Exercise-induced Myokines in Health and Metabolic Diseases

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Agenda

Exercise and Myokines

Role of Myokines in the Metabolism
- Pathways
- Body Cross talk
- Specific Effects

Implications for Metabolic Disorders

TLDR; Take Away Message

Notable Myokines:

Interleukin 15 (IL-15)

Brain-Derived Neurotrophic Factor (BDNF)

Leukemia Inhibitory Factor (LIF)

Irisin

Fibroblast Growth Factor 21 (FGF-21)

Secreted Protein Acidic and Rich in Cysteine (SPARC)
Why even bother?
The Benefits of Exercise

Extensive and Interwoven!

Cognitive
- Learning and Memory
- Processing Speed

Psychological
- Mood Regulation
- Reduced Stress Levels

Immune System
- Disease Prevention
- Reduced inflammation

Metabolic
- Insulin sensitivity
- Improved body composition

*Energy and Homeostasis
- Reduction in positive energy balance
- Endorphin release

Cardiovascular/Respiratory
- Decreased resting HR/BPM
- Increase Oxygen uptake
The benefits of exercise go beyond the restoration of energy balance.

Why?
Myokines!

Small proteins produced by myocytes (muscle cells) released during contraction i.e exercise.

- Highly involved in metabolism and homeostasis
- Involved in complex body cross talk
- Endocrine, paracrine and autocrine (local) effects
- Upregulation of Leptin
- Counteract inflammatory adipocytes
Location, Location, Location!

**Receptor sites:** Skeletal muscle, pancreas, liver, adipose tissue, bone, immune, and brain cells

Wide variety of pathways allows for complex body cross talk leading to a:

**CASCADE of systemic effects**
Notable Myokines

**Interleukin 15 (IL-15):** Muscle Growth

**Irisin:** Lipolysis (store release)

**Leukemia inhibiting Factor (LIF):** Muscle support/repair

**Brain Derived Neurotrophic Factor (BDNF):** Increased Fat oxidation (utilization as fuel)

**Fibroblast Growth Factor 21 (FGF-21):** Increased Glucose uptake

**Secreted Protein and Rich in Cysteine (SPARC):** Decreased Adipogenesis (fat synthesis)
Myokines vs Cytokines

BODY COMPOSITION

FAT
Adipocyte Communication

MUSCLE
Myokine Communication

Ant-Inflammatory Forces

Inflammatory forces

Metabolic disease

Sedentary lifestyle
Proinflammatory adipokines

Regular exercise
Myokines

Fat accumulation
Adipose tissue inflammation
Adipocyte dysfunction

Mitochondrial biogenesis
Antioxidant capacity
Muscle hypertrophy
Interleukin 15 (IL-15) and Receptor

- Member of the 4-α-helix bundle family of cytokines
  - Specifically, part of the IL-2 superfamily
- IL-15 mRNA is highly expressed in skeletal muscle (SKM)
- Has two isoforms
  - Short 21-amino acid and long 48-amino acid signal peptides
    - Short responsible for intracellular regulation (speculated)
    - Long responsible for cell-cell communication
- Acts upon IL-15Rα, IL-2Rβ subunit and γ chain (γC)
  - IL-15Rα has a high-affinity to IL-15
  - IL-15Rα components
    - Short cytoplasmic tail
    - Transmembrane domain
    - Stalk
    - Hinge region
    - Cytokine-binding domain, a.k.a. Sushi domain
IL-15 Secretion

- Long isoform of IL-15 and IL-15Rα combine in ER to form a complex
  - Two forms of IL-15Rα
    - Soluble IL-15Rα (sIL-15Rα)
    - Membrane-bound IL-15Rα (mbIL-15Rα)
- IL-15/sIL-15Rα complex will be secreted from cell and can act in a paracrine, autocrine, or endocrine fashion
- IL-15/mbIL-15Rα complex is bound to membrane and can act in juxtacrine or autocrine fashion
- mbIL-15Rα can also be secreted by itself to form a heterotrimeric receptor with IL-2Rβ subunit and γc
- Release from IL-15Rα leads to circulating free IL-15?
IL-15 Signalling

- IL-15 signal transduction can occur through two ways
  - Heterodimeric receptor comprised of IL-2Rβ and γC
    - Low-affinity to IL-15
    - Mediated through trans-presentation of IL-15/mbIL-15α complex or IL-15/sIL-15Rα
  - Heterotrimeric receptor comprised of mbIL-15Rα, IL-2Rβ, and γC
    - High-affinity to IL-15
    - Studies show that SKM express more high-affinity receptors, thus more sensitive to free IL-15
    - Can also act through cis-presentation
IL-15 Expression

- **Humans**
  - Treadmill running (70% max heart rate for 30 min)
    - Serum IL-15↑
  - Resistance exercise (3d/wk, 75% of one rep max, 6-10 reps)
    - Plasma IL-15↑
    - IL-15Rα gene↑
  - Leptin
    - IL-15↑
    - Fat-muscle crosstalk

- **NOTE!**
  - Conflicting data in regards to increased IL-15 expression and secretion due to exercise
IL-15 Benefits

- Increased glucose uptake and GLUT4 translocation
  - JAK3/STAT3 \( \rightarrow \) hypoxia-inducible factor-1\(\alpha\) (HIF-1\(\alpha\))
  - Aids in controlling obesity and Type II Diabetes
- Protective against oxidative stress
- Muscle hypertrophy
  - Stimulation and accumulation of contractile proteins
- Enhanced mitochondrial activity
  - PPAR\(\delta\)-dependent mechanism
- Inhibition of lipid accumulation in adipose tissue
  - Adiponectin stimulation
- Modulation of NREM and protect against neuroinflammation
  - More research needed
Interleukin 6 (IL-6) as a Myokine

- Expression
  - Circulating IL-6↑ up to 100 fold and correlated with duration/intensity of exercise
  - IL-6 transcription↑ due to 30 min of exercise
  - IL-6↑ due to leptin

- Benefits
  - Inhibition of pro-inflammatory cytokines
    - Tumor necrosis factor alpha (TNF-α) and Interleukin 1 beta (IL-1β)
  - Regulate satellite cell-mediated hypertrophic muscle growth
  - Induce glycogen breakdown and lipolysis
    - AMPK
  - Adipocyte browning
    - Uncoupling protein 1 (UCP1) expression
  - Enhance insulin sensitivity → Enhance GLUT4 expression
**IL-15 References**


Brain-derived Neurotrophic Factor (BDNF)

- Part of the mammalian neurotrophin family
  - Along with nerve growth factor (NGF), neurotrophin-3, and neurotrophin-4 (also called neurotrophin-5)
  - BDNF vastly expressed in brain
  - Evidence that sensory neurons synthesize BDNF
  - Promotes survival of certain dorsal root ganglion neurons
  - Key structural features of neurotrophins include a tertiary fold and cystine knot
- Activates tropomyosin-related kinase B (TrkB)
  - Binds directly, dimerizes the receptor and activates the tyrosine kinase
- Also expressed in skeletal muscle
  - BDNF skeletal mRNA goes levels increase as a result of muscle contraction and exercise
    - Doesn’t get released into circulation
- Affects peripheral metabolism in an autocrine or endocrine fashion
  - Effects size of adipose tissue
First, What Exactly do Neurotrophins Do?

- Variety of roles in both the CNS and PNS
  - Survival and regeneration of damaged nerves
  - Proliferation
  - Neuronal growth
  - Formation of synapses
  - Membrane fusion
  - Apoptosis regulation
  - Regulate expression of crucial proteins (neurotransmitters and ion channels)
  - Involved in neuronal plasticity, learning, and memory
  - Glucose and energy metabolism regulation
BDNF Production/Release

- pro BDNF synthesis
- Endoplasmic reticulum
- NUCLEUS BDNF mRNA
- Golgi apparatus
- pro BDNF
- PC1 secretory vesicles
- mBDNF
- Trafficking to dendrites/axonal terminals
- intracellular cleavage
- membrane
- extracellular cleavage
- plasminogen
- tPA
- Plasmin
- MMP
- mBDNF
- pro BDNF
BDNF signaling pathways

Brain-derived neurotrophic factor signaling pathway
More signalling...
Muscle Contraction and BDNF Signalling

A  Presynaptic stimulation without contraction

1. 1 Hz stimulation
2. Synthesis
3. Phosphorylation
4. Activation of P44/42 kinase
5. mBDNF
6. Muscle contraction

B  Presynaptic stimulation with contraction

1. 1 Hz stimulation
2. Synthesis
3. Phosphorylation
4. Activation of P44/42 kinase
5. mBDNF
6. Muscle contraction
BDNF and Exercise

- Exercise increases BDNF in the brain, plasma, and skeletal muscle
- Enhanced Fatty Acid Oxidation (FAO)
  - AMPK-dependent
  - AMPK phosphorylates Acetyl-CoA carboxylase 2 (ACCβ)
    - Inhibits ACC
    - Decreases malonyl-CoA content
    - Relieves inhibition of carnitine palmitoyl transferase 1
  - FAO!!!
- BDNF mRNA ↑ after exercise
  - However, the muscle-released BDNF is not released into circulation
Implications of decreased BDNF

- Type 2 diabetes
- Obesity
- Dementia
- Alzheimer’s
Other Roles of BDNF

- Reduces food intake
- Lowers blood glucose
- Energy Homeostasis
  - Feeding behavior and insulin sensitivity
  - Circadian rhythm-dependent
    - Expression greater during dark phase in hippocampus and cerebellum (in rodents)
    - Greater during the light phase in retina and visual cortex (in rodents)
- Circadian rhythm regulation
  - Infusing BDNF in rat suprachiasmatic nucleus (SCN) causes large phase advances
  - Controlled by neural circuits in the hypothalamus
  - Disruptions associated with metabolic syndrome and obesity
BDNF References


Leukemia Inhibitory Factor (LIF)

General Function:

- Multifunctional *secreted cytokine* that is the member of the interleukin 6 (IL-6) family implicated in broad biological functions involving cell survival, proliferation, and differentiation
- Implicated in differentiation of certain leukemic cells, neuronal development, stem cell self-renewal, inflammatory response
- Depending on the specific cellular receptors the LIF binds to and the cell type, LIF action can trigger paradoxically opposite effects in different target cells
Leukemia Inhibitory Factor (LIF) Receptor/Signaling

- LIF receptor contains 2 signaling chains: gp130 and LIFRβ
- LIF binds with high affinity to both gp130 and LIFRβ→triggers the activation of JAK1→initiates cascade of tyrosine phosphorylation (specifically, JAK 1 phosphorylates 5 tyrosines on each receptor chain)→stimulates 3 distinct signaling pathways: JAK/STAT, MAP-kinase, and PI3 kinase pathways=contribute to self-renewal, differentiation, and survival
- Whether signaling is skewed towards self-renewal/differentiation/survival is cell-specific
- Long story short: LIF binding to 2 receptor chains (gp 130 and LIFR), initiates activation of JAK1 which then stimulates activation of the 3 pathways: JAK/STAT, MAP-kinase, and PI3 kinase pathways
LIF Role in Skeletal Muscle

- Newly discovered myokine that affects both intact muscles and isolated muscle cells
- “Contraction induced myokine” → LIF mRNA levels increased after resistance exercise and LIF proteins secreted when artificially synthesized muscle fibers were electrically stimulated
- Produced by skeletal muscle
- Enhances cell proliferation through JAK/STAT and PI3K signalling pathways, critical role in muscle hypertrophy and regeneration
### LIF Expression in Exercise Related Activities

<table>
<thead>
<tr>
<th>Myokine</th>
<th>Subjects</th>
<th>Exercise</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIF</td>
<td>Human</td>
<td>Cycle ergometer exercise (3 h, VO$_2$ max 60%)</td>
<td>LIF mRNA↑ (increased 4.5-fold after exercise)</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>Resistance exercise (bout of heavy resistance exercise)</td>
<td>LIF mRNA↑ (increased 9-fold after exercise)</td>
</tr>
<tr>
<td></td>
<td>MDX mice</td>
<td>Voluntary wheel running (2 wk)</td>
<td>LIF mRNA ↓ LIF receptor ↓</td>
</tr>
</tbody>
</table>

- LIF expression during exercise remains controversial as relationship between changes in LIF mRNA levels and circulating levels of LIF proteins are not clearly established. Can be affected by exercise duration/type
- LIF short half life 6~8 mins
- **Evidence from the focus paper study:**
  - Cycle ergometer exercise (human) → ↑ in LIF mRNA levels; little to no change in LIF protein levels
  - Heavy resistance exercise (human) → ↑ in LIF mRNA levels; little to no change in LIF protein levels
  - 2 weeks of voluntary wheel running (MDX mice) → ↓ in LIF mRNA levels??
Summary of LIF Benefits in Skeletal Muscle

- Skeletal muscle hypertrophy and regeneration → ALSO significantly increases muscle glucose uptake through PI3K/mTORC2/Akt pathway
- Regulate skeletal muscle disease e.g. muscular dystrophy
- Myoblast survival in dystrophic (weakening/degenerating) muscle
- Conclusion → LIF promotes an alternative therapeutic way to stimulate skeletal muscle regeneration in an autocrine/paracrine manner post injury
LIF’s Connection to Type II Diabetes

Deficient leukemia inhibitory factor signaling in muscle precursor cells from patients with type 2 diabetes

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- Impairment of development of muscle precursor cells may be part of muscle pathophysiology in patients with Type II diabetes
- In diabetic myoblasts → lack of increase in LIF stimulated cell proliferation & LIF induced phosphorylation of signal transducer and activator of transcription STAT 1 and STAT 3 were impaired = impairment of LIF signaling and LIF stimulated cell proliferation
References (LIF):


Irisin

- It’s a myokine
  - Peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\)) coactivator-1\(\alpha\) (PGC1-\(\alpha\)) dependent myokine
- Increased levels produced during exercise
- Has effects in several regions of the body
  - Capable of causing the browning of white adipose tissue
  - Stimulates glucose uptake
  - Involved in muscle growth
  - Stimulates glycogenesis in liver
  - And much more! (maybe)
- Has potential to be a therapeutic agent
Irisin Levels and Exercise

- Irisin levels in both mice and humans rise during exercise
- Positive correlation was seen between circulating irisin and changes in muscle mass
  - Higher irisin levels = more changes in muscle mass
- Negative correlation was seen between circulating irisin levels and changes in fat mass and body fat percentage
  - Higher irisin levels = lower fat mass and body fat percentage

| Irisin | Mice | Voluntary wheel running (free wheel running, 3 wk) | Human | Endurance exercise (cycle, VO2 max 65%, 4-5 sessions/10 wk) | Human | Acute exercise (80 m spirit runs, 3 d/1 wk) | Plasma irisin level ↑ | Plasma irisin level ↑ | Serum irisin level ↑ | 63 | 67 |
SAY WHAT NOW?
Browning of White Adipose Tissue

- Exercise causes an increase in PGC1-\(\alpha\) expression in skeletal muscles
  - PGC1-\(\alpha\) is known to stimulate mitochondrial biogenesis, angiogenesis and fiber-type and slow twitching movement
  - Side-note: there is some evidence linking reduced expression of PGC1-\(\alpha\) with Parkinson's Disease
- PGC1-\(\alpha\) triggers expression of fibronectin type III domain-containing protein 5 (FNDC5)
  - FNDC5 is an encoder gene for irisin, causing irisin to be secreted into the bloodstream
  - In rodent model, FNDC5 treatment improved glucose tolerance and elevated expression of mitochondrial genes that increased oxygen consumption
- Increased levels of irisin stimulates browning of the white adipose tissue
- Browning of adipose tissue (or fat tissue) induced by irisin has metabolic effect that increases energy expenditure and reduces adiposity
- Exogenous administration of irisin in mice induced adipocyte browning in subcutaneous fat through p38 MAPK and ERK1/2 activation
Castillo-Quan, Jorge Iván. "From White to Brown Fat through the PGC-1α-Dependent Myokine Irisin: Implications for Diabetes and Obesity."
Irisin and Glucose

- Irisin plays a beneficial role on skeletal muscle
  - Through action of AMPK irisin stimulates glucose uptake and lipid metabolism
  - Through induction of IGF-1 and suppression of myostatin irisin improves muscle growth
- FNDC5 overexpression in mice reduced serum lipid levels
  - Overexpressed FNDC5 stimulated lipolysis via the cAMP_PKAp_perilipin/HSL pathway in adipocytes
- Irisin reduces gluconeogenesis and lipogenesis in liver
  - Irisin regulates GSK3, FOX01, and SREBP2
Irisin References

Castillo-Quan, Jorge Iván. “From White to Brown Fat through the PGC-1α-Dependent Myokine Irisin: Implications for Diabetes and Obesity.”


Discrepancies in Results

- Early tests showed discrepancies in the rise of irisin levels following exercise.
- Main theory: ELISA kits used were not able to accurately detect the irisin resulting in inaccurate measurements.
- Using antibody-independent mass spectrometry, a rise in circulating irisin levels were detected in both acute and chronic exercise.
- Irisin was officially discovered in 2012 and there is still much more to be looked into:
  - Researcher hope that irisin can be utilized as a therapeutic agent for people with obesity.
  - Research is being done into irisin and its effects on non-insulin sensitive tissues such as bone, the heart and blood vessels.
Fibroblast Growth Factor 21

What do we already know about Fibroblast Growth Factor 21?
Things we know about FGF-21

1. FGF21 is an endocrine hormone that plays a part in the progression of metabolic regulation by controlling glucose and lipid metabolism.

2. FGF-21 is secreted during starvation/fasting and in a ketogenic state, and decreases after refeeding.

3. Expressed in peripheral tissues such as the liver, white and brown adipose tissue, skeletal muscles, and in the pancreas.

4. FGF-21 has been identified as a genetic mechanism responsible for the sweet tooth behavioral phenotype, a trait associated with cravings for sweets and high sugar consumption, in both humans and mice.
Understanding the Effects of FGF-21

Increases

- Insulin Sensitivity in Diabetic Rats

Decreases

- Plasma Glucose
- Triglycerides
Several studies have determined FGF-21 to be a key factor for downstream Peroxisome proliferator-activated receptor alpha or PPAR-α.

- PPAR-α is a transcription factor and a major regulator of lipid metabolism in the liver. PPAR-α is activated under conditions of energy deprivation and is necessary for the process of ketogenesis, a key adaptive response to prolonged fasting and starvation.
Studies

Recent studies suggested that FGF-21 levels were elevated in metabolic diseases, including insulin resistance, metabolic syndrome, and type 2 diabetes.

Studies demonstrated an increased FGF-21 expression in muscle and plasma in response to insulin stimulation.
In healthy humans, FGF-21 levels increased after 2 weeks of treadmill exercise.

FGF-21 levels also increased in mice and humans from a single bout of acute exercise.

Data from these studies might suggest that increased FGF-21 levels lead to increased lipolysis and decreased glucose levels after a high-intensity exercise.
New Studies

FGF-21 is elevated after exercise
FGF-21 References


SPARC

- Secreted protein acidic and rich in cysteine
  - Also known as BM-40
- Initially identified in the bone as osteonectin
  - Most studies on regulation of SPARC are related to bone
- In muscle fibers
  - SPARC secretion increases in muscles during regeneration and following resistance exercise and muscle hypertrophy.
What does SPARC do?

- In general SPARC plays a role in...
  - Skeletal tissue remodeling
    - Which allows SPARC to play a key role in adipocyte differentiation and adipose tissue turnover
  - Suppression of colon tumorigenesis
  - Inhibiting adipogenesis
    - And enhances the production of osteoblasts
  - In glucose metabolism
SPARC and Exercise

- SPARC secretion increases in muscles during regeneration and following muscle growth and increase in the size of muscle cells
- Increase in SPARC serves as protective measure against adipogenesis and inflammation

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<thead>
<tr>
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<th>Mice</th>
<th>Men</th>
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<tbody>
<tr>
<td>1.</td>
<td>Acute Exercise (treadmill running, 30 min or until exhaustion)</td>
<td>1. Acute Exercise (a single bout of cycling, VO2 max 70%, 30 min)</td>
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<tr>
<td></td>
<td>-</td>
<td>2. Cycling (VO2 max 70%; 4 weeks)</td>
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<tr>
<td>Results:</td>
<td>SPARC levels decreased immediately after exercise (levels decreased immediately after exercise)</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td>1. Serum SPARC level increase (gradually decreased)</td>
<td>1. Serum SPARC level increase with no changes to resting state</td>
</tr>
<tr>
<td></td>
<td>2. Serum SPARC level increase with no changes to resting state</td>
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</tbody>
</table>
SPARC and Exercise

- Several epidemiological studies have shown that regular exercise can prevent the onset of colon cancer, however the underlying mechanism is unclear.
- Primary culture of SPARC-null mice cells vs. wild-type mice
  - Increased adipocyte and fat accumulation in SPARC-null
  - Regular exercise enhanced apoptosis in colon mucosal cells and increased cleaved forms of caspase-3 and caspase-8 in wild-type
- Exercise stimulates SPARC secretion from muscle tissues and that SPARC inhibits colon tumorigenesis by increasing caspase-3 and caspase-8-dependent apoptosis.
Figure: Exercise prevents tumorigenesis of colon cancer through muscle-derived SPARC. Animal and human experiments reveal exercise induces SPARC production and release from skeletal muscle tissue that increases SPARC protein levels in plasma. Elevation of SPARC in plasma decreases the formation of chemical-induced aberrant crypt foci in mouse colon through the increase of apoptosis of colon cells.
SPARC and Fat Accumulation

- SPARC is a myokine that reduces fat accumulation
- SPARC is involved in the regulation of adipocyte differentiation and adipose tissue turnover
  - Wnt/Beta-catenin pathway
  - Inhibits adipogenesis & enhances osteoblastogenesis
- SPARC decreases adipogenesis indirectly
  - Regulating expression, deposition and organization of extracellular matrix protein
  - Fibronectin inhibits adipogenesis and laminin enhances adipogenesis
  - These changes inhibit rearrangement of F-actin and stress fibers form preadipocyte cell structure that allows fat accumulation
Wnt/B-catenin Signaling & Adipogenesis

Wnt/B-catenin signaling in preadipocytes is initiated by expression of Wnt10b, Wnt10a, and Wnt6.

Binding with one of these Wnt’s to transmembrane frizzled receptors & LRP coreceptors inhibits GSK3B leading to hypophosphorylation and stabilization of Beta-catenin in the cytoplasm.

B-catenin is translocated to the nucleus where it binds TCF/LEF transcription factors and activates downstream targets to inhibit preadipocyte differentiation.
SPARC and Glucose Metabolism

- SPARC is involved in glucose metabolism via the AMPK signaling pathway
  - AMPK is an energy-sensing pathway which plays a critical role in regulating glucose and fat metabolism in skeletal muscle during exercise and in sensing intracellular ATP levels
    - SPARC may regulate glucose metabolism via AMPK activation
- Relationship between SPARC and insulin resistance in T2D
  - Overexpression of SPARC may increase the intracellular AMP to ATP ratio
    - Enhancing glucose uptake via AMPK activation
    - There is a positive correlation between serum SPARC levels and insulin resistance which indicates that SPARC plays an important role in the development of insulin resistance in T2D
- SPARC is involved in regulating glucose metabolism making it an attractive molecule for prospective pharmacological or genetic manipulation
SPARC & Glucose Metabolism Summary

- SPARC secreted by adipose tissue has been linked with insulin resistance and glucose metabolism
  - SPARC circulatory level is positively correlated with BMI in humans
  - SPARC seems to promote insulin resistance
  - However, little is known about its specific role in glucose metabolism in skeletal muscle
- SPARC contributes to adipose-tissue fibrosis
- This supports SPARC’s utility in the prevention and treatment of type 2 diabetes and metabolic syndrome
  - Diabetes is associated with dysfunction of glucose metabolism and insulin resistance


Myokines & Metabolic Disorders

A potential treatment for obesity, alzheimer’s, and type 1 and type 2 diabetes.
Take Away Messages!

1. Exercise is holistically beneficial!

2. Calorie restriction is not the answer!

3. Body Composition is important!(not BMI)

TLDR; Disease prevention, cardiovascular benefits and therapeutic effects on metabolic disorders of exercise result from myokine secretion.
References

