet Gynecol 123:180-184.

Malina RM (1990): Research on secular trends in auxology. Anthropol Anz 48:209-227.

McBrien NA & Adams DW (1997): A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. Invest Ophthalmol 38:321-333.

McCarty CA, Livingston PM & Taylor HR (1997):. Prevalence of myopia in adults: implications for refractive surgeons. J Refract Surg 13:229-234.

Merimee TJ, Rimoin DL & Cavalli-Sforza LL (1972):. Metabolic studies in the African Pygmy. J Clin Invest 51:395-401.

Mertz JR & Wallman J (2000): Choroidal retinoic acid synthesis: a possible mediator between refractive error and compensatory eye growth. Exp Eye Res 70:519-527.

Meyer C, Mueller MF, Duncker GI & Meyer HJ (1999): Experimental animal myopia models are applicable to human juvenile-onset myopia. Surv Ophthalmol 44 (Suppl 1):S93-S102.

Morgan RW & Munro M (1973): Refractive problems in northern natives. Can J Ophthalmol 1973;8:226-228.

Mori M, Ghyselinck NB, Chambon P & Mark M (2001): Systemic immunolocalizaton of retinoid receptors in developing and adult mouse eyes. Invest Ophthalmol Vis Sci 42:1312-1318.

Mutti DO, Zadnik K & Adams AJ (1996): Myopia. The nature vs. nurture debate goes on. Invest Ophthalmol Vis Sci 37:952-957.

Mutti DO, Zadnik K & Murphy CJ (1999): Naturally occurring vitreous chamber-based myopia in the Labrador retriever. Invest Ophthalmol Vis Sci 1999;1577-1584.

Nam SY, Lee EJ, Kim KR, Cha BS, Song YD, Lim SK, Lee HC & Huh KB (1997): Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int J Obes Relat Metab Disord 21:355-359.

Neel JV, Weder AB & Julius S (1998): Type I diabetes, essential hypertension, and obesity as "syndromes of impaired genetic homeostasis": the "thrifty genotype" hypothesis enters the 21st century. Perspect Biol Med 1998;42:44-74.

Nesse RM & Williams GC (1994): Why We Get Sick. New York. Times Books: 91-106.

Norton TT & Siegwart JT Jr (1995): Animal models of emmetropization: matching axial length to the focal plane. J Am Optom Assoc 66:405-414.

O'Dea K (1984): Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. Diabetes 33:596-603.

Parssinen O, Era P & Leskinen AL (1985): Some physiological and psychological characteristics of myopic and non-myopic young men. Acta Ophthalmol (suppl) 173:85-87.

Pendse GS & Bhave B (1954): Refractive and body growth. Indian Medical Research Memoirs, 38. Kapur, India. Job Press Ltd.

Post RH (1962): Population differences in vision acuity: A review, with speculative notes on selection relaxation. Eugen Quart 9:189-212.

Raviola E & Wiesel TN (1985): An animal model of myopia. N Engl J Med 1985;312:1609-

15.

Reaven GM (1994): Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease. Diabetologia 37:948-952.

Reiser S, Bohn E, Hallfrisch J, Michaelis OE 4th, Keeney M & Prather ES (1981): Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. Am J Clin Nutr 34:2348-2358.

Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE 4th & Prather ES (1979): Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. Am J Clin Nutr 32:2206-2216.

Riccardi G & Rivellese AA (2000): Dietary treatment of the metabolic syndrome – the optimal diet. Br J Nutr 83 (suppl 1):S143-S148.

Roche AF (1979): Secular trends in human growth, maturation, and development. Monogr Soc Res Child Dev 44:1-120.

Rosner M, Laor A & Belkin M (1995): Myopia and stature: findings in a population of 106,926 males. Eur J Ophthalmol 5:1-6.

Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL & Willett WC (1997): Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 20:545-550.

Schaefer O (1969):. Carbohydrate metabolism in Eskimos. Arch Environ Health 18:144-147.

Schaefer O (1970): Pre- and post-natal growth acceleration and increased sugar consumption in Canadian Eskimos. Can Med Assoc J 103:1059-1068.

Schaefer O (1971): When the Eskimo comes to town. Nutr Today 6:8-16.

Schaefer O (1977): Changing dietary patterns in the Canadian North: Health, social and

economic consequences. J Can Diet Assoc 38:17-25.

Scholz D (1970): Relations between myopia and school achievements, growth and social factors. Offentl Gesundheitswes 32:530-535.

Seko Y, Tanaka Y & Tokoro T (1995): Influence of bFGF as a potent growth stimulator and TGF-beta as a growth regulator on scleral chondrocytes and scleral fibroblasts in vitro. Ophthalmic Res 27:144-152

Skeller E (1954): Anthropological and ophthalmological studies on the Angmagssalik Eskimos. Meddr Gronland 107:167-211.

Sorsby A, Benjamin B & Sheridan M (1961): Refraction and its components during the growth of the eye from the age of three. Medical Research Council, Special Report Series No. 301. London. Stationary Office.

Sperduto RD, Seigel D, Roberts S, Rowland M (1983): Prevalence of myopia in the United States. Arch Ophthalmol 101:405-407.

Spielman RS, Fajans SS, Neel JV, Pek S, Floyd JC & Oliver WJ (1982). Glucose tolerance in two unacculturated Indian tribes of Brazil. Diabetologia 23:90-93.

Stefansson V (1919): My Life with the Eskimo. New York. MacMillan Company.

Teasdale TW & Goldschmidt E (1988): Myopia and its relationship to education, intelligence and height. Preliminary results from an on-going study of Danish draftees. Acta Ophthalmol Suppl 185:41-43.

Teikari JM (1987): Myopia and stature. Acta Ophthalmol 65:673-676.

Teuteberg HJ (1986). Periods and turning-points in the history of european diet: a preliminary outline of problems and methods. In: Fenton A, Kisban E (eds.) Food in Change. Eating Habits from the Middle Ages to the Present Day. Atlantic Highlands, NJ. Humanities Press Inc.:11-23.

Thorburn AW, Brand JC, O'Dea K, Spargo RM & Truswell AS (1987a): Plasma glucose and insulin responses to starchy foods in Australian Aborigines: a population now at high risk of diabetes. Am J Clin Nutr 46:282-285.

Thorburn AW, Brand JC & Truswell AS (1987b): Slowly digested and absorbed carbohydrate in traditional bushfoods: a protective factor against diabetes? Am J Clin Nutr 45:98-106.

Travers SH, Labarta JI, Gargosky SE, Rosenfeld RG, Jeffers BW & Eckel RH (1998): Insulin-like growth factor binding protein-I levels are strongly associated with insulin sensitivity and obesity in early pubertal children. J Clin Endocrinol Metab 83:1935-1939.

Troilo D & Wallman J (1991): The regulation of eye growth and refractive state: an experimental study of emmetropization. Vision Res 31:1237-1250.

Trowell H (1985): Dietary fibre: a paradigm. In: Trowell H, Burkitt D, Heaton K, Doll R (eds.) Dietary Fibre, Fibre-Depleted Foods and Disease. New York. Academic Press: 1-20.

Valentinis B, Bhala A, DeAngelis T, Baserga R & Cohen P (1995): The human insulin-like growth factor (IGF) binding protein-3 inhibits the growth of fibroblasts with a targeted disruption of the IGF-I receptor gene. Mol Endocrinol 9:361-367.

Vessby B (2000): Dietary fat and insulin action in humans. Br J Nutr 83 (suppl1):S91-S96.

Walkingshaw R (1964): Control of progressive myopia through modification of diet. In: The First International Conference on Myopia. Chicago. The Professional Press: 55-74.

Wallman J (1994): Nature and nurture of myopia. Nature 371:201-202.

Wallman J (1990): Myopia and the control of eye growth. Introduction. Ciba Found Symp 155:1-4.

Wendling O, Chambon P & Mark M (1999): Retinoid X receptors are essential for early

mouse development and placentogenesis. Proc Natl Acad Sci U.S.A. 96:547-551.

Wilson ME (1998): Premature elevation in serum insulin-like growth factor-I advances first ovulation in rhesus monkeys. J Endocrinol 158:247-57.

Wingert TA (1995). Epidemiology of ametropia of U.S. army recruits. Mil Med 160:89-91.

Wolever TM, Jenkins DJ, Jenkins AL & Josse RG (1991): The glycemic index: methodology and clinical implications. Am J Clin Nutr 54:846-854.

Wong L, Coggon D, Cruddas M & Hwang CH (1993): Education, reading, and familial tendency as risk factors for myopia in Hong Kong fishermen. J Epidemiol Community Health 47:50-53.

Wong WW, Copeland KC, Hergenroeder AC, Hill RB, Stuff JE & Ellis KJ (1999): Serum concentrations of insulin, insulin-like growth factor-I, and insulin-like growth factor binding proteins are different between white and African American girls. J Pediatr 135:296-300.

Yang Q, Mori I, Shan L, Nakamura M, Nakamura Y, Utsunomiya H, Yoshimura G, Suzuma T, Tamaki T, Umemura T, Sakurai T, Kakudo K (2001): Biallelic Inactivation of retinoic acid receptor B2 gene by epigenetic change in breast cancer. Am J Pathol 158:299-303.

Young FA, Leary GA, Baldwin WR, West DC, Box RA, Harris E & Johnson C (1969): The transmission of refractive errors within Eskimo families. Am J Optom Arch Am Acad Optom 46:676-685.

Young FA, Beattle R & Newby FJ (1954): The Pullman study: a visual survey of Pullman school children. Am J Opt 31:111.

Zadnik K, Mutti DO, Friedman NE & Adams AJ (1993): Initial cross-sectional results from the Orinda Longitudinal Study of Myopia. Optom Vis Sci 70:750-758.

Ziegler E (1969): Height and weight of British men. Lancet 1:1318.

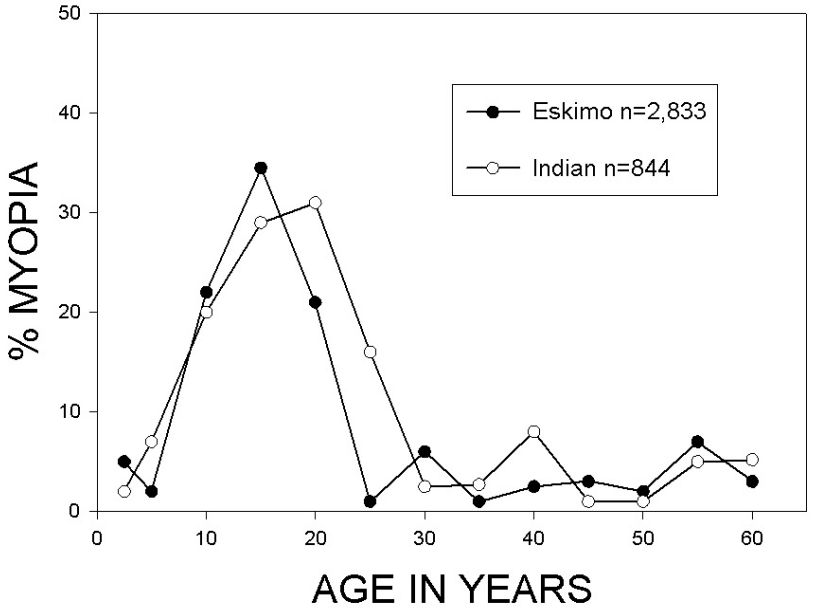
Ziegler E (1967): Secular changes in the stature of adults and the secular trend of the modern

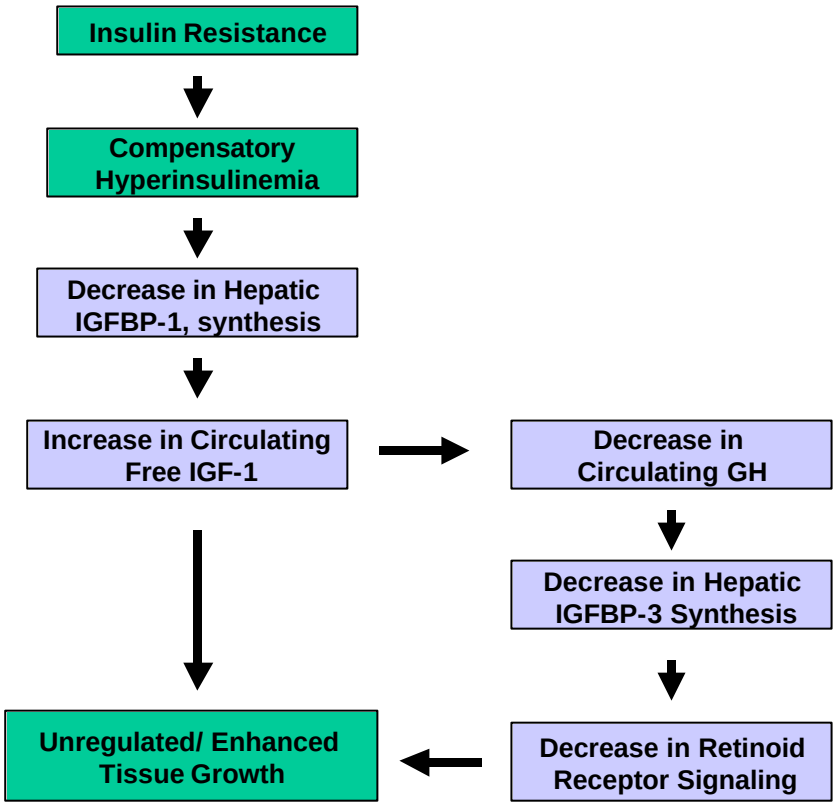
sugar consumption. Z Kinderheilkd 99:146-166.

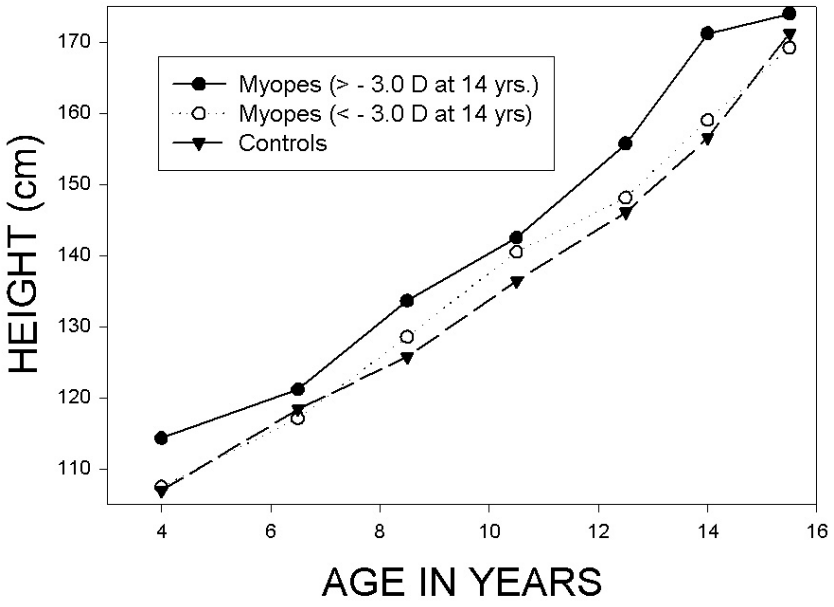
Zylbermann R, Landau D & Berson D (1993): The influence of study habits on myopia in Jewish teenagers. J Pediatr Ophthalmol Strabismus 30:319-322.

Correspondence to: Dr. Loren Cordain, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO 80523 USA; Tel (970) 491-7436; Fax (970) 491-0445; email

cordain@cahs.colostate.edu


50
40
30
20
10
0
% MYOPIA
0
10
20
30
40
50
60
AGE IN YEARS
Eskimo n=2,833
Indian n=844


Insulin Resistance
Compensatory Hyperinsulinemia
Decrease in Hepatic IGFBP-1, synthesis
Increase in Circulating Free IGF-1
Decrease in Circulating GH
Decrease in Hepatic IGFBP-3 Synthesis
Decrease in Retinoid Receptor Signaling
Unregulated/ Enhanced Tissue Growth


Myopes (> - 3.0 D at 14 yrs.)
Myopes (< - 3.0 D at 14 yrs)
Controls
HEIGHT (cm)
170
160
150
140
130
120
110
4
6
8
10
12
14
16
AGE IN YEARS

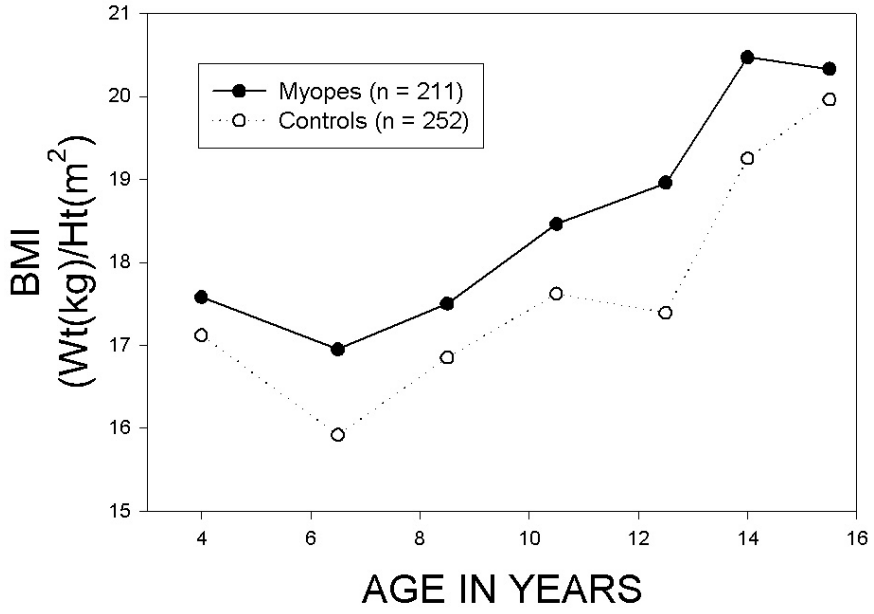

BMI
(Wt(kg)/Ht(m2))
Myopes (n = 211)
Controls (n = 252)
21
20
19
18
17
16
15
4
6
8
10
12
14
16
AGE IN YEARS

Table 1.

Western Refined Foods			Unrefined Traditional Foods		
Food	Glycemic Index	Glycemic Load	Food	Glycemic Index	Glycemic Load
Rice krispie 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

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Legends to Figures and Tables

Figure 1. Moderate myopia (1.00-5.00 D) by age in Indians and Eskimos of the Yukon and Northwest territories. Adapted from Morgan et al. (1973)

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

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

Figure 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).

Table 1. Glycemic indices and loads (glycemic index x 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).