# Recent research in exercise and type 2 DM

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8주간의 저항성 운동이 제 2형 당뇨 쥐(Zucker rat)의

# 근섬유 조성과 GLUT4 발현에 미치는 영향

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연구 1 (김지연)

## Skeletal muscle plasticity in T2DM

#### MHC type I Oxidative phenotype

Electrical stimulation Exercise training Pharmacological stimuli Genetic manipulations



MHC type II Glycolytic phenotype

Myotonia Neuromuscular dystrophies Type 2 diabetes Skeletal muscle disuse



#### ◀ Figure. Different skeletal muscle fiber type distribution in the normal glucose tolerant (NGT) group and type 2 diabetic group.

In patients with type 2 diabetes, the slow oxidative (SO) fiber fraction was reduced by 16%, whereas the fast glycolytic (FG) fiber fraction was increased by 49%. \*P 0.05 for NGT vs. type 2 diabetic subjects.

(Andreas Oberbach et al., 2006)

# The effects of resistance training on type 2 DM

- **Resistance training can..**
- ✓ Enhance insulin sensitivity
- $\checkmark$  Increase in the activity and content of mitochondria
- ✓ Increase oxidative capacity
- ✓ Lower body fat mass, fat distribution and increase lean body mass which lead to ameliorate insulin resistance
- ✓ Improve glucose uptake capacity
- $\checkmark \quad \text{Make fiber type shift (fast glycolytic} \rightarrow \text{slow oxidative)}$



To test whether 8 weeks of resistance training could convert muscle fiber type distribution and enhance glucose metabolism including GLUT4 protein expression in Zucker diabetic fatty(ZDF) rats.

#### **Animal Model**

### ZDF (Zucker Diabetic Fatty) vs. ZLC (Zucker Lean Control)



### **Experimental Design**



### **Exercise protocol**



- BD: Birth Day, BW: Body Weight, MW: Maximal Weight

### Laddering exercise & Grip strength





#### Intraperitoneal glucose tolerance test (IPGTT)







## RESULTS (1) Body weight and muscle weight

#### **Table 1. Body weight and gastrocnemius muscle characteristics**

	ZLC-Con	ZDF-Con	ZDF-Ex
Variable		Mean ± S.E.M.	
Body weight (g)	272 ± 5.35	364.5 ± 13.57*(.002)	371.5 ± 17.42(.925)
Muscle wet weight (mg)	$586.25 \pm 17.60$	505 ± 15.14(.070)	556.25 ± 30.85(.285)
Muscle wet weight/body weight (mg/g)	2.16±0.09	1.39±0.03 <b>**(.000)</b>	1.50±0.18(.512)

Values are mean ± S.E.M.; n=4/group; \* significantly different from ZLC-Con group (p<0.05); \*\* significantly different from ZLC-Con group (p<0.001).

## **RESULTS (2)** Exercise performance

#### **Table 2. Weekly exercise performance changes**

	1 wk	2 wk	3 wk	4wk	5wk	6wk	7wk	8wk			
Variable		Mean ± S.E.M.									
Maximal weight lifted (g)	240 ± 12.25	330 ± 21.21	420 ± 46.19	497.5 ± 36.14	625 ± 31.75	670 ± 34.88	745 ± 26.3	785 ± 2.89			
Maximal weight lifted / body weight (g/g)	1.77 ± 0.18	1.62 ± 0.08	1.77 ± 0.10	1.83 ± 0.07	2.12 ± 0.03	2.13 ± 0.02	2.15 ± 0.01	2.13 ± 0.09			

Values are mean ± S.E.M.; n=4/group

## RESULTS (3) Grip strength

#### **Table 3. Grip strength test**

	ZLC-Con	ZDF-Con	ZDF-Ex
Variable		Mean ± S.E.M.	
Grip strength (g)	1099.48 ± 50.55	704.74 ± 53.73*( <b>.009</b> )	918.09 ± 99.05(.141)
Grip strength/muscle weight (g/g)	$1877.39 \pm 78.67$	1389.86 ± 64.22(.072)	1671.94 ± 210.02(.344)
Grip strength/body weight (g/g)	$4.04 \pm 0.18$	1.93 ± 0.08**(.000)	2.52 ± 0.37(.248)

Values are mean ± S.E.M.; n=4/group; \* significantly different from ZLC-Con group (p<0.05); \*\* significantly different from ZLC-Con group (p<0.001).

### **RESULTS (4)** Glucose tolerance (IPGTT)

#### **Table 4. Changes of fasting blood glucose level**

	ZLC-Con ZDF-Con		ZDF-Ex	
Variable (mg/dL)		Mean ± S.E.M.		
Fasting blood glucose level of	$07 \pm 2.02$	$109.5 \pm 12.71(.564)$	$111.5 \pm 2.97(.050)$	
1 <sup>st</sup> week of training	97 ± 3.03	$108.5 \pm 12.71(.304)$	$111.3 \pm 2.87(.939)$	
Fasting blood glucose level of	100 25 + 2 54	$217.25 \pm 71.60(.160)$	$115.75 \pm 0.62(.047)$	
4 <sup>st</sup> week of training	100.23 ± 5.34	$217.25 \pm 71.09(.109)$	$113.73 \pm 2.03(.247)$	
Fasting blood glucose level of	102 75 + 4 49	$272 \pm 22.5(**(000))$	$124.75 \pm 0.07 \pm (0.00)$	
8 <sup>st</sup> week of training	$102.73 \pm 4.48$	$272 \pm 23.30^{(.000)}$	$134.73 \pm 8.871(.000)$	

Values are mean  $\pm$  S.E.M.; n=4/group; \* significantly different from ZLC-Con group (p<0.05); \*\* significantly different from ZLC-Con group (p<0.001); †† significantly different from ZDF-Con group (p<0.001).

#### - ZDF-Con - ZDF-Ex 500 -**Figure 1. Blood glucose level** 450 during IPGTT 400 Blood glucose level (mg/dL) 350 -**ZDF-Con** \*\* 300 -Ĭ 250 200 -## # 150 -**ZDF-Ex** 100 **ZLC-Con** 50 0 15 30 60 90 120 ò

Time (min)

### **RESULTS (4)** Glucose tolerance (AUC)

#### **Table 5. Changes of glucose area under the curve (AUC)**

	ZLC-Con	ZDF-Con	ZDF-Ex
Variable (mg/dL·min)		Mean ± S.E.M.	
AUC of 1 <sup>st</sup> week of training	$13310.63 \pm 418.66$	19282.5 ± 2203.49*( <b>.027</b> )	14814.38 ± 468.36(.094)
AUC of 4 <sup>st</sup> week of training	13957.5 ± 268.49	28005 ± 3180.01*(.001)	19556.25 ± 844.31 <sup>+</sup> (.029)
AUC of 8 <sup>st</sup> week of training	15931.88 ± 1880.11	45429.38 ± 3099.8**(.000)	21099.38 ± 701.63 <sup>++</sup> (.000)

Values are mean  $\pm$  S.E.M.; n=4/group; \* significantly different from ZLC-Con group (p<0.05); \*\* significantly different from ZLC-Con group (p<0.001); † significantly different from ZDF-Con group (p<0.05); †† significantly different from ZDF-Con group (p<0.001).



### **RESULTS (5)** Immunofluorescence staining – GLUT4

**Figure 3** . Immunofluorescence staining for medial gastrocnemius muscle GLUT4 protein





Figure 4. GLUT4 protein expression in gastrocnemius muscle



# RESULTS (7)

Immunohistochemical staining – Myosin Heavy Chain (MHC)

**Figure 5. Immunohistochemical staining on cross sectional area of gastrocnemius muscles** 



### **RESULTS (8)** Immunohistochemical staining – Myosin Heavy Chain (MHC)





연구 2 (김희재)



## 동물 당뇨모델 (Zucker)에서 운동에 따른 Myokine의 변화

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### Animal study (Zucker)









### Animal study (Zucker)



# Myokine

Cytokines and other peptides that are **produced**, **expressed**, and **released** by **muscle fibers** and exert autocrine, paracrine or endocrine effects.





Bente K. Pedersen (2012)

## IL-15: A role in muscle-fat cross talk

There are several reports about IL-15 as a **potent regulator** of <u>fat mass</u> and <u>muscle-fat cross-talk</u>. So, IL-15 is thought to be a principal myokine to prevent metabolic syndrome involving obesity and diabetes.



# Interleukin-15

#### IL-15 seems to play a role in reducing adipose tissue mass

When IL-15 was administered to adult rats for 7 days, it resulted in a 33% decrease in white adipose tissue mass.



(Biochimica et Biophysica Acta 1526 (2001) 17~24)

# Interleukin-15

#### Change of IL-15 protein following resistance exercise



Plasma IL-15 protein concentration before and **after resistance exercise** at the beginning (*session 1*) and end (*session 30*) of the resistance exercise training intervention (n = 124). J Appl Physiol. 2004 Dec;97(6):2214-9.

## Effect of Treadmill Exercise on Interleukin-15 Expression and Glucose Tolerance in Zucker Diabetic Fatty Rats

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#### - Endurance training (treadmill exercise)

Туре	Intensity	Duration	Frequency	Contents
Endurance Exercise	15 ~ 20 m/min	60 min	5 times/week	Exercise Group

#### Effect of treadmill exercise on IL-15 in Zucker rats



Fig. 1 (A) **Body weight** and (B) **fasting glucose levels were reduced** following treadmill exercise

Fig. 2 **Glucose tolerance** was **significantly improved** following treadmill exercise

DMJ, 2013 Accepted

#### Effect of treadmill exercise on IL-15 in Zucker rats



Fig. 3. **IL-15 protein expression** was increased in SOL of ZDF rats



Fig. 4. Body weight and fasting glucose levels were negatively correlated with IL-15 protein expression in SOL of ZDF rats

DMJ, 2013 Accepted

# BDNF: A role in neurobiology and metabolism



In response to muscle contractions, **BDNF mRNA** and **protein** expression are <u>markedly</u> <u>increased</u> in human skeletal muscle after exercise. **BDNF mRNA and protein expression** were increased in human skeletal muscle after exercise; however, muscle derived BDNF appears **not to be released into the circulation**.

#### High intensity Cycle exercise





24 h

### Muscle BDNF and Type 2 DM

**BDNF mRNA levels are up-regulated** in hindlimb skeletal muscle of diabetic rats: effect of denervation *(Exp Neurol. 1996; 141(2):297-303)* 

Altered neurotrophin mRNA levels in peripheral nerve and skeletal muscle of experimentally diabetic rats. (J Neurochem. 1995;64:2131-7)



### Effect of resistance training on BDNF expression in diabetic skeletal muscles: relation to muscle quality



Experimental group

-ZLC control (ZLC con, n= 6) -ZDF control (ZDF con, n=6) -ZDF exercise (ZDF ex, n=5)



1 week adaptation

IPGTT, Grip-strength test PET-CT Tissue collection

8 weeks training

In Preparation: unpublished data

# Changes of body weight, grip-strength and plasma glucose

	Body weight Pre-Ex Post-Ex		Grip-s	strength	Plasma glucose		
			Pre-Ex Post-Ex		Pre-Ex	Post-Ex	
ZLC Con	110.16 ± 2.04	256.33 ± 5.07	3023.4 ± 125.4	3231.84 ± 132.3	105.43 ± 2.54	100.33 ± 2.75	
ZDF Con	116.66 ± 2.29	370.04 ± 9.87*	2975.3 ± 105.3	2760.14 ± 98.4*	110.33 ± 2.98	210.33 ± 34.97*	
ZDF Ex	116.96 ± 2.21	341.4 ± 1.21 <sup>#</sup>	3004.3 ± 98.43	3191.23 ± 100.3 <sup>#</sup>	109.43 ± 0.92	141.63 ± 24.19 <sup>#</sup>	

\*: ZLC Con vs. ZDF Con #: ZDF Con vs. ZDF Ex

#### **Glucose tolerance test (IPGTT, AUC)**



\*: ZLC Con vs. ZDF Con #: ZDF Con vs. ZDF Ex Muscle Volume, Muscle Quality (measured by PET-CT)



\*: ZLC Con vs. ZDF Con #: ZDF Con vs. ZDF Ex

#### **BDNF** expression in skeletal muscle



#### **Relation of BDNF to FBG & muscle strength**



연구 3



### 유산소 및 저항성 운동이 비만인의 혈중 Irisin에 미치는 영향

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# Irisin is a PGC1- $\alpha$ dependent myokine that drives brown fat like development of whit fat.



(Kelly, Science 2012)

# Introduction of irisin

**RTICLE** 

Nature 2012, Pontus Boström et al

doi:10.1038/nature10777

### A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis

Pontus Boström<sup>1</sup>, Jun Wu<sup>1</sup>, Mark P. Jedrychowski<sup>2</sup>, Anisha Korde<sup>1</sup>, Li Ye<sup>1</sup>, James C. Lo<sup>1</sup>, Kyle A. Rasbach<sup>1</sup>, Elisabeth Almer Boström<sup>3</sup>, Jang Hyun Choi<sup>1</sup>, Jonathan Z. Long<sup>1</sup>, Shingo Kajimura<sup>4</sup>, Maria Cristina Zingaretti<sup>5</sup>, Birgitte F. Vind<sup>6</sup>, Hua Tu<sup>7</sup>, Saverio Cinti<sup>5</sup>, Kurt Højlund<sup>6</sup>, Steven P. Gygi<sup>2</sup> & Bruce M. Spiegelman<sup>1</sup>



## Major findings from irisin paper

Nature 2012, Pontus Boström et al

- Muscle-specific PGC1-a transgenic mice have increased brown/beige fat cells in the subcutaneous depot
- FNDC5 is induced with forced PGC1-a expression or exercise, and turns on brown/beige fat gene expression
- FNDC5 is a potent inducer of the brown/beige fat gene program
- FNDC5 is proteolytically cleaved and secreted from cells
- Detection of irisin in mouse and human plasma
- Irisin induces browning of white adipose tissues in vivo and protects against diet-induced obesity and diabetes





Irisin in serum from 3 weeks exercised mice followed by 12 h rest Irisin in plasma from human subjects before and after 10 weeks of endurance exercise

Irisin induces browning of white adipose tissues in vivo and protects against diet-induced obesity and diabetes

Nature 2012, Pontus Boström et al

#### BRIEF COMMUNICATIONS ARISING

# Controversial report

#### Is irisin a human exercise gene?

ARISING FROM P. Boström et al. Nature 831, 463-468 (2012)



Irisin is not routinely activated by exercise in humans



Irisin expression is not related to diabetes status in humans

# Controversial results regarding irisin and clinical parameters

 Irisin levels showed a positive correlation with body weight and BMI(Joo Young Huh,2012 ; Andreas Stengel,2013).





# Controversial results regarding irisin and clinical parameters

 Irisin was positively correlated with circulating insulin and glucose (Andreas Stengel, 2013).



# Controversial results regarding irisin and clinical parameters

• Irisin levels were negatively associated with obesity (Jose Maria, 2013; Yeon Kyung Choi, 2013).





## **Circulating irisin level with exercise**



#### (Metabolism, Huh et al., 2012)

8 week training program involving 3 training sessions per week.

2 or 3 set of runs on an indoor track with two 80m sprint runs in each set. A resting period of 20 min between sets.



#### (Nature, Timmons et al, 2012)

6 week of endurance cycle training program involving four times a week (45min) at 75% of peak aerobic capacity(peak VO<sub>2</sub>).

### Background

Irisin is a potent metabolic regulator for obesity.

There is small evidence of effects of exercise on circulating irisin in obesity.

In particular, there is no evidence of resistance training on circulating irisin.

### **Purpose of study**



### **Participants**

Body mass index > 25kg/m<sup>2</sup>

Body fat percentage > 25% Male > 30% Female

Stable body weight Sedentary lifestyle



## **Study Design**



### Measurements

Variables	Analysis Method	Model	Company
Body Composition Analysis	BIA	In body 370	Biospace, Korea
Irisin	ELISA analysis	Irisin ELISA Kit	AVISCERA BIOSCIENCE
Blood Lipid profiles	Lipid test		The Green Cross Reference Lab, Korea
Muscle Strength	Isokinetic Contraction Measurement	Cybex Humac Norm	Humac Norm, USA
Cardiopulmonary Endurance	Treadmills Ergometers	Quark	Cosmed, USA
Subcutaneous Fat Thickness	Ultrasound	BX2000	Intelametrix, USA

### **Exercise Programs (aerobic)**



### **Exercise Programs (resistance)**



# **Descriptive Characteristics**

There were significant training effects on body composition in both exercise groups compare to control.

Anthropometric Measures	Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p-value
	Pre	Post	Pre	Post	Pre	Post	
Age(yrs)	25.8±5.5	25.8±5.5	25.7±4.1	25.7±4.1	26.4±2.9	26.4±2.9	
Height(cm)	167.2±5.4	167.5±5.5	168.3±7.7	168.5±7.8	172.1±5.6	172.1±5.7	0.147
BodyWeight(kg)	74.1±7.6	74.1±7.7	75.3±12.7	73.1±13.4*	80.3±12.8	77.7±13.4*	0.030
Skeletal Muscle Mass(kg)	32.8±4.9	28.2±4.8	28.4±6.4	28.4±6.5	32.5±4.8	32.9±5.1	0.271
Skeletal Muscle Mass(kg) / Body Weight(kg)	0.38±0.0	0.37±0.0	0.37±0.0	0.38±0.0*	0.40±0.0	0.42±0.0**	0.000

# **Descriptive Characteristics**

Anthropometric Measures	Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p-value
	Pre	Post	Pre	Post	Pre	Post	
Body Fat Mass (kg)	23.1±4.0	23.8±3.4	23.7±4.8	22.2±4.8*	22.1±7.3	19.5±7.3**	0.000
Body fat (%)	31.1±5.7	32.1±5.2	32.4±4.8	30.6±4.8**	28.0±4.4	24.7±5.1***	0.000
BMI (kg/m)	26.5±2.0	26.4±2.1	26.4±2.4	25.3±2.5**	27.0±3.4	26.0±3.6*	0.035
Waist(cm)	89.7±4.4	85.5±6.7	90.76.6±	80.9±8.8***	92.8±8.8	84.6±10.6**	0.069
Hip(cm)	104.2±3.2	104.1±4.2	104.9±4.2	101.5±5.9*	105.0±5.9	102.4±6.4*	0.077
WHR	0.86±0.0	0.82±0.0	0.86±0.0	0.79±0.0**	0.88±0.0	0.82±0.0*	0.351
Subcutaneous Fat Thickness (mm)	31.9±7.9	33.3±3.2	31.3±9.1	27.4±6.6*	28.1±8.7	25.3±8.2	0.343

# **Descriptive Characteristics**

Total cholesterol level was changed in resistance training group.

Blood Profiles Measures	Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p- value
	Pre	Post	Pre	Post	Pre	Post	
Total –C (mg/dL)	204.7±37.6	203.1±34.6	187.4±27.6	182.1±25.8	188.1±23.0	169.0±24.6*	0.300
LDL-C (mg/dL)	124.2±28.8	121.7±35.0	112.5±29.5	105.5±23.2	116.7±26.0	101.3±26.7	0.362
HDL-C (mg/dL)	61.5±16.6	62.6±16.7	59.9±12.8	63.3±12.1	55.4±8.5	54.6±13.0	0.612

There were significant training effects on peak torque value (PK) per body weight in both exercise groups compare to control.

Peak Torque/ Body Weight		Con (N:	itrol =8)	Aerobic Training Resistance Training (N=10) (N=10)		e Training =10)	p- value	
(Newto	n_Meter)	Pre	Post	Pre	Post	Pre	Post	
_	Extensor R	207±55.7	199.8±64.3	232.5±44.7	228.6±46.3	226.9±38.7	250.5±28.6**	0.036
Peak	Flexor R	107.0±41.4	109.3±30.5	96.7±24.2	112.7±25.5**	126.5±28.1	138.8±18.2	0.289
forque 60°/sec	Extensor L	179.5±51.4	186.5±59.4	204.4±43.3	215.1±48.1	213.8±34.7	239.6±29.4*	0.421
	Flexor L	103.3±32.1	106.5±32.1	89.5±23.1	106.8±20.4*	124.1±31.4	133.7±24.2	0.384

Peak Torque/ Body Weight (Newton_Meter)		Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p- value
		Pre	Post	Pre	Post	Pre	Post	
Peak	Extensor R	123.1±36.3	127.6±33.1	143.9±32.8	145.7±31.3	153.2±20.5	167.3±19.3**	0.187
Torque	Flexor R	64.6±30.9	69.6±21.1	65.4±14.5	75.6±20.0	86.0±21.8	93.4±17.1	0.832
<b>180°</b>	Extensor L	111.5±30.5	120.6±39.8	135.5±28.1	141.2±26.9	143.3±28.9	161.9±15.7*	0.311
/sec	Flexor L	60±19.8	65.3±24.8	62.3±10.4	65.9±11.6	82.2±19.3	86.5±14.9	0.887

There were significant increase on average power per repetition per body weight in both exercise groups compare to control.

Average Power per		Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p- value
Body Weight		Pre	Post	Pre	Post	Pre	Post	
Average	Extensor R	124.8±35.3	124.6±40.9	147.7±27.9	145±27.0	146.8±25.2	165.9±21.0*	0.017
Power	Flexor R	80.6±30.5	84±23.6	77.3±18.9	88.2±19.0*	94.2±23.4	107.8±15.9*	0.415
tition	Extensor L	112±33.6	117.2±42.4	128.4±26.6	141.4±30.7*	133.7±20.6	159.3±16.6**	0.097
60°/sec	Flexor L	78.6±25.8	82.3±26.7	54.2±19.2	62±16.2*	94.5±26.1	106.1±18.6	0.485

Average Power per		Control (N=8)		Aerobic Training (N=10)		Resistance Training (N=10)		p- value
Body Weight		Pre	Post	Pre	Post	Pre	Post	
Average	Extensor R	187.1±47.5	198.1±59.8	238.7±49.9	223.8±46.6	262.4±34.6	298.4±112.8	0.245
Power p	Flexor R	106.0±48.6	109.5±37.5	113.1±24.5	120.5±26.9	146.8±39.0	151.2±21.1	0.952
er Repetit	Extensor L	167.3±44.9	185.0±68.4	223.9±48.2	219.7±38.0	230.9±50.2	258.4±31.8*	0.152
180°/sec	Flexor L	94.5±28.5	103.1±35.6	107.8±17.9	104.9±17.8	139.4±31.6	142.9±19.7	0.463
Grip Strength (Kg)/ Body Weight(Kg)		0.38±0.0	0.37±0.0	0.46±0.0	0.47±0.0	0.46±0.0	0.52±0.0	0.038

VO2max increased in both exercise intervention groups and the aerobic training group showed more significant improvement.



Change of VO2max showed negative correlation with change of WHR and glucose



Circulating Irisin level increased in both training group but resistance intervention showed more significant increase.



Change of Irisin showed positive correlation with change of muscle mass.



Change of Irisin showed negative correlation with change of fat mass and body fat percentage



# Thanks for your attention