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COMMENTARY

Fat cell lipolysis and future weight gain

Obesity and type 2 diabetes mellitus have been increasing worldwide, and are considered to be related to physical inactivity and dysregulated eating behavior. Although environmental factors are important in the progression of obesity, the contribution of adipose tissue dysfunction and related genetic factors have been less clear.

Adipose tissue is a metabolic and endocrine organ known to secrete a variety of bioactive molecules termed adipocytokines/adipokines, including fatty acids, adiponectin, leptin and interleukin-6. Dysregulated production of adipocytokines in obesity is closely associated with dyslipidemia, insulin resistance and atherosclerosis. Adipocytes store energy as triglyceride. In the fasting state, the adipose tissue mobilizes fatty acids and glycerol by lipolysis to various tissues for energy expenditure. However, in obese adipose tissue, steady-state (basal) lipolytic activity is high, and excessive flow of fatty acids and glycerol is involved in impaired lipid and glucose metabolism, particularly in the liver.

Adipose tissue mass is determined by the amount of stored and removed triglycerides in adipocytes. However, little is known about adipose lipid turnover in humans. Arner *et al.*[1] recently reported in *Cell Metabolism* that insufficient lipolysis in adipose tissue might be linked to future weight gain and impaired glucose metabolism. It has been shown that triglycerides are renewed six times during the average 10-year lifespan of human adipocytes[2]. However, in obesity, adipose lipid turnover, reflected by the triglyceride removal rate, is decreased, whereas the amount of triglyceride stored each year is increased. Lipid removal rate correlates with cyclic adenosine monophosphate-induced lipolysis, but not with basal lipolysis[2].

Arner *et al.*[1] carried out comprehensive analysis of subcutaneous adipocytes obtained from two female cohorts before and after ≥10-year follow up (Table 1). High steady-state (basal) and low stimulated lipolysis by isoprenaline, noradrenaline or dibutyryl cyclic adenosine monophosphate predicted future weight gain (odds ratio ≥4.6) and development of impaired glucose metabolism (odds ratio ≥3.2; Table 2)[1]. At study baseline, low expression levels of several lipolysis-regulating genes, such as guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-12 (GNG12), cyclic adenosine monophosphate-dependent protein kinase type II-β regulatory subunit (PRKAR2B), monoacylglycerol lipase (MGLL), fatty acid binding protein 4 (FABP4), and aquaporin 7 (AQP7), were found in adipose tissue of weight gainers. For example, AQP7, a glycerol channel in adipocytes, is associated with glycerol release from adipose tissue, and *Aqp7* knockout mice developed insulin resistance and showed adipocyte hypertrophy[3]. Furthermore, human genetic variants of AQP7 have been linked to obesity and type 2 diabetes, suggesting that AQP7 might be a suitable pharmacological target for obesity and type 2 diabetes[4]. Arner *et al.*[1] also showed a lack of association between baseline fatty acid oxidation and weight change, and concluded that adipocyte hypertrophy at baseline was unlikely to be associated with future weight gain.

Steady-state (basal) lipolysis is higher and hormone-induced lipolysis is lower in the obese adipose tissue[5]. The study of Arner *et al.*[1] showed that, even at study baseline, higher steady-state (basal) and lower stimulated lipolysis activity were linked to future weight gain. The authors stipulated that a high steady-state (basal) lipolysis or insufficient lipolysis, which cannot be adequately accelerated by catecholamine stimulation, might shift the balance in lipid turnover towards uptake, which facilitates fat mass growth[1].

Body fat distribution varies considerably among individuals. Irrespective of body mass index (<25 or ≥25 kg/m^2), visceral fat accumulation, which results from dysregulated eating behavior and physical inactivity, can lead to type 2 diabetes, dyslipidemia, hypertension and atherosclerotic cardiovascular diseases, conceptualized as the metabolic syndrome[6]. In contrast, subcutaneous fat mass/total fat mass is associated with a low risk of cardiovascular diseases. There is also a sex difference in body fat distribution; that is, men are more affected by visceral fat obesity and women are more affected by subcutaneous fat obesity[7]. It has been reported that the lipolytic effect of catecholamines is more pronounced in visceral than subcutaneous adipose tissue[8]. In contrast, the steady-state (basal) lipolytic activity is higher in subcutaneous than visceral fat adipose tissue[5]. As the study by Arner *et al.*[1] is limited to subcutaneous fat in women, further studies are required in the future that include men and focus on fat distribution.

How can we combat low stimulated lipolytic activity? Endurance exercise training is reported to increase catecholamine-stimulated adipocyte lipolysis[9]. Therefore, individuals with constitutionally low stimulated lipolytic activity might benefit from exercise in addition to a low caloric diet. Baseline measurement of lipolytic activity in adipose tissue or

*Corresponding author. Hitoshi Nishizawa
Tel.: +81-6-6879-3732
Fax: +81-6-6879-3739
E-mail address: hitoshin1127@endmet.med.osaka-u.ac.jp
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Table 1. Clinical and Adipocyte Characteristics at First and Second Examination

	First Examination			Difference between Second and First Examination or Number of Subjects at Second Examination		
Parameter	Weight Stable	Weight Gain	p Value	Weight Stable	Weight Gain	p Value
Age (years)	39 ± 6	38 ± 8	0.69	13 ± 1	13 ± 1	0.22
Body weight (kg)	86 ± 17	93 ± 14	0.15	−0.6 ± 3.3	13.1 ± 6.4	–
BMI (kg/m^2)	31 ± 6	34 ± 5	0.051	−0.2 ± 1.2	4.8 ± 2.3	–
Obesity (yes/no)	23/13	14/4	0.30	23/13	17/1	0.02
Physical activity (score)	1.9 ± 0.7	1.8 ± 0.7	0.54	0.2 ± 0.7	0.0 ± 1.0	0.35
RQ	0.84 ± 0.05	0.84 ± 0.05	0.86	N/A	N/A	–
P-glucose (mmol/L)	5.1 ± 0.6	5.3 ± 0.5	0.19	0.5 ± 0.5[a]	1.0 ± 0.7[a]	0.008
S-insulin (mU/L)	9.8 ± 5.9	11.1 ± 4.7	0.41	0.6 ± 6.5	8.5 ± 13.1[a]	0.005
$HOMA_{IR}$	2.3 ± 1.4	2.7 ± 1.3	0.30	0.43 ± 1.7	3.1 ± 4.7[a]	0.0038
P-triglycerides (mmol/L)	1.1 ± 0.7	1.0 ± 0.4	0.53	−0.26 ± 0.51[a]	0.17 ± 0.31[a]	0.002
P-HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.3	0.48	0.2 ± 0.3[a]	0.1 ± 0.2[a]	0.26
P-total cholesterol (mmol/L)	4.7 ± 0.8	4.6 ± 0.8	0.49	−0.07 ± 0.84	0.07 ± 0.71	0.53
S-leptin (ng/mL)	30 ± 22	38 ± 17	0.15	14 ± 24[a]	43 ± 42[a]	0.002
IFG or T2DM (yes/no)	2/34	2/16	0.46	8/28	11/7	0.005
Nicotine use (yes/no)	6/30	2/16	0.59	3/33	7/18	0.56
Menstruation (regular/not regular or absent)	32/4	16/2	0.99	17/19	7/11	0.56
Pharmacologic therapy (yes/no[b])	0/36	0/18	–	8/28	6/12	0.58
Number of children	1.1 ± 1.4	1.2 ± 1.5	0.85	0.4 ± 0.9	0.3 ± 0.8	0.58
Living with partner (yes/no[c])	18/13	11/5	0.48	23/11	11/7	0.64
Low income (yes/no[d])	23/13	12/6	0.84	18/18	7/11	0.44
Own household (yes/no)	36/0	18/0	–	36/0	18/0	–
Fat cell volume (pL)	678 ± 237	764 ± 181	0.18	−96 ± 147	46 ± 156	0.0022
Log basal lipolysis (μmol glycerol/2 hr/g lipid)	−0.04 ± 0.24	0.14 ± 0.21	0.007	−0.12 ± 0.36	−0.25 ± 0.25[a]	0.19
Log NA/basal lipolysis	0.53 ± 0.25	0.36 ± 0.19	0.008	−0.09 ± 0.27	0.07 ± 0.27	0.049
Log ISO/basal lipolysis	0.73 ± 0.27	0.52 ± 0.22	0.005	0.06 ± 0.33	0.18 ± 0.24[a]	0.20
Log dcAMP/basal lipolysis	0.66 ± 0.26	0.48 ± 0.19	0.007	0.08 ± 0.30	0.18 ± 0.23[a]	0.22
Log ISO/NA lipolysis	0.18 ± 0.12	0.16 ± 0.14	0.50	0.16 ± 0.20[a]	0.11 ± 0.12[a]	0.36

Values are mean ± SD or numbers and compared by unpaired or paired t test and chi-square. BMI, body mass index; RQ, respiratory quotient; N/A, not analyzed; P, fasting plasma; S, fasting serum; $HOMA_{IR}$, homeostasis model assessment insulin resistance; HDL, high-density lipoprotein; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; NA, noradrenaline; ISO, isoprenaline; dcAMP, dibutyryl cyclic AMP.

[a]Significant change over time at $p < 0.05$ or better.

[b]Against diabetes, dyslipidemia, or hypertension.

[c]No information from some subjects.

[d]Low income herein defined as <30,000 USD/year.

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Table 2. Prospective Value of Lipolysis Measures

Parameter	High Basal	Low NA/Basal	Low ISO/Basal	Low dcAMP/Basal	High Basal/Low Stimulated
Weight gain	6.7 (1.81–24.9); 0.002	4.6 (1.30–15.9); 0.013	5.9 (1.60–21.9); 0.004	4.6 (1.30–15.9); 0.013	7.4 (1.9–28.9); 0.002
T2DM/IFG	3.2 (0.90–11.6); 0.065	5.3 (1.34–20.4); 0.012	4.4 (1.17–16.9); 0.022	5.3 (1.35–20.4); 0.012	4.5 (1.12–18.1); 0.027
Increased $HOMA_{IR}$	11.9 (1.67–84.5); 0.008	10.6 (1.48–76.1); 0.012	9 (1.32–61.1); 0.017	23.8 (2.65–213); 0.0016	20 (2.2–181); 0.003

Subjects in cohort 1 were subdivided into high or low lipolysis measures based on median values. Composite results for individuals displaying high basal and concomitant low isoprenaline/basal are also detailed. Results are shown as odds ratios (95% confidence intervals); p values (using likelihood ratio test) for changes over time in individual clinical parameters. NA, noradrenaline; ISO, isoprenaline; dcAMP, dibutyryl cyclic AMP; T2DM/IFG, type 2 diabetes mellitus/impaired fasting glucose; $HOMA_{IR}$, homeostasis model assessment insulin resistance.

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algorithm for estimation of fat cell lipolysis might be helpful for assessment of the risk for future weight gain and type 2 diabetes[1].

DISCLOSURE

The authors declare no conflict of interest.

Hitoshi Nishizawa, Iichiro Shimomura*
Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan

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