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

By

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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 (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.
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(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

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 (≤ 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 hyperinsulineemic 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 pericocular 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-1 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.

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.
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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

Unregulated/Enhanced Tissue Growth

Decrease in Retinoid Receptor Signaling
Table 1.

<table>
<thead>
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<th>Western Refined Foods</th>
<th>Glycemic Index</th>
<th>Glycemic Load</th>
<th>Food</th>
<th>Glycemic Index</th>
<th>Glycemic Load</th>
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<tr>
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<td>Boiled broad beans</td>
<td>79</td>
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<tr>
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<td>66.9</td>
<td>Boiled couscous</td>
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<td>Table sugar (sucrose)</td>
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<tr>
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<td>Peanuts</td>
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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).