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

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Failure to match focal length of eye’s optics with axial length produces myopia


Myopia: An Evolutionary Perspective

- Virtual all mammalian & bird eyes are usually slightly hyperopic at birth and move towards emmetropization during growth & development.
- Except for recent evidence with domestic dogs, myopia is unique to humans.


Myopia: An Evolutionary Perspective

- In all free living vertebrates myopia represents a severe developmental defect.
- That in most cases would result in an early death.


Myopia: An Evolutionary Perspective

- Despite the enormous selective pressures that would tend to eliminate myopic genes in all pre-agricultural and pre-technological human societies.
- Myopia is extremely prevalent in western societies, afflicting:


- 25-35 % of European descent populations.
- 50 % or more of Asian descent populations.
Myopia: An Evolutionary Perspective

- It has been suggested that:
- As non-westernized populations acculturate:
- A relaxation of the evolutionary selective pressure that would normally eliminate the gene or genes that evoke myopia
- Was responsible for myopia’s increased incidence in westernized societies
- Moreover, these selective pressures would have been completely eliminated with the wide scale availability of spectacle lenses in the past 200 yrs.
- A number of lines of evidence suggest otherwise:

Myopia Incidence in Hunter Gatherers

- Using a retinoscope and cycloplegia, Holm (1937) refracted 2,364 members (age 20-65 yrs) of several hunter gatherer tribes in Gabon
- Of the 3,624 eyes examined:
  1. 9 eyes were myopic (-0.50 to -1.00 D)
  2. 4 eyes were myopic (-3.00 to -9.00 D)
- Yielding a total population myopia incidence rate of 0.4 %

Myopia Incidence in Hunter Gatherers

- Using a retinoscope and cycloplegia, Skeller (1954) refracted 775 Angmagssalik Eskimos (age 2-69 yrs)
- Of the 1,123 eyes examined:
  1. 9 eyes were myopic (-1.00 D)
  2. 4 eyes were myopic (-1.25 D)
- Yielding a total population myopia incidence rate of 1.2%

Myopia Incidence in Hunter Gatherers

- Using a cycloplegic, Young et al. (1969) refracted 508 recently acculturated Eskimos in Barrow, Alaska
  1. The right eyes of 131 subjects over 41 yrs of age yielded only two myopic (-0.25 D) eyes (1.5 % of the population)
  2. The right eyes of 284 subjects between (11 and 40 yrs) of age showed that 51 % had myopia of > 0.25 D
- These subjects were born between (1880 and 1927) and most grew up in isolated communities along the coast of Alaska living in traditional ways, without formal schooling.
- These subjects were born between (1928 and 1957) and most had attended the BIA school established at Barrow in 1932

Hence, within ~ a single generation (30 yrs), the incidence of myopia increased 34 fold
Morgan et al. (1973) reported a similar age related decline in myopia incidence in Indians and Eskimos living in the Yukon and Northwest Territories.

Possible interpretations:

1. Birth Cohort Effect
2. Actual changes in refractive error with age

Cross sectional studies like these cannot distinguish these effects.

Prospective Data (The Beaver Dam Study) indicate:

1. Strong birth cohort effect
2. Lesser change in actual refraction:
   a. (43-59 yr subjects), the 10 yr change was +0.53 D
   b. (>70 yr subjects), the 10 yr change was -0.41

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Myopia Incidence in Amazon Indians

- Only 2.7% of 259 Amazon Indians showed Myopia of -1.00 D or More

Conclusions: Visual Acuity in Humanity's Native Hunter-Gatherer Environment:

- Myopia occurs in (0-3 %) of the population
- With most refractive errors < -1.00 D
- Moderate to high myopia (-3.00 D to -9.00 D) occurs in ~ (1 person per 1,000)
- Emmetropia or slight hypermetropia represent the normal refractive state under which the current human genome was selected
- When novel environmental conditions associated with modern civilization are introduced into the hunter gatherer lifestyle:
  a. Within a single generation, myopia incidence rates equal or exceed those in western populations
Both Genetics & Environment Influence the Development of Myopia

- Within the visual sciences community there is an emerging consensus that myopia develops from:
  - Genetic Factors (currently unknown)
  - 1. Twin studies twins¹
  - Environmental Factors (almost exclusively – excessive near work)
    - 1. Epidemiological studies of education levels²
    - 2. Animal studies²
    - 3. Prospective studies of microscopists²

¹ Dirani M et al. Heritability of refractive error and ocular biometrics: The genes in myopia (GEM) twin study. Invest Ophthalmol Vis Sci 2006;47:4756-61

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Refractive Status in Partially Westernized Populations

- Garner et al. (1999) measured visual acuity in 2 groups of genetically similar children but with varying degrees of western acculturation
  - 555 children in the urban environ of Kathmandu had a 21.7 % prevalence of myopia
  - 270 children living in the rural and village of Khumjung had a 2.9 % rate of myopia
  - Both groups had compulsory schooling
  - Khumjung is an isolated village without electricity, supermarkets, and few western processed foods


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Both Genetics & Environment Influence the Development of Myopia

- The exact manner genetic factors interact with environmental factors to elicit myopia is unclear
  - Modern civilization brings not only literacy, reading and increased near work
  - But other environmental factors that may disrupt the emmetropization process during growth & development


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Refractive Status in Partially Westernized Populations

- Garner et al. (1985) measured visual acuity in 977 school children (6-17 yrs) on S. Pacific island of Vanuatu
  - Only 1.3 % of subjects had myopia of > -0.25 D
  - Despite engaging in 8 hrs of schooling per day

Lewallen et al. (1995) examined 352 students attending a teachers college in Malawi. Students came from rural areas where they had complete primary school and 2 yrs of secondary school. Blantyre Teacher’s Training College, Malawi, Africa.

- All engaged in regular reading
- Only 4.1% had a refractive error of more negative or equal to (-) 0.50 D.

Refractive Status in Partially Westernized Populations

Conclusions: Refractive Status in Partially Westernized Populations

- In rural areas with little exposure to westernized lifestyles, the near work of reading does not elicit myopia incidence rates much beyond rates (~ 1-4%) than in hunter-gatherers.
- It could be that the quantity and intensity of rural schooling is less than urban schooling.
- It could also be argued that additional environmental factors in urban areas, which are not present in rural areas influence myopia rates.

Conclusions: Refractive Status in Partially Westernized Populations

- Kathmandu, Nepal: Urban Market Center (Myopia Incidence: 21.7%)
- Village of Khumjung, Nepal (Myopia Incidence: 2.9%)

- Additional urban environmental factors:
  - Electricity, running water, television, radio, automobiles, etc.
  - High availability of western processed foods

Myopia and Illiteracy

- Illiterate hunter gatherers and literate rural villagers have similar low myopia rates (~1-4%)
- Literate urban dwellers have high myopia rates (20-50% or >)

Illiterate urban dwellers:

1. Cairo, Egypt: 1173 subjects (11-39% of sample had myopia)1
2. 152 Hong Kong fisherman who had never attended school (18.4% myopia rate)2

Taken together, the data suggest that environmental factors present in urban environments but not in rural areas may elicit myopia.

Myopia and Illiteracy

- It is possible that illiterate urban workers engage in other near work besides reading which evokes myopia.
- Anthropological studies of non-westernized Eskimos indicate they may engage in long hours of near work (sewing, tool making etc.) in dimly lit snow houses.
- But do not develop myopia.


Myopia and Illiteracy (cont.)

- 3 unique qualities of the printed page are potent inducers of form deprivation and hence myopia:
  1. Narrow range of luminance
  2. Achromaticity of text
  3. High spatial frequency of text reduces activity of non-foveal retinal neurons
- Taken Together: These data suggest that environmental factors other than near work in urban illiterates may underlie the development of myopia.


When Non-Westernized Societies Acculturate, They Not Only Become Literate, But they Change Their Diets

- Minimally Processed, Wild Plants
- Minimally Processed, Wild Animals
- Highly Processed, Refined Foods

Urban vs. Rural Environmental Factors Potentially Influencing Myopia: Sugar Availability

- High sucrose diets produce refractive changes in a myopic direction in both rats and rabbits that did not occur on sucrose free diets.
- Myopes have more dental carries than non-myopes.
- Degree of myopia is related to caries incidence.
- Progressive myopes have more caries than stable myopes.

Diet, Hyperinsulinemia and Myopia

Although the excessive near work of reading is almost universally recognized as the sole environmental factor underlying myopia,

Diet, particularly the glycemic index, is a well recognized agent underlying chronic hyperinsulinemia.

A condition which may play a key role in the pathogenesis of myopia by disrupting hormonally mediated regulation of vitreal chamber growth.


What are High Glycemic Foods: The Glycemic Index (GI)

1. Subject eats an amount of food containing 50 or 25 g CHO
2. Over 2 hr period blood glucose is measured at 0,15,30,45,60,90, 120 min & plotted on graph & area under curve calculated
3. Response of test food is compared to reference value (usually glucose with a glycemic index (GI) of 100)

Glycemic Indices of Food

<table>
<thead>
<tr>
<th>Western Refined Foods</th>
<th>Glycemic Index</th>
<th>Glycemic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td></td>
<td>Food</td>
</tr>
<tr>
<td>Instant rice</td>
<td>91</td>
<td>Baked Potato</td>
</tr>
<tr>
<td>Rice krispie cereal</td>
<td>88</td>
<td>Millet</td>
</tr>
<tr>
<td>Corn flake cereal</td>
<td>84</td>
<td>Whole meal porridge</td>
</tr>
<tr>
<td>Instant potatoes</td>
<td>83</td>
<td>Pita bread</td>
</tr>
<tr>
<td>Tapioca</td>
<td>81</td>
<td>Brown rice</td>
</tr>
<tr>
<td>Jelly beans candy</td>
<td>80</td>
<td>Sweet corn</td>
</tr>
<tr>
<td>Vanilla wafer cookies</td>
<td>77</td>
<td>Sweet potato</td>
</tr>
<tr>
<td>Doughnut</td>
<td>76</td>
<td>Yam</td>
</tr>
<tr>
<td>Waffles</td>
<td>76</td>
<td>Rice</td>
</tr>
<tr>
<td>Cheerio cereal</td>
<td>74</td>
<td>Hominy corn</td>
</tr>
<tr>
<td>Soda crackers</td>
<td>74</td>
<td>Tortilla</td>
</tr>
<tr>
<td>Corn chips</td>
<td>73</td>
<td>Lime beans</td>
</tr>
<tr>
<td>White bread</td>
<td>70</td>
<td>Lentils</td>
</tr>
<tr>
<td>Mashed potatoes</td>
<td>70</td>
<td>Fresh peach</td>
</tr>
<tr>
<td>Mars bar</td>
<td>68</td>
<td>Kidney beans</td>
</tr>
<tr>
<td>Soft drink</td>
<td>68</td>
<td>Peas</td>
</tr>
<tr>
<td>Green pea soup</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Ice cream</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Pizza</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

HIGH G.I. FOODS > 70
MEDIUM G.I. FOODS 55-70
LOW G.I. FOODS < 55

Foster-Powell K et al. Am J Clin Nutr 2002;76:5-56

High Glycemic Foods

- ALMOST ALL REFINED GRAINS HAVE HIGH GLYCEMIC INDICES
- Rice Chex Cereal 89
- Corn flakes 84
- Pretzels 83
- Rice Krispie Cereal 82
- Rice Cakes 82
- Rye bread 76
- Waffles 76
- Total Cereal 76
- Graham crackers 74
- Cheerios 74
- Bagels 72
- Short grain white rice 72
- Corn chips 72
- White bread 70
- Whole Wheat bread 69

Foster-Powell K et al. Am J Clin Nutr 2002;76:5-56
Fruits & Vegetables: Low Glycemic Load Carbohydrates

- Almost all fruits & veggies have low glycemic loads (Glycemic index x CHO content 100 g portion)
- Parsnips 19.5
- Sweet Potato 13.1
- Banana 12.1
- Yam 11.5
- Pineapple 8.2
- Grapes 7.7
- Carrots 7.5
- Kiwi fruit 7.4
- Beets 6.3
- Apple 6.0
- Pear 5.4
- Watermelon 5.2
- Orange 5.1

Foster-Powell K et al. Am J Clin Nutr 2002;76:5-56

Legumes & Nuts: Low Glycemic Load Carbohydrates

- Almost all nuts & legumes have low glycemic loads (Glycemic index x CHO content 100 g portion)
- Broad beans 15.5
- Baked beans 10.4
- Navy beans 10.0
- Garbanzo beans 9.0
- Black eyed peas 8.5
- Lima beans 7.6
- Black beans 7.1
- Peas 6.8
- Cashews 6.3
- Kidney beans 6.2
- Lentils 5.8
- Peanuts 2.6

Foster-Powell K et al. Am J Clin Nutr 2002;76:5-56

Glycemic & Insulin Response to Animal Foods (Meat, Fish, Eggs)

- Animal foods usually contain no carbohydrate
- However, they do elicit both glucose and insulin responses
- The insulin response is caused by a direct stimulatory effect of increased circulating levels of dietary amino acids on the pancreas and by:
  - The secretion of two insulinotropic gut hormones in response to the meal: (1) Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)
  - However, the glucose and insulin response are minimal relative to high GI carbohydrates

Glycemic Index/Insulin Metabolism (Dairy):

- Milk, Skim Milk, Fermented Milk and yogurts have low glycemic indices
  - Skim Milk 32
  - Whole Milk 27
  - Reduced Fat Yogurt 27
  - Non Fat Yogurt 24
  - Fermented Milk (3% fat) 11
  - But paradoxically have insulin indices similar to:
    - White Bread 100
    - Yogurt 115
    - Fermented Milk 98
    - Whole Milk 90
    - Skim Milk 90

Foster-Powell K et al. Am J Clin Nutr 2002;76:5-56
High Fructose Corn Syrup

- Although pure (100%) fructose has a low GI (23)
- It is highly insulinotropic when blood glucose is even moderately elevated
- Because the most common forms of fructose (HFCS 42, 55) are mixtures of high GI glucose & fructose
- The most common manufactured forms of HFCS elicit both high glycemic & insulinotropic responses

(Fructose + Glucose) – 3 versions:
1. HFCS 42: 42% fructose (GI = 23) + 53% glucose (GI = 100)
2. HFCS 55: (55% fructose + 42% glucose) – soft drinks
3. HFCS 90: (90% fructose + 8% glucose) – “low cal” foods


Insulin Resistance: What is it?

- When skeletal muscle resists insulin mediated uptake of glucose:
- “Clinically defined insulin resistance occurs”
- Skeletal muscle is principal site of insulin resistance, other tissues develop insulin resistance:
  1. Adipose tissue
  2. Liver
  3. Endothelial cells
  4. Other peripheral tissues

Insulin Resistance: Compensatory Hyperinsulinemia

- When insulin resistance occurs:
- Long term glucose levels do not necessarily rise
- Because the pancreas secretes more insulin
- The maintenance of normal glucose via increased insulin secretion is referred to as:
- COMPENSATORY HYPERINSULINEMIA:
- The fundamental metabolic disturbance underlying the Metabolic Syndrome

Per Capita Percentages of Highly Glycemic and Highly Insulinemic Foods in the U.S. Diet (1990-99)

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Food Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.3</td>
<td>Refined Sugars</td>
</tr>
<tr>
<td>20.3</td>
<td>Refined Grains</td>
</tr>
<tr>
<td>6.3</td>
<td>Potatoes</td>
</tr>
<tr>
<td>6.3</td>
<td>Dairy (except cheese)</td>
</tr>
<tr>
<td>2.5</td>
<td>Other Foods</td>
</tr>
</tbody>
</table>

47.7% of the energy in the typical U.S. diet comes from foods capable of promoting insulin resistance
Insulin Resistance: Impairment of Signaling Pathway

- GLUT4 is the major insulin-stimulated glucose transporter &
- Is the rate controlling step in insulin-mediated glucose uptake in muscle
- Muscle cell surface GLUT4 content is severely reduced in Type 2 Diabetics
- The precise metabolic step or steps impairing GLUT4 expression are still unclear

Muscle Cell

GLUT4
Insulin Receptor
Tyrosine Kinase
Enzyme Phosphorylation Cascades

GLUT4
Muscle Cell

Insulin Resistance: Proximate Causes

- Chronically elevated glucose
- Chronically elevated non-esterified free fatty acids
- Chronically elevated VLDL in the post-prandial and fasting states

High Glycemic Foods May Promote the 4 Proximate Causes of Insulin Resistance

- Chronically elevated glucose
- Chronically elevated non-esterified free fatty acids
- Chronically elevated VLDL in the post-prandial and fasting states

How May High Glycemic Load Foods Induce Peripheral Insulin Resistance

- High glycemic load carbohydrates elevate VLDL synthesis
- Increased triglyceride (TAG) concentration in muscle cells inhibits entry of glucose (insulin resistance) which:
  - Causes increased pancreatic secretion of insulin (hyperinsulinemia)
  - Glucose enters adipocytes, along with VLDL-TAG causing adipose tissue hypertrophy & insulin resistance which,
  - Increases adipocyte lypolysis which elevates NEFA which contributes to muscle insulin resistance
GI Affects Day-long Concentrations of Insulin
7 healthy male subjects after 3 days of feeding

Kiens and Richter Am J Clin Nutr 1996;63:47

Glycemic Index & Insulin Resistance
Inulin response in 30 patients following Oral Glucose Tolerance Test (OGTT) after 4 weeks on high or low GI diets

Frost et al. Metabolism 1996;45:669-72

Relationship of Circulating Insulin Levels to IGF-1 and IGFBP-1 Levels
Pancreas Secretes:
1. Insulin → Free IGF-1 is a potent mitogen (growth stimulator) for all cells in the body
   ≈ Most of IGF-1 is not free and is bound to at least 6 IGF Binding Proteins
   ≈ Hence, the presence or lack of IGFBPs determines the concentration of free IGF-1 in plasma

Liver Secretes:
1. Insulin like Growth Factor-1 (IGF-1)
2. IGF-1 Binding Protein (IGFBP-1)

Brismar K et al. J Clin Endocrinol Metab 1994;79:872-78

Relationship of Circulating Insulin Concentrations to IGF-1 and IGFBP-1 Concentrations

Blood concentrations of insulin and IGFBP-1 vary inversely throughout the day
The suppression of IGFBP-1 by insulin elevates circulating concentrations of free IGF-1
Relationship of Circulating Insulin Concentrations to IGF-1 and IGFBP-1 Concentrations

- Recent experiments show that compensatory hyperinsulinemia that characterize adolescent obesity:
  1. Suppress IGFBP-1
  2. Increase IGF-1
  3. Increase pubertal development
  4. Increase Height


IGF-1 Acts Systemically to Increase Stature & Reduce Pubertal Age:

- Low concentrations of IGF-1 are associated with short stature & high levels are associated with increased stature in humans
- Human recombinant IGF-1 therapy improves linear growth
- Hyperinsulinemic adolescents with elevated IGF-1 are more sexually mature than subjects with superior insulin sensitivity
- Recombinant IGF-1 therapy in primates increases tempo of puberty

Ituri Pygmies maintain Low IGF-1


Relationship of Circulating Insulin Concentrations to IGFBP-3 and the RXRα Nuclear Receptor

- IGFBP-3 inhibits growth and promotes apoptosis (programmed cell death) in many but not all cell lines¹
- IGFBP-3 is reduced by insulin indirectly via negative feedback upon growth hormone²
- IGFBP-3 is a ligand for the RXRα nuclear receptor & interferes with formation of the RXR:RAR heterodimer¹
- The ligand for the RARα is all trans retinoic acid (ATRA)³
- In sclera, ATRA inhibits glycosaminoglycan synthesis, thereby thinning the sclera and promoting axial elongation⁴
- Hence, low concentrations of IGFBP-3 may augment axial elongation by further inhibiting glycosaminoglycan synthesis⁴

2. Bristain K et al. J Clin Endocrinol Metab 1994;79:872-78
Insulin Resistance & Myopia

- With myopia the eyeball has grown too long for the refractive power of the lens and cornea
- This elongation is chiefly caused by excessive near work resulting in a blurred image in the non-foveal retina
- The blurred retinal image induces axial elongation by increasing the all trans retinoic acid (ATRA) synthesis from the retina/choroid to the scleral chondrocytes
- ATRA inhibits glycosaminglycan synthesis, thereby thinning the sclera and promoting axial elongation
- Diet induced hyperinsulinemia lowers IGFBP-3
- Hence, low concentrations of IGFBP-3 may augment axial elongation by further inhibiting glycosaminglycan synthesis


Insulin Resistance & Myopia: Corroborative Date

- Most, but not all studies show myopes to be taller than non myopes
- Perhaps a diet induced IGF-1 effect


Insulin Resistance & Myopia: Corroborative Date

- Myopic children have greater body mass indices (Wt/ht²) than non-myopes
- Perhaps because of insulin resistance & accelerated growth


Insulin Resistance & Myopia: Corroborative Date

- Hyperinsulinemia & Insulin resistance occur more frequently in women with early menarche compared to normal menarche
- Cross sectional and prospective studies show an earlier age of menarche in female myopes
- Who were also taller

Observations from a number of Scandinavian studies demonstrate an increased incidence of myopia in Type 2 diabetics1,2


Apolipoprotein A-I (ApoA-I) is the major protein component of high density lipoprotein (HDL) in plasma

A recent molecular proteomics study demonstrated that apoA-1 serves as a cellular “STOP” signal for scleral growth in myopia1

Lowered HDL is a ubiquitous symptom of insulin resistance and the metabolic syndrome2

High glycemic load carbohydrates lower HDL

These data suggest that insulin resistance may enhance vitreal chamber growth by reducing the ApoA-1 STOP signal for scleral tissue


Thank You!