

# The Effect of Xanthigen on the Expression of Brown Adipose Tissue Assessed by $^{18}\text{F}$ -FDG PET

Kwang-Min Kim<sup>1</sup>, Sang-Man Kim<sup>2</sup>, Doo-Yeon Cho<sup>1</sup>, Soo-Jung Park<sup>1</sup>, and Nam-Seok Joo<sup>1</sup>

<sup>1</sup>Department of Family Practice and Community Health, Ajou University School of Medicine, Suwon;

<sup>2</sup>Green Cross Reference Lab, Seoul, Korea.

Brown adipose tissue (BAT) is related with energy expenditure, in contrary to fat-storing white adipose tissue. Recent studies have shown that cold exposure could be related with the expression of BAT in adult subjects assessed by  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET). In addition, the application in previous clinical trials showed positive effect of xanthigen containing fucoxanthin and puniolic acid on body weight and liver fat content. In this short-term intervention study, we evaluated the effect of xanthigen on the expression of BAT by  $^{18}\text{F}$ -FDG PET. Two healthy obese premenopausal women were enrolled and xanthigen 600 mg (2 capsules including fucoxanthin 3 mg, puniolic acid 174 mg) was given for 3 months without dietary and exercise intervention. Body composition and dietary intake were assessed monthly. Laboratory test and  $^{18}\text{F}$ -FDG PET were performed before and after intervention. After intervention, there was neither weight reduction nor remarkable laboratory change. However, BAT, assessed by  $^{18}\text{F}$ -FDG PET, was detected in both cervical, supraclavicular and paravertebral space in one subject, even though her body weight showed mild increase. This result suggested that xanthigen can induce BAT in a healthy adult. However, a further large well-controlled study is needed.

**Key Words:** Xanthigen, brown adipose tissue, FDG PET

## INTRODUCTION

Early investigation<sup>1,2</sup> showed that brown adipose tissue (BAT) was observed in subjects during cold exposure, assessed by  $^{18}\text{F}$ -fluorodeoxyglucose (FDG)-positron emission tomography (PET). Furthermore, fucoxanthin from edible seaweed, *Undaria pinnatifida*, exhibited antiobesity effect through UCP1 expression in white adipose tissues,<sup>3</sup> and a clinical trial using xanthigen containing fucoxanthin and puniolic acid showed positive effects on weight loss, body fat and liver fat content in obese non-diabetic women. In the present study, therefore,

we conducted a pilot study for application and evaluation of short term effect of xanthigen on BAT expression in two healthy obese premenopausal women and the results described.

## CASE REPORT

Two premenopausal healthy obese women with body mass index  $>30\text{ kg/m}^2$  were voluntarily enrolled in this pilot study after informed written consent. They were enrolled in the mid August and the study was conducted until mid November. After the enrollment, the subjects were requested to visit our department every month for measurement of body weight and body composition, and dietary record during the 3 month intervention period. For 3 months, xanthigen 600 mg (2 capsules including fucoxanthin 3 mg and puniolic acid 174 mg) was given to the study subjects. They were instructed to take xanthigen before going to bed and not to change their regular lifestyle such as exercise or physical activity and dietary intake. The effect of xanthigen on the expression of BAT, as well as the changes of body weight and metabolic markers were evaluated. Institutional Review Board in Ajou University of Hospital ap-

**Received:** June 16, 2015 **Revised:** August 24, 2015

**Accepted:** September 2, 2015

**Corresponding author:** Dr. Nam-Seok Joo, Department of Family Practice and Community Health, Ajou University School of Medicine, 164 World cup-ro, Yeong-tong-gu, Suwon 16499, Korea.

Tel: 82-31-219-5324, Fax: 82-31-219-5218, E-mail: jhcmc@hanmail.net

•The authors have no financial conflicts of interest.

© Copyright: Yonsei University College of Medicine 2016

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

proved the study (AJIRB-MED-FOD-14-196). Body composition was measured by dual-energy X-ray absorptiometry (DXA, DISCOVERY-W fan-beam densitometer, Hologic Inc., Malborough, MA, USA). We assessed three day dietary recall before intervention and every scheduled visit during the study period. Subjects were asked to fast and prohibited from par-enteral infusion of sugar-containing fluids at least 6 hours before  $^{18}\text{F}$ -FDG PET scanning. They were also asked not to undertake strenuous exercise for 1 day before examination. Blood glucose concentration was measured immediately before an intravenous administration of  $^{18}\text{F}$ -FDG to ensure a level below 150 mg/dL. After an injection of 370 MBq  $^{18}\text{F}$ -FDG, the subjects were instructed to rest comfortably for 60 minutes and to empty the bladder just before scanning. All laboratory tests and  $^{18}\text{F}$ -FDG PET were conducted before and after intervention.

The results indicated no weight reduction by this intervention trial. Small sample size makes it difficult to clearly confirm the effect of xanthigen (Table 1). Nevertheless, we assessed regional BAT by  $^{18}\text{F}$ -FDG PET in both subjects before and after intervention. Regional measured areas included the neck, sh-

oulders, and clavicles. Interestingly, after 12 week intervention, regional BAT in one subject (A) was detected, as compared to baseline examination. In the other subject (B), however, there was no significant focal FDG uptake, suggesting BAT before and after intervention (Fig. 1).

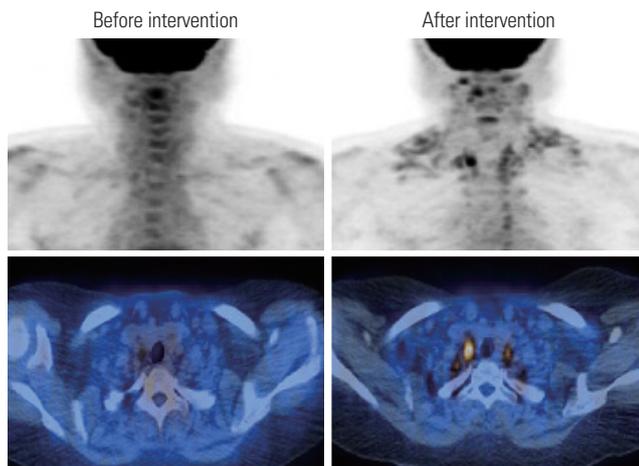
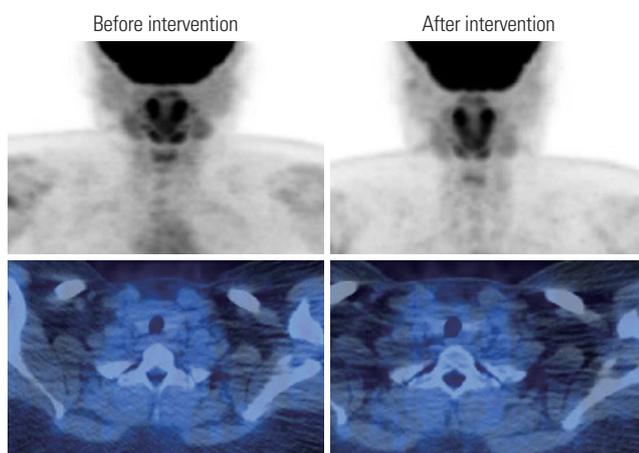
## DISCUSSION

In this small pilot study, we identified the expression of BAT by  $^{18}\text{F}$ -FDG PET after 3 months of xanthigen application, even though there was no weight reduction, indicating that xanthigen containing fucoxanthin and punicalic acid can induce BAT in adult adipose tissues. A previous study already demonstrated the positive effect of xanthigen on body weight and liver fat due by increasing resting metabolic rate.<sup>4</sup> Fucoxanthin can induce UCP1 in adipose tissue<sup>3</sup> and can be expressed as a form of beige adipose tissue. Beige cells resemble white cells with extremely low basal expression of UCP1, but like classical brown fat, they respond to cyclic AMP stimulation with high UCP1 expression and respiration rates.<sup>5</sup> However, another study showed

**Table 1.** Changes of Body Composition, Metabolic Parameters before and after Intervention

Variables	Subject A				Subject B			
	0 wk	4 wks	8 wks	12 wks	0 wk	4 wks	8 wks	12 wks
Age (yrs)	37.0				28.0			
Height (cm)	161.0				157.0			
Bwt (kg)	94.6	98.3	96.3	96.4	90.3	92.8	91.1	92.1
BMI (kg/m <sup>2</sup> )	36.5	38.4	37.2	37.2	36.6	37.6	37.0	37.4
Fat mass (kg)	50.6	51.7	51.9	52.1	43.9	45.4	44.5	45.3
Muscle mass (kg)	41.7	44.4	42.1	42.0	44.2	45.1	44.4	44.6
SBP (mm Hg)	131.0	123.0	133.0	128.0	131.0	131.0	116.0	118.0
DBP (mm Hg)	78.0	69.0	83.0	79.0	71.0	77.0	69.0	68.0
FBS (mg/dL)	81.0			92	105.0			97.0
Insulin (uIU/mL)	3.3			5.7	10.3			8.8
AST (mg/dL)	20.0			18.0	31.0			21.0
ALT (mg/dL)	12.0			13.0	35.0			17.0
GGT (mg/dL)	9.0			11.0	34.0			29.0
TC (mg/dL)	192.0			214.0	233.0			232.0
TG (mg/dL)	59.0			86.0	113.0			230.0
HDL-C (mg/dL)	71.0			87.0	55.0			52.0
LDL-C (mg/dL)	109.0			109.0	155.0			133.0
TSH (uIU/mL)	0.12			1.29	1.89			2.08
FT4 (ng/dL)	1.56			1.39	1.23			1.26
hsCRP (mg/dL)	0.59			1.02	0.63			0.42
Homocysteine (uM/L)	10.3			10.4	11.3			15.2
FFA (uEQ/L)	702.0			816	256.0			391.0
Cortisol (ug/dL)	6.4			11.2	10.8			18.0
Total calories (kcal)	1798.2	2400.3	1388.3	1297.3	1679.2	1897.2	1775.4	1802.4

Bwt, body weight; BMI, body mass index; Fat mass, total body fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; FT4, free thyroid; hsCRP, high-sensitive C-reactive protein; FFA, free fatty acid; Total calorie, daily total energy intake.

**Subject A****Subject B**

**Fig. 1.** Brown adipose tissue was assessed by  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography-CT before and after intervention. In subject A (above 4 pictures), multifocal brown fat uptake in both cervical, supraclavicular and paravertebral space was noticed after 3 months xanthigen intervention. In subject B (below 4 pictures), however, there was no demonstrable focal  $^{18}\text{F}$ -FDG uptake to suggest brown fat.

that all human BAT abundantly expressed beige cell-selective genes, but the expression of classical brown fat-selective genes were nearly undetectable.<sup>6</sup> There seems to be an important physiological cross-talk between the constitutive (BAT) and recruitable (beige) brown fat cells.<sup>7</sup>

The sympathetic nervous system is currently seen as the main effector for brown fat function<sup>8</sup> and white adipocytes of pure white fat that are subject to adrenergic stimulation are able to undergo a process of direct transformation into brown adipocytes.<sup>9</sup> Under cold exposure, the sympathetic nerve system is activated via the expression of cold receptor TRPM8 in human adipocytes inducing their “browning”. This suggests a possible role of this receptor in the control of adipose tissue metabolism and body energy balance.<sup>10</sup> Likewise, therapeutic effects can be expected from the use of specific drugs or food compounds such as xanthigen that are able to induce a program of brown

fat differentiation, including UCP1 expression and enhanced oxidative metabolism in white adipose cells.<sup>3,11</sup> In animal studies, dietary fucoxanthin was found to accumulate in the heart and liver as fucoxanthinol and as amarouciaxanthin A in adipose tissue;<sup>12</sup> their metabolites were confirmed.<sup>13</sup> A recent review article highlighted the effect of fucoxanthin on obesity, metabolic syndrome, and diabetes therapy,<sup>14,15</sup> as well as many other BAT activating factors.<sup>16</sup>

This study has some limitations. First, the confounding factors such as cold exposure or total calorie intake changes were not well controlled. Second, we could not confirm the causal-relationship of xanthigen application and BAT expression by such short-duration and small case report study. Long-term intervention trial is needed.

Nevertheless, this is the first study to evaluate BAT expression, by using  $^{18}\text{F}$ -FDG PET in the adult human, after xanthigen application for 3 months. Furthermore, we clearly confirmed the BAT in one subject after intervention, supporting the previous studies that showed a positive effect of xanthigen on the increase of energy expenditure and BAT induction in obese subjects. Nevertheless, a large intervention study is needed in future.

## ACKNOWLEDGEMENTS

We specially thank Bokkee Min, Seongho Yun, and Sukyung Kwon, who are managers of NOVAREX Company. They generously funded for this pilot study and also supplied xanthigen in the study. We also thank Professor Joon-Keo Yoon, Department of Nuclear Medicine and Molecular Imaging, Ajou University Hospital for measurement of BAT by  $^{18}\text{F}$ -FDG PET.

## REFERENCES

1. van Marken Lichtenbelt WD, Vanhomerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med* 2009;360:1500-8.
2. Yoneshiro T, Aita S, Matsushita M, Kameya T, Nakada K, Kawai Y, et al. Brown adipose tissue, whole-body energy expenditure, and thermogenesis in healthy adult men. *Obesity (Silver Spring)* 2011; 19:13-6.
3. Maeda H, Hosokawa M, Sashima T, Funayama K, Miyashita K. Fucoxanthin from edible seaweed, *Undaria pinnatifida*, shows anti-obesity effect through UCP1 expression in white adipose tissues. *Biochem Biophys Res Commun* 2005;332:392-7.
4. Abidov M, Ramazanov Z, Seifulla R, Grachev S. The effects of Xanthigen in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. *Diabetes Obes Metab* 2010;12:72-81.
5. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang AH, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 2012;150:366-76.
6. Sharp LZ, Shinoda K, Ohno H, Scheel DW, Tomoda E, Ruiz L, et al. Human BAT possesses molecular signatures that resemble beige/brite cells. *PLoS One* 2012;7:e49452.
7. Schulz TJ, Huang P, Huang TL, Xue R, McDougall LE, Townsend KL, et al. Brown-fat paucity due to impaired BMP signalling induc-

- es compensatory browning of white fat. *Nature* 2013;495:379-83.
8. Broeders E, Bouvy ND, van Marken Lichtenbelt WD. Endogenous ways to stimulate brown adipose tissue in humans. *Ann Med* 2015; 47:123-32.
  9. Frontini A, Vitali A, Perugini J, Murano I, Romiti C, Ricquier D, et al. White-to-brown transdifferentiation of omental adipocytes in patients affected by pheochromocytoma. *Biochim Biophys Acta* 2013; 1831:950-9.
  10. Rossato M, Granzotto M, Macchi V, Porzionato A, Petrelli L, Calcagno A, et al. Human white adipocytes express the cold receptor TRPM8 which activation induces UCP1 expression, mitochondrial activation and heat production. *Mol Cell Endocrinol* 2014;383: 137-46.
  11. Bonet ML, Oliver P, Palou A. Pharmacological and nutritional agents promoting browning of white adipose tissue. *Biochim Biophys Acta* 2013;1831:969-85.
  12. Hashimoto T, Ozaki Y, Taminato M, Das SK, Mizuno M, Yoshimura K, et al. The distribution and accumulation of fucoxanthin and its metabolites after oral administration in mice. *Br J Nutr* 2009;102: 242-8.
  13. Sangeetha RK, Bhaskar N, Divakar S, Baskaran V. Bioavailability and metabolism of fucoxanthin in rats: structural characterization of metabolites by LC-MS (APCI). *Mol Cell Biochem* 2010;333:299-310.
  14. Maeda H. Nutraceutical effects of fucoxanthin for obesity and diabetes therapy: a review. *J Oleo Sci* 2015;64:125-32.
  15. Gammone MA, D'Orazio N. Anti-obesity activity of the marine carotenoid fucoxanthin. *Mar Drugs* 2015;13:2196-214.
  16. Lee YH, Jung YS, Choi D. Recent advance in brown adipose physiology and its therapeutic potential. *Exp Mol Med* 2014;46:e78.