Dr. Nikhil Dhurandhar
John H. Hernandez Professor in Health Promotion
Louisiana State University
INFECTOBESITY: Obesity of Infectious Origin

Nikhil V. Dhurandhar
John H. Hernandez Endowed Professor in Health Promotion
Infection and Obesity Laboratory
Pennington Biomedical Research Center
Louisiana State University System
Baton Rouge, Louisiana
“Most Obese persons will not stay in treatment for Obesity. Of those who stay in treatment, most will not lose weight, and of those who do lose weight, most will regain it.”

- Albert Stunkard, 1958
The Bombay Hospital Journal, Vol. 29, No. 4, 1987

EXPERIENCE WITH 10,000 CASES OF OBESITY

V. A. DHURANDHAR
N. V. DHURANDHAR

This is a comment on experience gained during the treatment of 10,000 cases of Obesity. The age group was from 3 years to 73 years and the proportion of females to males was 3:1. Findings regarding S. cholesterol, S. triglycerides, S. uric acid, Body fat % etc. of a section of the group were statistically analysed with a computer and discussed. Patient’s ideas and attitudes about gaining, losing and maintaining weight are revealed which can lead to better understanding and treatment of Obesity.
TREATMENT VS. RESEARCH

e.g. CANCER / HIV
Just one big meal does not cause obesity.

Just one small meal does not fix obesity.
The search for effective & meaningful approaches.
OBESITY

A complex disease with multi-factorial etiology.

It requires a multi-factorial treatment and prevention approach.
CAUSE-SPECIFIC APPROACH

Different prevention & treatment strategies

BETTER RESULTS?
Ten Putative Contributors to the Obesity Epidemic

EMILY J. McALLISTER,1 NIKHIL V. DHURANDHAR,1 SCOTT W. KEITH,2 LOUIS J. ARONNE,3 JAMIE BARGER,4,5 MONICA BASKIN,6 RUTH M. BENCA,7 JOSEPH BIGGIO,8 MARY M. BOGGIANO,9 JOE C. EISENMMANN,10 MALELOPEI 11 KEVIN P. FONTAINE 12 PETER CLUCKMAN 13

Infections; Endocrine disrupters; Sleep debt;
Pharmaceutical iatrogenesis; Ambient temperature;
Intrauterine and Intergenerational effects; Epigenetics;
Maternal age; Assortative mating
Is Obesity an infectious disease?
Is Gastric Ulcer an infectious disease?
Causes of gastric ulcer?

Hurry

Worry

and Curry
THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Barry J. Marshall

J. Robin Warren

2005

“for their discovery of the Bacterium Helicobacter pylori and its role in Gastritis and peptic ulcer disease.”
Obesity of infectious origin
Significance of Infectobesity Research

1) Obesity has multifactorial etiology, but the treatment is not cause-specific

2) Specific prevention / treatment strategies

3) Small pox eradication!
Chickens: SMAM-1 increases adiposity & reduced serum lipids

Obese Humans: SMAM-1 is associated with greater BMI and lower lipids
Adipogenic microbes

5. Avian adenovirus SMAM-1. Dhurandhar et al, 1992
AD-36 INCREASES ADIPOSITY IN ANIMAL MODELS

AD-36 INCREASES ADIPOSITY IN MARMOSETS

Weight change

Body fat %

Total Body Fat (%)
Virus-induced obesity

Mechanism of Action?
A Human Adenovirus Enhances Preadipocyte Differentiation
Sharada D. Vangipuram,* Jonathan Sheele,∗ Richard L. Atkinson,§ Thomas C. Holland,† and Nikhil V. Dhurandhar*†

Adipogenic Human Adenovirus Ad-36 Induces Commitment, Differentiation, and Lipid Accumulation in Human Adipose-Derived Stem Cells
Magdalena Pasarica,∗ Nazar Mashtalir,∗ Emily J. McAllister,∗ Gail E. Kilroy,∗ Juraj Koska,b Paska Permana,b Barbora de Courten,b,c Minghuan Yu,d Eric Ravussin,a Jeffery M. Gimble,a and Nikhil V. Dhurandhar∗a

Adipogenic Cascade Can Be Induced Without Adipogenic Media by a Human Adenovirus
Miloni A. Rathod1,2, Pamela M. Rogers2, Sharada D. Vangipuram1, Emily J. McAllister2 and Nikhil V. Dhurandhar2

ORIGINAL ARTICLE
Novel genes and cellular pathways related to infection with adenovirus-36 as an obesity agent in human mesenchymal stem cells
H-N Na1,3, H Kim2,3 and J-H Nam1
Mechanism of action of Ad36

Adipose tissue expansion by increasing proliferation, commitment, differentiation and lipid accumulation in adipocyte progenitors / ASC
Virus-induced obesity

A causative role in humans?
Do certain infections cause human obesity?

Challenges:

1. Obesity has insidious onset.
2. Multiple etiological factors – difficult to attribute to a factor
3. A combination of infection with other factors needed?
4. Ethical reasons preclude experimental infection of humans
Twin Study

Body weight of twins is similar

Hypothesis:

Ad36 infected co-twins will be heavier compared to uninfected co-twins.
Twin pairs (n=26) discordant for Ad-36 antibodies

<table>
<thead>
<tr>
<th></th>
<th>Antibody +</th>
<th>Antibody -</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>33.0 ± 15.7</td>
<td>33.0 ± 15.7</td>
</tr>
<tr>
<td><strong>Sex (% F / M)</strong></td>
<td>77 / 23</td>
<td>77 / 23</td>
</tr>
<tr>
<td><strong>BMI: (kg/m²)</strong></td>
<td>24.5 ± 5.2</td>
<td>23.1 ± 4.5*</td>
</tr>
<tr>
<td><strong>Body fat (%)</strong></td>
<td>29.6 ± 9.5</td>
<td>27.5 ± 9.9**</td>
</tr>
</tbody>
</table>

Longitudinal study – 10 y follow up

Serum samples of 1,400 Mexican American individuals

Exposure to Ad36 was associated with:

a) greater fat % at baseline,

b) greater increase in fat %

Lin WY et al. Diabetes Care, Nov 2012
<table>
<thead>
<tr>
<th>Participants</th>
<th>Country</th>
<th>Adenovirus</th>
<th>Screening method</th>
<th>Prevalence of infection</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhurandhar et al.14 1997</td>
<td>India</td>
<td>SMAM-1</td>
<td>Antibodies by agar precipitation</td>
<td>19%</td>
<td>SMAM-1-positive participants had significantly greater bodyweight and higher BMIs and significantly lower cholesterol and triglycerides than seronegative participants.</td>
</tr>
<tr>
<td>Atkinson et al.15 2005</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 30% Non-obese 11%</td>
<td>Ad36-positive individuals had significantly higher BMIs and lower cholesterol and triglycerides than seronegative counterparts. Ad36 positivity was not related to age.</td>
</tr>
<tr>
<td>Atkinson et al.15 2005</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 22% Non-obese not reported</td>
<td>Among Ad36-discordant twins, the Ad36-positive twin had significantly higher BMI and more body fat than their uninfected sibling.</td>
</tr>
<tr>
<td>Pasarica et al.16 2008</td>
<td>USA</td>
<td>Ad36</td>
<td>Viral DNA by nested PCR</td>
<td>27% positive for Ad36 DNA in subcutaneous adipose tissue</td>
<td>Ad36-DNA-positive participants developed eight times more adipocytes than their seronegative counterparts.</td>
</tr>
<tr>
<td>Trovato et al.17 2009</td>
<td>Italy</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 65% Non-obese 33%</td>
<td>Ad36-positive participants had significantly higher BMIs and waist-to-hip ratios, and were significantly older, than seronegative individuals.</td>
</tr>
<tr>
<td>Goossens et al.18 2009</td>
<td>Netherlands and Belgium</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 6% Non-obese 4%</td>
<td>Ad36 positivity was not associated with BMI or sex, but increased significantly with age.</td>
</tr>
<tr>
<td>Broderick et al.19 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 34% Non-obese 39%</td>
<td>Ad36 positivity was not associated with BMI or lipid concentrations. African Americans were more likely to be Ad36-positive than white participants. Women were significantly more likely to be Ad36-positive than men. Older people were more likely to be Ad36-positive than younger people.</td>
</tr>
<tr>
<td>Trovato et al.14 2009</td>
<td>Italy</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>NAFLD 32% Non-NAFLD 47%</td>
<td>Ad36 positivity was associated with higher BMI and greater fat mass in NAFLD patients than in Ad36-negative.</td>
</tr>
<tr>
<td>Na et al.20 2010</td>
<td>South Korea</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 29% Non-obese 14%</td>
<td>Ad36 positivity was significantly associated with an increase in BMI and higher serum cholesterol and triglyceride concentrations than being Ad36 negative.</td>
</tr>
<tr>
<td>Atkinson et al.18 2010</td>
<td>South Korea</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese and overweight 30% Non-obese not reported</td>
<td>Ad36 positivity was significantly associated with BMI Z score and waist circumference, but not with lipid concentrations.</td>
</tr>
<tr>
<td>Gabbert et al.21 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 22% Non-obese 7%</td>
<td>Ad36-positive obese participants had significantly higher BMIs, waist circumferences, and waist-to-height ratios than their Ad36-negative counterparts. Ad36-positive non-obese individuals had significantly higher BMIs and waist-to-hip ratios and were significantly older than seronegative counterparts.</td>
</tr>
<tr>
<td>Salehian et al.22 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Viral DNA by nested PCR</td>
<td>Adult with abnormal adiposity was positive for Ad36 DNA in adipose tissue. Two of eight obese adults without abnormal fat were positive for Ad36 DNA in adipose tissue.</td>
<td>Ad36 DNA is present in adipose tissue of obese participants. Abnormal adiposity was associated with Ad36 DNA in adipose tissue.</td>
</tr>
</tbody>
</table>

BMI = body-mass index. NAFLD = non-alcoholic fatty liver disease.
AD-36 STUDIES

Korea, China

Australia

USA:
CA, GA, MD, MO, (WI, MI, LA, VA)

Canada; Mexico

Sweden, Belgium, The Czech Republic; Italy; Poland, Turkey

Turkey
Association of Adenovirus 36 Infection with Obesity and Metabolic Markers in Humans: A Meta-Analysis of Observational Studies

Tomohide Yamada, Kazuo Hara*, Takashi Kadowaki
Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Japan

Ad36 & BMI
3.19 (1.44, 4.93), P<0.001;

Ad36 & Obesity
1.90 (1.01, 3.56), P=0.047;
EXPOSURE TO AD36 IS ASSOCIATED WITH OBESITY IN HUMANS


Serological data analyses show that adenovirus 36 infection is associated with obesity: A meta-analysis involving 5739 subjects.

Virus-induced obesity

Implications
Obesity Prevention & Treatment
Adenovirus 36 as an Obesity Agent Maintains the Obesity State by Increasing MCP-1 and Inducing Inflammation

Ha-Na Na and Jae-Hwan Nam

C57BL6 mice

WT vs MCP1 KO mice
Reduction of adenovirus 36-induced obesity and inflammation via the use of mulberry extract.

Na HN¹, Park S, Jeon HJ, Kim HB, Nam JH.

Prevention of Ad36-induced obesity

SHORT COMMUNICATION

Proof-of-concept for a virus-induced obesity vaccine; vaccination against the obesity agent adenovirus 36

H-N Na and J-H Nam
OBESITY
OBESITIES
OBESITIES

Unique prevention & treatment strategies for:

- Ad36-induced obesity
- Other adipogenic pathogens?
- Other types of “obesities”
A. United States Patents approved:
   1. Number 6,127,113. Viral Obesity methods and Compositions.
   2. Number 6,664,050. Viral Obesity methods and Compositions
   3. Number US 8,008,436B2: Adenovirus 36 E4orf1 gene & protein & their uses

B. Patents filed:
   2. Enhanced glycemic control using Ad36E4orf1 and AKT1 inhibitor

C. Provisional patent filed:
   1. Compositions and methods for improving glucose uptake
National Institutes of Health
American Diabetes Association
Federal Emergency Management Agency
American Egg Board
The Mathile Institute
Vital Health Interventions
Kellogg
Genentech
Novartis
Hoffman La Roche
Lei Cao, Ohio State University, NIH 121CA178227-01

Rena S. Day, University of Texas, FEMA

Melinda Sothern, NIH R01,

Jonathan Shaw, Baker IDI Heart Institute, Australia – NHMRC - proposal

Jae-Hwan Nam, South Korea, - proposal
COLLABORATORS / CONTRIBUTORS

Richard Atkinson, MD
Barbara Israel, PhD
Thomas Holland, PhD
David Allison, PhD
David Abbott, PhD
Joseph Kemnitz, PhD
Peter Havel, PhD
Juraj Koska, MD
Paska Permana, PhD
Phil Scherer, PhD
Ronald Javier, PhD
Melinda Sothern, PhD
Nancy Butte, PhD
Claude Bouchard, PhD
William Cefalu, MD
Jeff Gimble, MD, PhD
Frank Greenway, MD
Alok Gupta, MD
William Johnson, PhD
Cedric Moro, PhD
Eric Ravussin, PhD
Zhong Wang, MD
Jianping Ye, MD
Aamir Zuberi, PhD
Elizabeth Floyd, PhD
Sita Aggarwal, PhD
Sharada Vangipuram, PhD
Minghuan Yu, MD, PhD
Bhavani Krishnan, MS
Mitali Kapila, MS
John Sheele, MS
Magdalena Pasarica, MD, PhD
Miloni Rathod, MS
Pamela Rogers, MS
Scott Loiler, PhD
Nazar Mashtalir
Olga Dubuisson, MD, PhD
Emily McAllister
Rashmi Krishnapuram, PhD
Heather Kirk-Ballard, MS
Thank you!

Batu Caves, Malaysia. March 2014
Ad36 increases inflammatory cytokines mRNA in adipose tissue of mice