Statural Growth Impairment in Pediatric Crohn’s Disease

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Learning Objectives

• Review what is known about the etiology of statural growth impairment and sex differences in statural growth impairment in pediatric Crohn’s disease

• Illustrate the importance of utilizing bone age in interpreting statural growth in pediatric Crohn’s disease

• Strategize next steps to improve our understanding of the underlying mechanisms of statural growth impairment in pediatric Crohn’s disease in order to optimize management

Outline

• Background

• Multicenter Growth Study

• Future Directions
Background:
Growth Impairment

Commonly Used Definitions of Growth Impairment

- Height below the 3rd-5th percentile
- Decrease in height velocity below the 3rd-5th percentile
- Fall off the child’s growth curve

Prevalence

<table>
<thead>
<tr>
<th>Metric</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative height Z score</td>
<td>72%</td>
</tr>
<tr>
<td>Height Z score &lt; -1.64</td>
<td>23%</td>
</tr>
<tr>
<td>Decreased height velocity prior to diagnosis</td>
<td>88%</td>
</tr>
<tr>
<td>Reduction in height velocity before intestinal symptoms</td>
<td>42%</td>
</tr>
<tr>
<td>Height velocity &lt; 4 cm/year</td>
<td>24%</td>
</tr>
</tbody>
</table>

Kanof et al, Gastroenterology, 1988
Meld et al, Gastroenterology, 1993
NIH/NIDDK’s Opportunities & Challenges in Digestive Diseases Research: Research Objectives

- Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents
- Define the mechanisms that produce growth delay in pediatric IBD patients
- Identify approaches that enable normal growth and development within the context of pediatric IBD

Etiologies of Statural Growth Impairment in Pediatric Crohn’s Disease

What We Know
Some reports point to disease severity as the major determinant of growth.

Motil et al, Gastroenterology, 1993
Griffiths et al, Gut, 1993
Wine et al, Pediatrics, 2004
Some reports point to disease severity as the major determinant of growth.

Motil et al, Gastroenterology, 1993
Griffiths et al, Gut, 1993
Wine et al, Pediatrics, 2004

Taken together, the available data suggest that the negative impact of inflammation on growth is greater in males.

Sex Differences in Statural Growth Impairment in Crohn’s Disease
What We Know
Growth of Children with Crohn’s disease

<table>
<thead>
<tr>
<th>Sex</th>
<th>Initial Height Z Score</th>
<th>Ultimate Height Z Score</th>
<th>Changes in Height Z Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>-1.01 (1.06)</td>
<td>-0.48 (0.91)</td>
<td>0.66 (1.27)</td>
</tr>
<tr>
<td>Male</td>
<td>-1.22 (1.30)</td>
<td>-1.02 (1.19)</td>
<td>0.16 (0.50)</td>
</tr>
</tbody>
</table>

P=0.02

Gupta et al, Pediatric IBD Consortium, Gastroenterology, 2006
Gupta et al, Pediatric IBD Consortium, Pediatrics, 2007
Griffiths et al, Gut, 1993
### Growth, Body Composition, & Nutritional Status in Children & Adolescents With Crohn’s Disease

#### Deficits in Growth & Nutritional Status in Males with Crohn’s versus Male Controls

<table>
<thead>
<tr>
<th>Male subjects</th>
<th>Control (n = 37)</th>
<th>CD (n = 44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAZ</td>
<td>0.36 ± 0.05</td>
<td>0.39 ± 0.10</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI</td>
<td>17.0 ± 2.6</td>
<td>18.5 ± 2.10</td>
<td>0.0001</td>
</tr>
<tr>
<td>AUC</td>
<td>0.00 ± 0.02</td>
<td>0.00 ± 0.02</td>
<td>0.33</td>
</tr>
<tr>
<td>FRF</td>
<td>-0.07 ± 0.04</td>
<td>0.00 ± 0.03</td>
<td>0.47</td>
</tr>
<tr>
<td>VMAG</td>
<td>0.59 ± 0.70</td>
<td>0.47 ± 0.35</td>
<td>0.08</td>
</tr>
<tr>
<td>FMR</td>
<td>0.49 ± 0.75</td>
<td>0.54 ± 0.34</td>
<td>0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female subjects</th>
<th>Control (n = 37)</th>
<th>CD (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAZ</td>
<td>-0.08 ± 0.06</td>
<td>-0.14 ± 0.19</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI</td>
<td>16.8 ± 2.1</td>
<td>17.4 ± 2.50</td>
<td>0.27</td>
</tr>
<tr>
<td>AUC</td>
<td>0.02 ± 0.05</td>
<td>0.02 ± 0.02</td>
<td>0.75</td>
</tr>
<tr>
<td>FRF</td>
<td>-0.08 ± 0.09</td>
<td>-0.11 ± 0.08</td>
<td>0.38</td>
</tr>
<tr>
<td>VMAG</td>
<td>0.54 ± 0.70</td>
<td>0.38 ± 0.34</td>
<td>0.08</td>
</tr>
<tr>
<td>FMR</td>
<td>0.42 ± 0.65</td>
<td>0.38 ± 0.33</td>
<td>0.12</td>
</tr>
</tbody>
</table>


### Nutritional Status & Growth in Pediatric Crohn’s Disease: A Population-Based Study

#### Sex Differences in Ht Z Score at Maximal Follow-Up

<table>
<thead>
<tr>
<th>Sex</th>
<th>Height Z Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (N=156)</td>
<td>-0.43</td>
<td>0.0002</td>
</tr>
<tr>
<td>Females (N=105)</td>
<td>-0.04</td>
<td></td>
</tr>
</tbody>
</table>

Vasseur et al, Am J Gastroenterol, 2010

### Final Adult Height Childhood- vs Adult- Onset Crohn’s Disease

<table>
<thead>
<tr>
<th>Sex</th>
<th>Childhood-Onset CD (N = 206)</th>
<th>Adult-Onset CD (N = 412)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>172.8 ± 7.4</td>
<td>176.4 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Females</td>
<td>162.2 ± 5.9</td>
<td>163.1 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>167.9 ± 8.6</td>
<td>170.3 ± 9.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pigneur et al, Inflamm Bowel Dis, 2010
NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males

NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early ’90s to increase the number of women in NIH-funded clinical research. Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice.

NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women’s Health, and me in the Nature Comment below.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

NIH OFFICE OF RESEARCH ON WOMEN’S HEALTH (ORWH)

Director’s Page

Considering Sex as a Biological Variable: in the NIH Guide

June 9, 2015

This week’s NIH Guide contains a announcement our expectation that PIs will account for the possible role of sex on experimental outcome in studies of animal and human subjects. Pending approval from the Office of Management and Budget, the NIH Office of Extramural Research will be updating instructions for applicants as part of NIH’s efforts to enhance reproducibility through rigor and transparency. In short, applicants will be asked to include SABV information in the Research Strategy section of applications, and study sections will be reviewing this information.
This new policy for grants sends a good message to scientists and drug makers on the importance of considering sex in designing research projects. If they want to understand diseases that appear to affect men and women differently and develop medicines effective for those diseases.
Male-Female Dichotomy in Risk for Developing Statural Growth Impairment

Window for furthering our understanding of the effects of inflammation on growth in both sexes

Major Endocrinologic Regulators of Statural Growth

- Growth Hormone/Insulin-Like Growth Factor-1 Axis
- Hypothalamic-Pituitary-Gonadal Axis
**Estrogen, Bone, Growth, & Sex: A Sea Change in Conventional Wisdom**

Aromatase Deficiency in Male & Female Siblings Caused by a Novel Mutation & the Physiological Role of Estrogens

Bone Age = 14 Years

Chronological Age = 24 Years
Estrogen: Consequences & Implications of Human Mutations in Synthesis & Action

Growth Hormone

IGF-1 IGFBP-3

Statural Growth

LH FSH

Testosterone -> Estradiol

Grumbach & Auchus, J Clin Endocrinol Metab, 1999
Hypotheses

• Primary:
  • IGF-1 levels are lower in males compared with females with Crohn’s disease

• Secondary:
  • Inflammatory markers predict IGF-1 levels in patients with Crohn’s disease

IGF-1 Z Scores Are Lower in Males

<table>
<thead>
<tr>
<th>Z Score</th>
<th>IGF-1 Z Scores</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Male</td>
<td>Sex Difference*</td>
<td></td>
</tr>
<tr>
<td>CA-Z (N=82)</td>
<td>-0.97 ± 1.08 (-2.87, 0.97)</td>
<td>-1.46 ± 1.10 (-3.61, 0.94)</td>
<td>-0.50</td>
</tr>
<tr>
<td>BA-Z (N=49)</td>
<td>-0.12 ± 1.49 (-2.73, 2.74)</td>
<td>-1.26 ± 1.16 (-3.23, 0.94)</td>
<td>-1.24</td>
</tr>
</tbody>
</table>

IGFBP-3 Z Scores Are Lower in Males

<table>
<thead>
<tr>
<th>Z Score</th>
<th>IGFBP-3 Z Scores</th>
<th>95% CI</th>
<th>P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Male</td>
<td>Sex Difference*</td>
<td></td>
</tr>
<tr>
<td>CA-Z (N=82)</td>
<td>-0.25 ± 1.11 (-1.79, 2.50)</td>
<td>-0.95 ± 1.06 (-3.08, 1.73)</td>
<td>-0.71</td>
</tr>
<tr>
<td>BA-Z (N=49)</td>
<td>0.27 ± 1.34 (-1.18, 3.44)</td>
<td>-0.98 ± 0.73 (-2.37, 1.03)</td>
<td>-1.26</td>
</tr>
</tbody>
</table>
**Inflammation Predicts IGF Z Scores**

<table>
<thead>
<tr>
<th>Marker</th>
<th>ESR</th>
<th>CRP</th>
<th>Albumin</th>
<th>BMI Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td>ΔR²</td>
<td>P Val</td>
<td>ΔR²</td>
<td>P Val</td>
</tr>
<tr>
<td>IGF-1 CA-Z</td>
<td>10.0</td>
<td>.002</td>
<td>17.1</td>
<td>.0001</td>
</tr>
<tr>
<td>IGF-1 BA-Z</td>
<td>9.1</td>
<td>.02</td>
<td>13.7</td>
<td>.003</td>
</tr>
<tr>
<td>IGFBP-3 CA-Z</td>
<td>5.5</td>
<td>.07</td>
<td>3.5</td>
<td>.07</td>
</tr>
<tr>
<td>IGFBP-3 BA-Z</td>
<td>5.6</td>
<td>.14</td>
<td>3.6</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of undernutrition in a rat model of colitis**

**Inflammatory Markers Correlate with Hormone Levels in Males**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol Z (CA)</td>
<td>-0.09* (0.73)**</td>
<td>-0.13 (0.63)</td>
</tr>
<tr>
<td>Estradiol Z (BA)</td>
<td>-0.11 (0.52)</td>
<td>-0.28 (0.28)</td>
</tr>
<tr>
<td>FSH Z (CA)</td>
<td>-0.35 (1.00)</td>
<td>-0.49 (0.04)</td>
</tr>
<tr>
<td>FSH Z (BA)</td>
<td>-0.27 (1.06)</td>
<td>-0.53 (0.02)</td>
</tr>
<tr>
<td>Testosterone Z (CA)</td>
<td>-0.12 (0.50)</td>
<td>0.07 (0.80)</td>
</tr>
<tr>
<td>Testosterone Z (BA)</td>
<td>-0.08 (0.64)</td>
<td>-0.06 (0.82)</td>
</tr>
<tr>
<td>LH Z (CA)</td>
<td>-0.31 (1.03)</td>
<td>-0.38 (1.03)</td>
</tr>
<tr>
<td>LH Z (BA)</td>
<td>-0.12 (1.43)</td>
<td>-0.52 (0.03)</td>
</tr>
<tr>
<td>Alb</td>
<td>0.18 (0.29)</td>
<td>0.23 (0.36)</td>
</tr>
<tr>
<td></td>
<td>0.20 (0.25)</td>
<td>0.20 (0.43)</td>
</tr>
<tr>
<td></td>
<td>0.40 (0.20)</td>
<td>0.48 (0.20)</td>
</tr>
<tr>
<td></td>
<td>0.26 (0.87)</td>
<td>0.51 (0.02)</td>
</tr>
</tbody>
</table>
Delayed Puberty and Response to Testosterone in a Rat Model of Colitis

- Colitic versus normal rats
- Testosterone reduced in colitic males
- No difference in estradiol levels in colitic vs normal females

Results

- Mean BA-Z score $= -1.4 \pm 1.5$ (std dev)
- BA-Z score $<-2$ in 41%
- Lower BA-Z scores in females ($p=.02$)
### Chronologic Age vs Bone Age for Interpretation of Growth

**TABLE 3.** Comparison between Chronological Age and Bone Age for Interpretation of Growth

<table>
<thead>
<tr>
<th>Growth Parameter</th>
<th>Z Score Difference*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>0.73</td>
<td>0.45 to 1.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.51</td>
<td>0.29 to 0.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.23</td>
<td>0.13 to 0.33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Z score difference = growth parameter BA-Z score minus growth parameter CA-Z score.

---

### Percentile Difference (CA vs BA for Interpretation of Growth)

<table>
<thead>
<tr>
<th>CA-Z Score</th>
<th>CA-Percentile</th>
<th>BA-Z score</th>
<th>BA-Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>2.3%</td>
<td>-1.27</td>
<td>10.2%</td>
</tr>
<tr>
<td>-1</td>
<td>15.9%</td>
<td>-0.27</td>
<td>39.4%</td>
</tr>
<tr>
<td>CA-Z Score</td>
<td>CA-Percentile</td>
<td>BA-Z score</td>
<td>BA-Percentile</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>-2</td>
<td>2.3%</td>
<td>-1.27</td>
<td>10.2%</td>
</tr>
<tr>
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<td>15.9%</td>
<td>-0.27</td>
<td>39.4%</td>
</tr>
</tbody>
</table>

Percentile Difference (CA vs BA for Interpretation of Growth)

Gupta et al, Inflamm Bowel Dis, 2013
Percentile Difference (CA vs BA for Interpretation of Growth)

<table>
<thead>
<tr>
<th>CA-Z Score</th>
<th>CA-Percentile</th>
<th>BA-Z score</th>
<th>BA-Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>2.3%</td>
<td>-1.27</td>
<td>10.2%</td>
</tr>
<tr>
<td>-1</td>
<td>15.9%</td>
<td>-0.27</td>
<td>39.4%</td>
</tr>
</tbody>
</table>

Take-Home Message

Bone age measurements allow clinically meaningful interpretation of statural growth—a dynamic marker of disease status.
Menarche in Pediatric Patients with Crohn’s Disease

Age at Menarche

CA at Menarche by Race in CD
Bone Age at Menarche in CD

If menarche has not occurred by a bone age > 14.0 years, endocrinology referral should be considered.

Additional Background

• Sex differences in inflammatory cytokine expression have been reported in hepatic ischemia, multiple sclerosis, and sepsis

• *In vitro* models suggest that inflammatory cytokines (TNF-α) reduce testosterone
  - Crockett et al, J Hepatol, 2006; Nguyen et al, J Neurol Sci 2003; Schneider et al, Arch Surg 1988

• Reduced androgen levels in males with CF, JIA, SLE

Additional Background

• Growth impairment is a common complication of many chronic inflammatory diseases

• Crohn’s disease - *model* for studying effects of inflammation on statural growth
Funded by NICHD R01 HD075929

Purpose

• Improve our understanding of mechanisms of growth impairment
  ➢ Develop new targeted medical treatment strategies to improve height velocity and final adult height
  ➢ Optimize current treatment approaches in high risk patients

• Identify high risk patients

Growth Study Team

- Neera Gupta, Principal Investigator
- Howard Andrews, Director, DCC
- Cheng-Shiu Lee, Biostatistician
- Robert Lustig, Pediatric Endocrinologist
- Joel Rosh, Site PI
- Francisco Sylvester, Site PI
Growth Study Goals

- Determine sex differences in the longitudinal impact of inflammation on
  - GH/IGF-1 axis
  - Hypothalamic-pituitary-gonadal axis
  - Height velocity
    • Most sensitive parameter for detecting impaired statural growth

- Determine whether sex differences in the inflammatory cytokine profile exist
  - TNF-α
  - IL-1β
  - IL-6
  - IL-1RA

- Explain the apparent sexual dimorphism in the impact of inflammation on growth?
Growth Study Goals

- Develop a predictive model for each sex
  - Identify pts at high risk for growth impairment refractory to standard therapeutic approaches
    - Narrow therapeutic window to intervene to improve growth
    - Candidates for early intervention with more aggressive therapy?

Participants

- N = 125
- Inclusion criteria based on bone age
  - Females: BA 9 – 12 years
  - Males: BA 10 -14 years
- Capture
  - puberty based on the lower BA limit
  - pubertal growth spurt based on the upper BA limit

Study Procedures

<table>
<thead>
<tr>
<th>Interval</th>
<th>2 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Study Procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Age</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Medical History</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Clinical &amp; Self-Tanner Exam</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Weight</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Nutrient Intake Assessment</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Mood State</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>
Future Directions

- Ancillary studies of enrolled cohort
- Growth in Pediatric Ulcerative Colitis
- Multicenter RCT
  - Eligibility criteria:
    - "high risk" patients identified by prediction models for each sex
  - Examine early intervention with aggressive therapy

My Professional Dream

Growth Center for Children with Chronic Inflammatory Diseases (GCC-CID’s)

- Multidisciplinary patient care and research center
  - Improve our understanding of the impact of inflammation on statural growth
  - Optimize treatment strategies
Take Home Messages

• Active inflammation may contribute to growth impairment in a patient who appears clinically well (no intestinal symptoms)

• Consider skeletal maturation and pubertal status in the interpretation of statural growth

• Statural growth should help guide therapeutic decisions

• Consider effects of sex on outcomes

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Take Home Messages

• Inform patients of opportunities to participate in research studies

• Collaborate—team science is essential

• Evidence-based medicine should drive our clinical care

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Research Funding

• NICHD R01 075929

• NIDDK K23 077734

• CDHNF (NASPGHAN Foundation)/CCFA Award for New Investigators

• CCFA Career Development Award
Thank You

@NeeraGuptaMD

#GrowthStudy
Dr. Neera Gupta, MD, MAS, a Pediatric Gastroenterologist at Weill Cornell Medical College and New York-Presbyterian Phyllis and David Komansky Center for Children’s Health, and her team are conducting a research study. We are looking for volunteers (males—ages 9 to 15 years—and—females—ages 8 to 13 years) who have Crohn’s disease.

We are learning about growth in pediatric patients with Crohn’s disease with the hope that we may improve the care of pediatric patients with inflammatory bowel disease.

If you have any questions about the study, or if you might be interested in participating, please contact:

Mr. Rafael Aguilar, Research Coordinator, at 646-962-4968 or raa2030@med.cornell.edu or Dr. Neera Gupta at (646) 962-3869.

Funded by:

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

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Growth Impairment Definitions for Our Study

- Height Velocity Z Score < -1.66
- Change in Height Velocity Z score of -0.5 from the screening visit
- Height Z Score < -1.66

*Z Scores Based on Bone Age*
Definition of “High Risk” for Our Study

• Patients who meet the definition of growth impairment despite standard treatment approaches

• Establish prediction model separately for each sex
  – well-known sex differences in growth impairment

NIH to balance sex in cell and animal studies

• Just over half of NIH-funded clinical research participants are women

• Example of importance of studying both sexes in clinical research:
  – Medications have
    • different preventive effects in women and men
    • different optimal dosing in women and men
    • higher rates of adverse reactions in women


NIH to balance sex in cell and animal studies

• Over-reliance on male animals and cells in pre-clinical research

• Obscures key sex differences that could help guide clinical studies

NIH to balance sex in cell and animal studies

• Lack of understanding about the potential magnitude of the effect of sex on the outcome being measured

• Inadequate analysis of data by sex
  – Irreproducibility in preclinical biomedical research


NIH to balance sex in cell and animal studies

• NIH developing policies requiring reporting of plans to balance male and female cells and animals in preclinical studies

• Policies will be rolled out in phases beginning October 2014


NIH Proceeds with Caution on Sex Balance in Biomedical Studies

"When they're done, it will be done, and the team will be sitting in the sun."
NIH Proceeds with Caution in Sex Balance on Biomedical Studies

- Funding rules have not yet changed
- NIH is gathering comments from researchers
  - Which research areas need sex balance the most
  - What challenges scientists face in including male and female subjects in their studies
- The NIH is also making videos and online tutorials to teach scientists who are new to studying both sexes how to design such studies
- Details about the policy and implementation plans are expected to roll out during the next year
Z Score

The Normal Curve

\[ Z = \frac{X - \text{mean}}{\text{standard deviation}} \]
Monitoring

- Biologic parental ht for calculation of target ht
  - Females: \[(Mother' s \text{ Ht (cm)} + Father' s \text{ Ht (cm)} - 13)/2\]
  - Males: \[(Mother' s \text{ Ht (cm)} + Father' s \text{ Ht (cm)} + 13)/2\]

- 3rd percentile for target ht = target ht - 8.5 cm

- 97th percentile for target ht= target ht + 8.5 cm

Enteral Nutrition

- P< .01 EN observational yr vs EN experimental yr
- P< .01 EN vs Controls (experimental yr)
**Surgery**

Height Velocities (cm/yr)

![Graph showing height velocities before and after surgery](ligon et al, Eur J Pediatr, 1990)

**6-Mercaptopurine**

Mean Linear Growth (cm)

![Graph showing mean linear growth with 6-MP and controls](markowitz et al, Gastroenterology, 2000)

No difference between groups

Study Time Period

Markowitz et al, Gastroenterology, 2000
Infliximab

P=0.014 HV-Z Change: Remission vs Partial Response
P= 0.04 Change in HT-Z: Efficacy
P=0.52 Change in HT-Z: Failure

Walters et al, Inflamm Bowel Dis, 2007
Crombe et al, Inflamm Bowel Dis, 2011

Growth Hormone

0.067

0.043

0.05

0.05

Mauras et al, Metabolism, 2002
Calenda et al, Inflamm Bowel Dis, 2005
Wong et al, J Pediatr Endocrin Metab, 2007
Denson et al, J Pediatr Gastroenterol Nutr, 2010
Wong et al, J Pediatr Endocrinol Metab, 2011

GH Dose mg/kg/day

0 2 4 6 8 10 12

Heyman
Mauras
Denson
Wong
Wong (per wk)

P=0.23

GH Pre-GH
GH Post-GH
Change in HV

Mauras et al, Metabolism, 2002
Denson et al, J Pediatr Gastroenterol Nutr, 2010
Wong et al, Clin Endocrinol, 2011
Won g et al, J Pediatr Endocrinol Metab, 2011

GH Dose: mg/kg/day

0 0.5 1 1.5 2 2.5 3

HT-Z Pre-GH
HT-Z Post-GH
Change in HT Z

Mauras et al, Metabolism, 2002
Calenda et al, Inflamm Bowel Dis, 2005
Wong et al, J Pediatr Endocrin Metab, 2007
Denson et al, J Pediatr Gastroenterol Nutr, 2010
Wong et al, J Pediatr Endocrinol Metab, 2011

GH Dose mg/kg/day

[per wk]
Testosterone


IGF-1

Rao et al, Gut, 2011, ABSTRACT
Z Score

The Normal Curve
Monitoring

- Biologic parental ht for calculation of target ht
  - Females: \( \text{Mother’s Ht (cm)} + \text{Father’s Ht (cm)} - \frac{13}{2} \)
  - Males: \( \text{Mother’s Ht (cm)} + \text{Father’s Ht (cm)} + \frac{13}{2} \)

- 3rd percentile for target ht = target ht - 8.5 cm

- 97th percentile for target ht = target ht + 8.5 cm

Growth Impairment Definitions for Our Study

- Height Velocity Z Score < -1.66

- Change in Height Velocity Z score of -0.5 from the screening visit

- Height Z Score < -1.66

*Z Scores Based on Bone Age*