Diabetes and Exercise:
Why Exercise Works When Insulin Does Not

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Type 2 Diabetes is Reaching Epidemic Levels

- A major factor leading to increased rates of type 2 diabetes is inactivity.
- Physical exercise is critical in the prevention of type 2 diabetes.
Diabetes and Exercise: Why Exercise Works When Insulin Does Not

- Background on Diabetes
- Skeletal Muscle Glucose Transport
- Studies in Human Subjects
- “The Exercise Pill”
Basic Physiology: Glucose concentrations in the blood rise after a meal. Insulin is released from the pancreas, binding to insulin receptors on tissues throughout the body, resulting in glucose entering the tissues.
Pancreas loses its ability to produce and secrete insulin. This is almost always caused by autoimmune attack and destruction of the β cells.
Type 2 diabetes
(adult-onset or non-insulin dependent)

Insulin is produced by the pancreas and levels in the blood are often normal or even high, but the tissues don’t respond - insulin resistance.
Diabetes Complications

- Leading cause of blindness
- Leading cause of kidney failure
- Leading cause of amputations
- Major cause of heart attacks
- Major cause of strokes
Diabetes is Reaching Epidemic Levels

Zimmet et al
WHO Data

2000 = 151 million
2010 = 221 million
2020 = 300 million

World
2000 = 151 million
2010 = 221 million
2020 = 300 million

2000 = 14.2
2010 = 17.5
23%

2000 = 26.5
2010 = 32.9
24%

World
2000 = 26.5
2010 = 32.9
24%

2000 = 9.4
2010 = 14.1
50%

2000 = 23%
2010 = 44%
Type 2 Diabetes is Reaching Epidemic Levels

![Graph showing incidence of diabetes (DPP)]

- **Risk reduction**
  - 31% by metformin
  - 58% by lifestyle

Cumulative incidence (%)

Years from randomization

- Placebo
- Metformin
- Lifestyle
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Effect of Exercise on Blood Glucose Concentrations in a Subject with Type 2 Diabetes

![Graph showing the effect of exercise on blood glucose concentrations. The graph depicts a downward trend in glucose levels from basal to 75 minutes of exercise at 70% VO$_2$max.](image-url)
Type 2 Diabetes

Blood Vessel

Glucose

Exercise

Muscle
Type 2 Diabetes

Blood Vessel

Glucose

Insulin

Muscle
What is the molecular basis for the ability of exercise to increase glucose uptake in skeletal muscle of patients with Type 2 diabetes?
Methods to Study Exercise and Muscle Contraction

- Muscle contraction system for cultured myotubes
- Contraction by direct electrical stimulation
- Contraction by sciatic and peroneal nerve stimulation
- Treadmill running exercise (acute and chronic studies)
- Wheel running exercise (chronic studies)
- Human exercise with biopsies
Glucose Transport System in Skeletal Muscle

- glucose transport is the rate limiting step in glucose utilization
- facilitated diffusion
- glucose transporter proteins
- GLUT1, GLUT4 expressed in skeletal muscle
- exercise, insulin most potent physiological stimuli
Under Basal Conditions GLUT4 is Primarily Intracellular
Exercise Regulation of Glucose Transport

Exercise

GLUT4-containing vesicle
Exercise Regulation of Glucose Transport

Exercise

GLUT4 Translocation

Glucose
Insulin Regulation of Glucose Transport

- Insulin Receptor
- Glucose
- GLUT4 Translocation
- Exercise
Insulin Stimulates GLUT4 Translocation in Skeletal Muscle

In vivo imaging of GLUT4-GFP

Mouse quadriceps muscle
Bar = 20 µm
(Lauritzen HPMM, Diabetes, 2006)
Contraction Stimulates GLUT4 Translocation in Skeletal Muscle

In vivo imaging of GLUT4-GFP

Mouse quadriceps muscle
Bar = 20 µm
Are there distinct mechanisms for insulin- and exercise-stimulated glucose transport?
Contraction + Insulin have Additive Effects on Glucose Transport in Skeletal Muscle

Glucose Transport

Arbitrary units

basal  maximal contraction  maximal insulin  contraction + insulin
Exercise and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms
What are the signaling mechanisms that mediate glucose transport in skeletal muscle?
Insulin Regulation of Glucose Transport

- Insulin Receptor
- IRS-1
- PI 3-Kinase
- p85-p110
- Akt
- GLUT4 Translocation

Exercise

Glucose
Exercise and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms

Exercise

Glucose

GLUT4 Translocation

GLUT4

Insulin Receptor

IRS-1

p85-p110

PI 3-Kinase

Akt

P

P

P

P

P
Exercise and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms

Exercise → GLUT4 Translocation

Insulin Receptor → IRS-1 → p85-p110 → PI 3-Kinase → Akt → GLUT4 Translocation

Glucose
Exercise and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms

Exercise

AMPK

GLUT4 Translocation

IRS-1
p85-p110
PI 3-Kinase

Akt

Insulin Receptor

Glucose
5’AMP-Activated Protein Kinase (AMPK)

• A member of metabolite-sensing protein kinase family

• Activated under conditions of low energy state, exercise

• Proposed to regulate numerous metabolic and transcriptional processes in multiple cell types

α1, α2 (α2 predominant in skeletal muscle)
β1, β2
γ1, γ2, γ3
5’AMP-Activated Protein Kinase (AMPK)

Activating T-loop phosphorylation site
5’AMP-Activated Protein Kinase (AMPK)
What is the evidence that AMPK mediates exercise-stimulated glucose transport?
ACIAR and the Regulation of Glucose Transport in Skeletal Muscle

Insulin Receptor

IRS-1

AICAR

AMPK

GLUT4 Translocation

Glucose

p85-p110

PI 3-Kinase

Akt
AICAR
(5-aminoimidazole-4-carboxamide-riboside)

ZMP

AMP

AICAR
Adenosine kinase

ZMP

AMPK

AMPK Activity
AICAR + Insulin have Additive Effects on Glucose Transport in Skeletal Muscle

Glucose Transport

Arbitrary units

basal  maximal AICAR  maximal insulin  AICAR + insulin
AICAR + Contraction do not have Additive Effects on Glucose Transport

Glucose Transport

Arbitrary units

basal  maximal AICAR  maximal contraction  AICAR + contraction
ACIAR and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms

**Insulin Receptor**

- IRS-1
- p85-p110
- PI 3-Kinase

**Glucose**

- GLUT4 Translocation

**Akt**

**AMPK**

**AICAR**

**Exercise**
Summary

Skeletal Muscle Glucose Transport

- Exercise and insulin increase glucose transport in skeletal muscle, resulting in glucose clearance from the blood.

- Exercise and insulin increase glucose transport through the translocation of GLUT4 transporters to the cell surface and transverse tubules in skeletal muscle.

- There are distinct proximal signaling mechanisms for exercise- and insulin-stimulated GLUT4 translocation.

- AICAR increases AMPK activity and can increase glucose transport in skeletal muscle.
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What is the physiological relevance of these findings for patients with type 2 diabetes?
Does exercise bypass defects in insulin action in skeletal muscle by utilizing alternative signaling mechanisms leading to increased GLUT4 translocation?
Skeletal Muscle Biopsy from Human Subjects
Are there defects in insulin- and exercise-stimulated GLUT4 translocation in patients with type 2 diabetes?
Insulin-stimulated GLUT4 Translocation is Impaired in Patients with Type 2 Diabetes
Exercise Causes Normal GLUT4 Translocation in Subjects with Type 2 Diabetes
Exercise and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms

Exercise

Glucose

Insulin Receptor

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ACIAR and Insulin Regulate Glucose Transport via Distinct Signaling Mechanisms
Exercise Increases AMPKα2 Activity In Controls and Subjects with Type 2 Diabetes

Exercise 70% \( \text{vo}_2\text{max} \)

Type 2 DM

Controls

(pmol/mg/min)

0.0

0.5

1.0

1.5

2.0

0 20 45 30’Rest

minutes
Exercise Can Bypass Defects in Insulin Signaling and GLUT4 Translocation in People with Type 2 Diabetes
Can we make a drug to activate AMPK leading to increased glucose transport in skeletal muscle?
Can we make a drug to activate AMPK leading to increased glucose transport in skeletal muscle?
Metformin

- Single most prescribed oral antidiabetic drug in the U.S.

- Cellular mechanism of action is unclear
  * Suppresses hepatic glucose production
  * Increases muscle glucose uptake
  * Inhibits Complex 1 of Respiratory Chain
AICAR and Metformin Share Metabolic Effects

- Inhibit Hepatic Glucose Production
- Stimulate Muscle Glucose Uptake
- Increase Lactic Acid Production
Does the mechanism of Metformin action involve the regulation of AMPK?
Effect of Metformin on AMPK Activity

(rat epitrochlearis muscles)
Effects of 4 and 10 Weeks of Metformin Treatment on AMPKα2 Activity (human vastus lateralis muscle)
Activation of AMPK Increases Skeletal Muscle Glucose Transport

GLUT4 Translocation
Studies in Human Subjects

- Exercise and insulin increase GLUT4 translocation in human skeletal muscle.

- Insulin signaling and GLUT4 translocation are impaired in patients with type 2 diabetes.

- Exercise-stimulated AMPK activation and GLUT4 translocation are normal in patients with type 2 diabetes.

- Activation of AMPK can increase glucose transport in skeletal muscle, making AMPK a drug target for treatment of type 2 diabetes.

- Metformin, the most widely used diabetes drug, works through stimulation of AMPK.
Multiple Signals Mediate Exercise-Stimulated Glucose Transport
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“It’s the exercise pill: the pill that helps you burn off calories just by sitting on the couch. It’s America’s dream.”

Pill may boost endurance without exercise
The Exercise Pill: AICAR

AMPK and PPARδ Agonists Are Exercise Mimetics

Vihang A. Narkar, Michael Downes, Ruth T. Yu, Emi Embler, Yong-Xu Wang, Ester Banayo, Maria M. Mihaylova, Michael C. Nelson, Yuhua Zou, Henry Juguilon, Heonjoong Kang, Reuben J. Shaw, and Ronald M. Evans
The Exercise Pill — Too Good to Be True?

Laurie J. Goodyear, Ph.D.
Effects of AICAR Treatment and Chronic AMPK Activation

**Acute Effects:**
- Increase glucose uptake (Hayashi, Winder, others, 1998)
- Lower blood glucose levels (Shulman, others, 1999)
- Increase in muscle glycogen (Winder, Holloszy, others, 1999)

**Chronic Effects:**
- Increase exercise endurance (Witters, 2007) (Evans, 2008)
- Increase in muscle glycogen (Winder, Holloszy, others, 1999)
- Increase in GLUT4, mitochondrial enzymes (Winder, Holloszy, others, 1999)
The Exercise Pill — Too Good to Be True?

- AICAR has a short half-life after intravenous infusion and poor bioavailability after oral ingestion.
- AICAR treatment causes lactic acidosis in humans.
- AMPK activation in the hypothalamus can stimulate appetite.
- Activating mutations of AMPK cause heart conduction abnormalities in humans (WPW syndrome).
Benefits of Regular Physical Exercise

**Pulmonary function**
- Increase lung capacity
- Improve sleep

**Increase blood volume**

**Improve pancreatic function**

**Improve liver function**
- Reduce fat stores

**Prevention of Diabetes**
- Increase glucose tolerance
- Increase insulin sensitivity
- Increase muscle glucose uptake
- Increase mitochondrial function

**Decrease Rates of Cancer**
- Colon, breast, endometrial

**Decrease** depression, anxiety
- Decrease Alzheimer's
- Decrease stroke
- Decrease appetite

**Improve cardiac function**

**Improve lipid profile**

**Lower blood pressure**
- Increase bone density
- Increase muscle strength
- Increase flexibility

**Increase** muscular strength
- Increase bone density
- Increase flexibility

**Increase** glucose tolerance
- Increase insulin sensitivity
- Increase mitochondrial function
- Increase blood volume
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