Physical Inactivity:
Effects on Healthy Aging and Chronic Disease

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Pennington Biomedical Research Center
An Inactivity Physiologists Perspective

Sitting too much is NOT the same as exercising too little, neither behaviorally nor the cellular responses.

Exercise is not the perfect antidote for a sedentary population (the ubiquitous problems caused by sitting too much).
The Young Field of Inactivity Physiology

For many key molecular mechanisms at the root cause of chronic disease caused by inactivity (generally sitting)....

...the study of inactivity physiology will provide more specific and more potent answers than even exercise physiology.
The Inactivity Physiology Paradigm

Plasma triglyceride metabolism in humans and rats during aging and phys. 
Int J Sports Nutr and Exer Metab, 2001

Inactivity Physiology vs. Exercise Physiology: An Essential Concept to 
Understand Lipoprotein Lipase Regulation 
ESSR, 2004

The Role of Low Energy Expenditure and Sitting on Obesity, 
Metabolic Syndrome, Type 2 Diabetes, and Cardiovascular Disease 
Diabetes, 2007

Too Little Exercise and Too Much Sitting: 
Inactivity Physiology and the Need for New Recommendations on Sedentary 
Current Cardiovascular Risk Reports, 2008

Sedentary Behavior and Inactivity Physiology. In: Physical Activity and Health 
2nd edition, C. Bouchard, S.N. Blair, and W. L. Haskell (Eds.), 2012

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INACTIVITY PHYSIOLOGY STUDIES

The Early Years
Exercise Physiology versus Inactivity Physiology: An Essential Concept for Understanding Lipoprotein Lipase Regulation

Marc T. Hamilton,¹,² Deborah G. Hamilton,¹ and Theodore W. Zderic¹

¹Department of Biomedical Sciences and ²Dalton Cardiovascular Research Center, University of Missouri-Columbia, Columbia, MO

HAMILTON, M.T., D.G. HAMILTON, and T.W. ZDERIC. Exercise physiology versus inactivity physiology: An essential concept for understanding lipoprotein lipase regulation. Exerc. Sport Sci. Rev., Vol. 32, No. 4, pp. 161–166, 2004. Some health-related proteins such as lipoprotein lipase may be regulated by qualitatively different processes over the physical activity continuum, sometimes with very high sensitivity to inactivity. The most powerful process known to regulate lipoprotein lipase protein and activity in muscle capillaries may be initiated by inhibitory signals during physical inactivity, independent of changes in lipoprotein lipase messenger RNA. Key Words: dose response, coronary heart disease (CHD), transcription, posttranslational, signaling, sedentary, aging
Inactivity Powerfully Impairs Lipoprotein Lipase

“The body’s vacuum for fatty lipoproteins in the vasculature becomes unplugged! ”

Bey and Hamilton, *J Physiol (Lond)* 2003
Lipoprotein Lipase Enzyme Function

- *essential* for plasma triglyceride clearance
- *essential* for tissue specific fat utilization
- *required* for healthy HDL cholesterol

LPL Activity In Capillaries Of Oxidative Muscle

Radioactive TG Uptake by muscle

Plasma HDL-C concentration
Suppression of skeletal muscle lipoprotein lipase activity during physical inactivity: a molecular reason to maintain daily low-intensity activity

Lionel Bey and Marc T. Hamilton

Standing/Light Ambulatory Control

HR-LPL activity (nmol FA g⁻¹ min⁻¹)

STR  FTR  FTW  STR  FTR  FTW  Diaphragm

Inactivity

Bey and Hamilton, J Physiology, 2003
Vigorous run training in the same animals

“In humans, lipoprotein lipase is related to healthy lipoprotein profiles after low-intensity activity ("control"), but not after exercise”. Harrison and Hamilton, *Lipids in Health Disease* 2012

<table>
<thead>
<tr>
<th>Lipid /Lipoprotein parameters</th>
<th>CON</th>
<th>EX-DEF</th>
<th>EX-BAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TG (mg/dL) (biochemical)</td>
<td>-0.98*</td>
<td>-0.36</td>
<td>-0.56</td>
</tr>
<tr>
<td>VLDL-TG (mg/dL)</td>
<td>-0.81*</td>
<td>-0.21</td>
<td>-0.68</td>
</tr>
<tr>
<td>Total VLDL particles (nmol/L)</td>
<td>-0.76*</td>
<td>+0.46</td>
<td>+0.25</td>
</tr>
<tr>
<td>Large VLDL particles (nmol/L)</td>
<td>-0.95*</td>
<td>-0.61</td>
<td>-0.68</td>
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<tr>
<td>Medium VLDL particles (nmol/L)</td>
<td>-0.24</td>
<td>-0.36</td>
<td>-0.25</td>
</tr>
<tr>
<td>Small VLDL particles (nmol/L)</td>
<td>-0.86*</td>
<td>+0.93*</td>
<td>+0.29</td>
</tr>
<tr>
<td>IDL particles (nmol/L)</td>
<td>-0.57</td>
<td>-0.14</td>
<td>-0.21</td>
</tr>
</tbody>
</table>
Revisiting the Classical Studies in 1953 by Morris

Death From CHD middle age men

Conductors

Drivers (sitters)

Hamilton Diabetes, 2007
Mortality Hazard Ratio

Mortality Hazard Ratio in 1,906 persons >50 yrs of age (averaging 63.8±10.5 yrs) from accelerometry (adjusted for age, gender, race/ethnicity, education)  
Inactivity Physiologists Ask

Could the average non-exercising American become even more unhealthy in the future if the trend continues?
FIG. 1. A major question raised by the inactivity physiology paradigm is whether the typical person who already does not perform structured exercise regularly will have increased risks of metabolic diseases in the coming years as a result of too much sitting. The red circle shadows the median of 13,344 middle-aged men and women (adapted from ref. 86). As described in the text, the majority of people in the general population already do not follow the prescription for enough moderate-vigorous exercise. It logically follows that in people who already do not exercise, it is impossible for higher rates of age-adjusted metabolic syndrome, type 2 diabetes, obesity, and CVD over the coming years to be caused by further exercise deficiency. Inactivity physiology is a discipline concerned with the future of people who may be sitting too much. (Please see http://dx.doi.org/10.2337/db07-0882 for a high-quality version of this figure.)
A Simple Inactivity Physiology Premise

Cells receive input from their environment every minute of every day.
Flat-line signals in medicine draw your attention
Inactivity Physiology focuses on the balance muscular contractile inactivity (commonly sitting) and abundant Low-Intensity Physical Activity (LIPA)

Hamilton et al. Diabetes, 2007
The Homeostasis for Expression of Hundreds of Genes is Rapidly Disturbed By Contractile Inactivity
The Specificity Principle

The signals harming the body during physical inactivity are specific and distinct from exercise. (one reason why “too much sitting is not the same as too little exercise”)
Inactivity Physiology is opening doors for understanding the elusive and dangerous condition of deep venous thrombosis (DVT).

Too much sitting can cause DVT – not too little exercise.
Identification of hemostatic genes expressed in human and rat leg muscles and a novel gene (LPP1/PAP2A) suppressed during prolonged physical inactivity (sitting)

Theodore W Zderic* and Marc T Hamilton*
Highlights in the discovery of a novel \textit{inactivity-responsive} gene:
Lipid Phosphate Phosphatase-1

1) \textit{Skeletal muscle is more than just a contractile machine}: 
Identified 17 genes expressed in skeletal muscle involved in hemostasis

2) LPP1 was the single key hemostatic gene suppressed during contractile inactivity

3) Traditional exercise training (1+ hr/day vigorous exercise) was not an effective antidote

4) Robust process in both rats and humans
LPP1 is Suppressed During Sitting & Resistant to Exercise
The exercising couch potato

Day With Less Sitting and Many Hours LIPA

Minutes per hour in each activity

Stepping
Standing
Sitting

Much Sedentary Time (sitting)

Minutes per hour in each activity

Sitting

Hamilton et al. Diabetes, 2007
Are Exercisers Less Sedentary?
Exercise Does Not Make You Sit Less!

Evidence that women meeting physical activity guidelines do not sit less: An observational inclinometry study.

Exercisers are not less sedentary (sit less) than people who do not exercise. Exercisers sit just as much as people who don’t exercise.

- Exercisers: ~20 min/week
- Non-exercisers: ~110 min/week
- Exercisers: ~300 min/week
Exercisers are not less sedentary (sit less) even on the days they exercise.
Sedentary  LIPA
Significant Implications of The Inactivity Physiology Paradigm

- for people who can not (or do not) exercise
- even for people who do exercise
- for novel human physiology insights (e.g. LPL & LPP1)
- and eventually, discovery of widespread solutions
Warning: Smoking may be hazardous to your health

“He's handsome and rugged. He lives in a world of galloping horses, open spaces and blood red sunsets. 
*He's the Marlboro Man!***
SEDENTARY BEHAVIOR GUIDELINES & RECOMMENDATIONS?