Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 925–930
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

The interaction between the interleukin 6 receptor gene genotype and dietary energy intake on abdominal obesity in Japanese men

Yixuan Song[a], Koichi Miyaki[a,b], Jungo Araki[a], Ling Zhang[a], Kazuyuki Omae[b], Masaaki Muramatsu[a,*]

[a]*Department of Molecular Epidemiology, Medical Research Institute, Tokyo Medical and Dental University, Chiyoda-ku, Tokyo 101-0062, Japan*
[b]*Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Shinjuku-ku, Tokyo 160-8582, Japan*

Received 12 June 2006; accepted 8 February 2007

Abstract

Previous reports have shown that the *Asp358Ala* (T/G) polymorphism of the interleukin 6 receptor (*IL6R*) gene is associated with obesity and type 2 diabetes mellitus, but few studies have examined this association in the Japanese population. We performed the current study to investigate the relationship between the *IL6R Asp358Ala* (T/G) polymorphism and obesity in healthy Japanese men. Two hundred eighty-five healthy Japanese men (age, 46.1 ± 11.5 years [mean ± SD]; waist circumference [WC], 83.9 ± 9.3 cm; body mass index, 23.3 ± 3.3 kg/m^2) employed by a Japanese company were enrolled in this study. Height, weight, and WC were measured, and daily energy intake levels were assessed by self-reported questionnaires. Genotyping of polymorphisms was performed by using melting curve analysis; no association was found between *IL6R* genotype and WC or body mass index. However, when the subjects were stratified by *IL6R* genotype, an association between WC and dietary energy intake level was found in the TT + GT–type subjects (P for linear regression = .048), but not in GG subjects (P for linear regression = .555). In addition, logistic regression analysis revealed that the interaction of *IL6R* (GG vs TT + GT) genotypes and dietary energy intake levels affected risk for abdominal obesity (P for interaction = .030). We concluded that the *IL6R Asp358Ala* (T/G) polymorphism appears to interact with energy intake and affect abdominal obesity in Japanese men. The interaction of this genotype and energy intake warrants further study.

1. Introduction

Obesity, especially abdominal obesity, is well known to play a pivotal role in the development of a number of metabolic abnormalities and predict the development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases [1]. The etiology of obesity is an imbalance between energy intake and energy expenditure. Excess energy is stored in fat cells that enlarge and increase in number resulting in elevated secretion of free fatty acids and numerous peptides [2]. Accumulating evidence indicates that obesity is a state of chronic, systemic, low-grade inflammation that accompanies increased levels of biomarkers for inflammation, such as leukocyte count, tumor necrosis factor α, interleukin 6 (IL-6), C-reactive protein, and fibrinogen [3,4]. Several studies have reported that circulatory IL-6 as well as C-reactive protein concentrations are positively correlated with obesity indices, such as body mass index (BMI) [5], waist circumference (WC) [6], or percentage of body fat [7].

Interleukin 6 is a multifunctional cytokine involved in the pathophysiology of various human diseases. IL-6 is secreted by different cell types including leukocytes, endothelial cells, skeletal muscle tissue [8], and adipose cells [9,10]. Several in vitro and in vivo studies have examined the physiologic and pathophysiologic roles of IL-6 in lipid metabolism and obesity. IL-6 inhibits lipoprotein lipase activity [11] and increases lipolysis [12]. In addition, IL-6 appears to increase energy expenditure and decrease fat mass via effects at the central nervous system level [13]. Such actions indicate that IL-6 is protective of obesity. Indeed, animal studies have shown that IL-6–deficient mice develop mature-onset obesity [14], whereas chronic IL-6 supplementation causes a decline in body fat in rats [15]. On the other hand, circulating IL-6 levels have been shown to be elevated in T2DM [16,17] or to contribute

* Corresponding author. Tel.: +81 3 5280 8060; fax: +81 3 5280 8061.
E-mail address: muramatsu.epi@mri.tmd.ac.jp (M. Muramatsu).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2007.02.006

Table 1
Genotype distribution and allele frequency of the *Asp358Ala* (T/G) *IL6R* polymorphism in study subjects

	No. of subjects	Genotype, number (%)			G allele frequency	P^a
		TT	GT	GG		
Total	358	132 (36.9)	172 (48.0)	54 (15.1)	0.39	.868
Male	321	118 (36.8)	157 (48.9)	46 (14.3)	0.39	.591
Female	37	14 (37.8)	15 (40.5)	8 (21.6)	0.42	.309
Subjects involved in this study[b]	285	101 (35.4)	144 (50.5)	40 (14.0)	0.39	.319

[a] P value for deviation from Hardy-Weinberg equilibrium by χ^2 test.
[b] Male subjects without diabetes are indicated.

to insulin resistance [18]. It seems that IL-6 causes insulin resistance and, partly through this, induces lipolysis and suppresses lipogenesis. Thus, the involvement of IL-6 in the pathogenesis of obesity, insulin resistance, and T2DM appears to be complex.

Interleukin 6 acts through a receptor complex comprising 2 subunits, an 80-kd glycoprotein IL-6 receptor (*IL6R*) and a ubiquitous 130-kd signal-transducing element, gp130 [19]. IL-6 first binds to IL6R, and this complex in turn binds to the gp130 molecules. *IL6R* gene maps to human chromosome 1q21, a region reported to have linkage to T2DM in Pima Indians [20], whites [21], and African Americans [22]. Several single nucleotide polymorphisms of the *IL6R* gene have been identified among Pima Indian [23], Korean [24], white, and African American subjects [25]. One of these single nucleotide polymorphisms, a nonsynonymous variant in exon 9, *Asp358Ala* (T/G, rs8192284), was found to associate with T2DM in Danish and Utahan white populations [25,26] and with obesity in Pima Indians [23]. In these studies, the Asp allele (T allele) recurrently conferred the risk for T2DM and obesity. Here, we undertook the current study to examine this polymorphism with regard to obesity in healthy Japanese men. The interaction between genetic variation and dietary energy intake level in obesity was also considered. The aim of the present study was to investigate the relationship between *IL6R* T/G polymorphism and obesity index as well as the interaction with dietary energy intake level in healthy Japanese subjects.

2. Methods

2.1. Subjects

The present study was performed as part of a larger study being carried out to investigate the association of lifestyle factors with obesity according to different genetic factors in Japanese workers. Three hundred fifty-eight healthy Japanese individuals (321 men and 37 women) working for a company in Kanagawa Prefecture participated in this study. We obtained complete replies to the food frequency questionnaire (FFQ) from 323 (291 men, 32 women) of the 358 workers. Because diabetes could influence body weight as a consequence of the disease, 6 men and 1 woman who had a medical history of diabetes were excluded. In addition, considering the low percentage of women included in this study and because men and women might have different risks for obesity [27], we performed the analysis focused on the 285 male workers without overt diabetes. Their mean (±SD) age, WC, and BMI were 46.1 ± 11.5 years, 83.9 ± 9.3 cm, and 23.3 ± 3.3 kg/m^2, respectively. Height, weight, WC, systolic and diastolic blood pressure, fasting plasma glucose levels, and serum lipid levels were measured in all subjects. WC was measured at the midpoint between the lower rib margin and the iliac crest with the subject standing and at minimal respiration. BMI was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI of 25 kg/m^2 or greater or WC of 85 cm or greater based on the criteria for "obesity" of the Japanese Society for the Study of Obesity [28]. In addition, information on age, current smoking, alcohol drinking, and energy intake levels of all subjects was obtained by means of a self-report questionnaire. The study was approved by the ethics review committee of the Medical Research Institute, Tokyo Medical and Dental University, and Keio University School of Medicine, Tokyo, Japan. Written informed consent was obtained from all participants.

2.2. Genotyping for IL6R gene polymorphism

A peripheral blood specimen was collected from each subject, genomic DNA was extracted by a standard method, and genotyping for the *IL6R* polymorphism was performed by polymerase chain reaction (PCR) followed by melting curve analysis [29] using a LightTyper Instrument (Roche Diagnostics, Penzberg, Germany). We designed PCR primers 5′-GACAGCACCAGCTAAGT-3′ (sense) and 5′-AATGCAGAGGAGCGTTC-3′(antisense) and hybridization probes 5′-CCTAGTGCAAGATTCTTCTTCAGTACC-fluorescein (sensor) and 5′-LC Red 640-TGCCCACATTCCTGGTTGCTGG-phosphate (anchor). PCR was performed with 0.05 μmol/L sense primer and 0.5 μmol/L antisense primer in a reaction mixture containing 0.2 μmol/L anchor probe, 0.2 μmol/L sensor probe, 10 ng of dried-down DNA, 4.0 mmol/L $MgCl_2$, 0.5 μL 10 × PCR buffer, 1 mmol/L 4 deoxy ribonucleotide triphosphates (dNTPs), and 0.5 U Faststart DNA Polymerase (Roche Diagnostics, Mannheim, Germany) in a total volume of 5 μL. The cycling program consisted of a 10-minute initial denaturation at 94°C and 40 cycles of denaturation at 94°C for 15 seconds, annealing at 55°C for 15 seconds, and extension at 72°C for 15 seconds followed by a final extension step at 72°C for 2 minutes. After

Table 2
Clinical and lifestyle data of subjects in each genotype group

	IL6R genotype group			*P*
	TT (n = 101)	GT (n = 144)	GG (n = 40)	
Age (y)	47.0 ± 11.7	46.1 ± 11.3	43.9 ± 12.0	.351
BMI (kg/m^2)	23.5 ± 3.1	23.3 ± 3.2	22.8 ± 3.8	.513
WC (cm)	84.3 ± 8.3	83.8 ± 9.6	83.5 ± 10.6	.862
BMI ≥25 kg/m^2 (%)	30.7	29.2	27.5	.926
WC ≥85 cm (%)	49.5	47.6	50.0	.938
Serum triglyceride (mg/dL)	134.7 ± 84.9	126.8 ± 81.7	124.3 ± 57.9	.696
Serum HDL cholesterol (mg/dL)	56.5 ± 13.8	54.8 ± 14.8	54.3 ± 11.1	.577
Fasting plasma glucose (mg/dL)	95.9 ± 22.2	100.6 ± 32.6	95.7 ± 22.9	.372
Systolic blood pressure (mm Hg)	134.7 ± 18.7	135.1 ± 17.7	129.8 ± 17.2	.268
Diastolic blood pressure (mm Hg)	82.2 ± 12.1	82.1 ± 12.8	78.6 ± 13.4	.272
Energy intake (kJ/d)	7634.5 ± 2027.3	7934.1 ± 2085.3	7481.8 ± 1610.4	.332
Current smoking (%)	64.0	60.4	47.5	.194
Alcohol drinking (%)	75.0	72.9	72.5	.923

Data are presented as mean ± SD or as otherwise indicated. No significant difference was found among 3 genotype groups compared by analysis of variance or χ^2 test.

completion of the PCR, denaturation and annealing as a preamble to melting was done by heating the mixture at 94°C for 60 seconds and then holding at 40°C for 60 seconds. The plate was then heated from 40°C to 80°C at a gradient of 0.1°C per second. Melting curve data were collected and classified using the LightTyper genotyping software and determination of TT, GT, and GG genotypes was made.

2.3. Assessment of dietary energy intake levels

The semiquantitative FFQ, which was evaluated by comparing the FFQ with the 7-day dietary records of 66 subjects by Takahashi et al [30], was used to calculate energy intake levels. In this study, all participants were asked about the consumption of food items in 29 food groups during the previous 1 or 2 months. Briefly, the subjects were asked to describe the quantities and frequencies of food consumption during breakfast, lunch, and dinner. Three portion-size categories (small/medium/large) were used to evaluate the quantities of consumption of food items. "Small" is half the size of "medium" and "large" is 1.5 times the size of "medium." When the frequency of consumption of a food was less than once or twice a month, the subject was instructed to answer "never." The FFQ illustrated the food items of each food group in quantities equal to medium to evaluate the quantities of consumption correctly. When the frequency of consumption of a food was low, the subjects were asked to answer the quantity consumed at one time and the frequency of consumption per week. The subjects were also asked to describe the quantity of consumption at one time and the frequency of consumption per week of alcoholic and nonalcoholic beverages. When the quantity of a unit of food consumed was almost identical among subjects, the subjects were asked to state only the frequency of consumption per week as the number of consumed units. Daily nutrient intake was calculated by multiplying the frequency of consumption of each food by the nutrient content of the portion size and summing the products for all foods items. The energy intake level of each subject was determined in the same manner. FFQ is frequently used for epidemiologic studies to investigate the association between diet and chronic diseases. FFQ has been reported to underestimate the absolute level of consumption of nutrients and food groups compared with diet records. However, it has been reported to be reasonably valid in ranking subjects and classifying them according to the consumption of many nutrients and food groups [31].

2.4. Statistical analysis

The allele frequency was determined by direct counting. Deviation of the genotype distribution from Hardy-Weinberg equilibrium was confirmed by χ^2 test. Differences in

Table 3
Association of energy intake levels with WC or BMI according to the *IL6R* T/G polymorphism

	WC						BMI					
	TT + GT (n = 244)			GG (n = 40)			TT + GT (n = 245)			GG (n = 40)		
	β	SE	*P*	*β*	SE	*P*	*β*	SE	*P*	*β*	SE	*P*
Energy intake levels	1.36	0.68	.048*	−1.35	2.26	.555	0.43	0.25	.084	0.25	0.84	.767
Age	0.12	0.05	.016*	0.19	0.15	.205	0.02	0.02	.182	0.05	0.06	.363
Current smoking	−1.20	1.15	.299	−4.17	3.32	.216	−0.53	0.42	.208	−0.88	1.24	.484
Alcohol drinking	4.93	1.26	<.001**	−1.86	3.81	.629	0.72	0.46	.119	−1.31	1.42	.362

P value shows the significance for linear regression analysis. *β* indicates regression coefficient.

* $P < .05$.

** $P < .01$.

Table 4
Percentage of the obesity and OR of each *IL6R* genotype group

Energy intake levels	*IL6R* polymorphism		Obesity (WC ≥85 cm)		Obesity (BMI ≥25 kg/m^2)	
	Genotype	n	%	OR (95% CI)	%	OR (95% CI)
1st Tertile	TT + GT	81	43.2	1 (Referent)	27.2	1 (Referent)
	GG	14	64.3	2.41 (0.71-8.18)	35.7	1.33 (0.38-4.70)
2nd Tertile	TT + GT	80	43.8	1 (Referent)	25.0	1 (Referent)
	GG	15	53.3	0.95 (0.28-3.23)	20.0	0.58 (0.14-2.35)
3rd Tertile	TT + GT	84	57.8	1 (Referent)	36.9	1 (Referent)
	GG	11	27.3	0.38 (0.09-1.61)	27.3	0.72 (0.16-3.19)
P for interaction				.030*		.408

Data were obtained by the logistic regression model.
* $P < .05$.

the mean values of age, clinical characteristics, current smoking, alcohol drinking, and energy intake levels between the genotype groups were compared by analysis of variance or χ^2 test. Multiple linear regression analyses were performed to examine whether the relationship of energy intake levels with the obesity indices differed according to the *IL6R* genotype groups adjusted for age, current smoking, and alcohol drinking. Multiple logistic regression was used to analyze whether interactions between the *IL6R* genotypes and dietary energy intake levels were associated with obesity indices, defined as BMI of 25 kg/m^2 or greater or WC of 85 cm or larger. Odds ratios (ORs) and 95% confidence intervals (CIs) were also estimated by means of a logistic regression model. In the 2 regression models, the subjects were classified into tertiles according to energy intake based on their replies to the FFQ (1st = 1, 2nd = 2, and 3rd = 3) and energy intake levels were used as categorical factors. All analyses were carried out using a Statistical Package for Social Sciences (SPSS) for Windows version 11.0 (SPSS, Chicago, IL). A *P* value less than .05 was considered statistically significant.

3. Results

3.1. Distribution of IL6R gene polymorphism

The distributions of the *IL6R* genotype and allele frequencies are shown in Table 1. The overall frequencies of the TT, GT, and GG genotypes were 36.9%, 48.0%, and 15.2%, respectively. The allelic frequencies of T and G were 0.609 and 0.391, respectively. No significant difference was found in the frequency of this polymorphism between genders. All genotype frequencies were in Hardy-Weinberg equilibrium, and the G allele frequency data were similar to data from other reports in Asian populations [24,32] or the public database from the International HapMap Project (http://www.hapmap.org/cgi-perl/snp_details?name%=8192284).

3.2. Clinical characteristics and lifestyle factors according to IL6R genotype groups

Table 2 presents comparisons of basic characteristics of the subjects among the GG, TT, and GT genotype groups. There were no notable differences in age, obesity indices (BMI and WC), prevalence of obesity, clinical characteristics such as serum triglyceride, serum HDL cholesterol, and fasting plasma glucose levels, and systolic or diastolic blood pressure. In addition, there was no difference in lifestyle factors including energy intake, smoking, and alcohol drinking status.

3.3. Interaction between IL6R genotype and dietary energy intake level on WC

We next assessed the association between *IL6R* genotypes and obesity indices by multiple regression analysis, adjusted for age, current smoking, alcohol drinking, and energy intake levels. WC and BMI did not correlate with the genotype groups TT, GT, and GG ($P = .279$ and $P = .704$ for BMI and WC, respectively), TT and GT + GG ($P = .449$ and $P = .679$ for BMI and WC, respectively), or TT + GT and GG ($P = .298$ and $P = .870$ for BMI and WC, respectively).

By stratified analysis, in the TT + GT and GG group there was a significant positive relation between dietary energy intake levels and WC ($\beta = 1.36$, $P = .048$) in TT + GT subjects (Table 3), whereas no relationship was found in GG subjects ($P = .555$). The β coefficient of GG type was −1.35, representing an inverse relation, which did not reach statistical significance. There was no association with BMI in TT + GT ($P = .084$) and GG ($P = .767$). In addition, the results revealed the association of age and alcohol intake with WC in TT + GT subjects.

The interaction between *IL6R* genotype and energy intake levels as categorical factors in relation to obesity was also analyzed by logistic regression analysis, adjusted for age, current smoking, and alcohol drinking. With regard to the TT + GT and GG group, an interaction between *IL6R* genotype and energy intake with WC (P for interaction = .030; Table 4) was detected, but no such interaction was observed for BMI ($P = .408$). This interaction disappeared in the TT, GT, and GG or the TT and GT + GG groups ($P = .160$ and 0.711 for WC; $P = .679$ and 0.984 for BMI, respectively). We also estimated odds ratios of obesity for GG subjects compared with TT + GT subjects in each energy intake group. The OR (95% CI) for obesity defined as WC in each energy intake group was 2.41 (0.71-8.18), 0.95 (0.28-3.23), and 0.38 (0.09-1.61), respectively,

indicating that the OR was smaller when energy intake level was higher.

4. Discussion

Previous studies have shown that the *IL6R Asp358Ala* (T/G) polymorphism is likely to contribute to the genetic susceptibility of insulin resistance and T2DM. In Danish [26] and Utahan [25] whites, correlations between the T allele and T2DM have been reported. In Pima Indians, no association was found for T2DM, but an association was found for BMI [23]. In this study, we examined whether this polymorphism was linked to abdominal obesity in Japanese men. There was no obvious association between genotype alone and WC or BMI. Rather, an interaction between genotype and dietary energy intake levels correlated with WC. The TT + GT subjects had a significant relationship between energy intake and WC, whereas GG subjects did not. In other words, TT + GT genotype seemed to be more susceptible to obesity than GG genotype under excess energy intake. Thus, the beneficial effects of diet in the prevention of obesity might be more significant in carriers of the TT or GT genotype.

To examine the interaction between *IL6R* and energy intake levels, we analyzed our data by using 3 categories: "TT, GT, and GG," "TT + GT and GG," and "TT and GG + GT." Only under the TT + GT and GG category did we detect an interaction between *IL6R* genotype and energy intake that related to WC. This result is partially consistent with that of Hamid et al [26] in which a significant difference in genotype distribution between diabetic patients and controls was found by applying a recessive genetic model (TT + GT and GG), whereas the difference was weak in a codominant model (TT, GT, and GG) and disappeared in a dominant model (TT and GG + GT). This implies that the T allele may be the risk allele involved in the development of obesity as well as T2DM.

The interaction was shown for WC, but not for BMI. One of the reasons may be that WC is a more sensitive index for abdominal obesity than BMI. WC appears to reflect the amount of visceral adipose tissue better than BMI and may be more important in the development of the metabolic syndrome [33]. Indeed, recent criteria set for the metabolic syndrome by the Japanese Society of Internal Medicine suggest that WC but not BMI was applied as the criterion for abdominal obesity [34]. It is tempting to speculate that the association of *IL6R* polymorphism and WC, but not BMI, might be an indication that visceral adipose tissue secretes 2 to 3 times more IL-6 than subcutaneous adipose tissue [35].

Although the molecular physiology underlying the relation between the *IL6R* genotype and obesity or T2DM is not known, recent reports have suggested a possible function for this polymorphism. The *IL6R* genotype was shown to be associated with soluble IL-6R (sIL6R) levels in serum, such that the subjects with the GG genotype had higher sIL-6R levels than those with either the GT or TT genotype [32]. sIL6R is produced through alternative splicing of the *IL6R* transcript [36] or proteolytic cleavage of the membrane-bound IL6R, a process known as shedding [37]. IL-6 and sIL6R bind to each other, and this complex further binds to gp130. The IL-6/sIL6R complex appears to potentiate the IL-6 activity on cells expressing the transmembrane *IL6R* [38] or widen the array of potential IL-6 targets to cells devoid of the transmembrane *IL6R* [19]. The physiologic role of sIL6R includes protection of IL-6 against proteolytic degradation at sites of inflammation [39] and regulation of IL-6 function in the brain [40]. With regard to energy intake, sIL6R level correlates with BMI [41], and diet or exercise decreases plasma levels of IL-6 [42] and sIL6R [43]. Taken together, the GG genotype, which relates to higher sIL6R levels, may modulate IL-6 activity, leading to a protective effect against obesity. Further epidemiologic and molecular biological investigations are needed to define the action of this ligand-soluble receptor system in the development of obesity, insulin resistance, and T2DM.

In summary, we have shown that the relationship between dietary energy intake and abdominal obesity was different among subjects with different genotypes of the *IL6R* gene *Asp358Ala* (T/G) polymorphism in Japanese men. Accumulation of such information may suggest ways to optimize prevention of obesity according to the genetic information of individuals.

References

[1] Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 2002;10:97S-104S.
[2] Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab 2004;89:2583-9.
[3] Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol 2004;25:4-7.
[4] Yudkin JS. Adipose tissue, insulin action and vascular disease: inflammatory signals. Int J Obes Relat Metab Disord 2003;27:S25-8.
[5] Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. JPEN J Parenter Enteral Nutr 2004;28:410-5.
[6] Ostberg JE, Attar MJ, Mohamed-Ali V, Conway GS. Adipokine dysregulation in Turner syndrome: comparison of circulating interleukin-6 and leptin concentrations with measures of adiposity and C-reactive protein. J Clin Endocrinol Metab 2005;90:2948-53.
[7] Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res 2001;9:414-7.
[8] Steensberg A, Febbraio MA, Osada T, et al. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. J Physiol 2001;537:633-9.
[9] Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 1997;82:4196-200.
[10] Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. Int J Obes Relat Metab Disord 1998; 22:1145-58.

[11] Greenberg AS, Nordan RP, McIntosh J, Calvo JC, Scow RO, Jablons D. Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice in vivo and in 3T3-L1 adipocytes: a possible role for interleukin 6 in cancer cachexia. Cancer Res 1992;52:4113-6.
[12] Van Hall G, Steensberg A, Sacchetti M, et al. Interleukin-6 stimulates lipolysis and fat oxidation in humans. J Clin Endocrinol Metab 2003; 88:3005-10.
[13] Jansson JO, Wallenius K, Wernstedt I, Ohlsson C, Dickson SL, Wallenius V. On the site and mechanism of action of the anti-obesity effects of interleukin-6. Growth Horm IGF Res 2003;13:S28-32.
[14] Wallenius V, Wallenius K, Ahren B, et al. Interleukin-6–deficient mice develop mature-onset obesity. Nat Med 2002;8:75-9.
[15] Wallenius K, Wallenius V, Sunter D, Dickson SL, Jansson JO. Intracerebroventricular interleukin-6 treatment decreases body fat in rats. Biochem Biophys Res Commun 2002;293:560-5.
[16] Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. Life Sci 2000;67:291-300.
[17] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-34.
[18] Fernandez-Real JM, Vayreda M, Richart C, et al. Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. J Clin Endocrinol Metab 2001;86:1154-9.
[19] Jones SA, Horiuchi S, Topley N, Yamamoto N, Fuller GM. The soluble interleukin 6 receptor: mechanisms of production and implications in disease. FASEB J 2001;15:43-58.
[20] Hanson RL, Ehm MG, Pettitt DJ, et al. An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. Am J Hum Genet 1998;63:1130-8.
[21] Das SK, Hasstedt SJ, Zhang Z, Elbein SC. Linkage and association mapping of a chromosome 1q21-q24 type 2 diabetes susceptibility locus in northern European Caucasians. Diabetes 2004;53:492-9.
[22] Elbein SC, Zheng W, Wang X, Zhang Z, Hasstedt SJ. Novel T2DM locus on chromosome 4 and confirmation of chromosome 1q21 T2DM linkage in multiplex African American families. Diabetes 2004;53:A270.
[23] Wolford JK, Colligan PB, Gruber JD, Bogardus C. Variants in the interleukin 6 receptor gene are associated with obesity in Pima Indians. Mol Genet Metab 2003;80:338-43.
[24] Kim LH, Lee HS, Kim YJ, et al. Identification of novel SNPs in the interleukin 6 receptor gene(IL6R). Hum Mutat 2003;21:450-1.
[25] Wang H, Zhang ZX, Chu W, Hale T, Cooper JJ, Elbein SC. Molecular screening and association analyses of the interleukin 6 receptor gene variants with type 2 diabetes, diabetic nephropathy, and insulin sensitivity. J Clin Endocrinol Metab 2005;90:1123-9.
[26] Hamid YH, Urhammer SA, Jensen DP, et al. Variation in the interleukin-6 receptor gene associates with type 2 diabetes in Danish whites. Diabetes 2004;53:3342-5.
[27] Larsson B, Bengtsson C, Bjöorntorp P, Lapidus L, Sjöostrom L, Svärdsudd K. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Goteborg, Sweden. Am J Epidemiol 1992;135:266-73.
[28] The Examination Committee of Criteria for "Obesity Disease" in Japan, Japan Society for the Study of Obesity. New criteria for "obesity disease" in Japan. Circ J 2002;66:987-92.
[29] Bennett CD, Campbell MN, Cook CJ, et al. The LightTyper: high-throughput genotyping using fluorescent melting curve analysis. Biotechniques 2003; 34:1288-9, 12942-5.
[30] Takahashi K, Yoshimura Y, Kaimoto T, Kunii D, Komatsu T, Yamamoto S. Validation of a food frequency questionnaire based on food groups for estimating individual nutrient intake. Jpn J Nutr 2001;59:221-32 [in Japanese].
[31] Tsubono Y, Kobayashi M, Sasaki S, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. J Epidemiol 2003;13:S125-33.
[32] Galicia JC, Tai H, Komatsu Y, Shimada Y, Akazawa K, Yoshie H. Polymorphisms in the IL-6 receptor (IL-6R) gene: strong evidence that serum levels of soluble IL-6R are genetically influenced. Genes Immun 2004;5:513-6.
[33] Buchholz AC, Bugaresti JM. A review of body mass index and waist circumference as markers of obesity and coronary heart disease risk in persons with chronic spinal cord injury. Spinal Cord 2005;43:513-8.
[34] Oda E, Watanabe K. Japanese criteria of metabolic syndrome. Circ J 2006;70:364.
[35] Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83:847-50.
[36] Horiuchi S, Koyanagi Y, Zhou Y, et al. Soluble interleukin-6 receptors released from T cell or granulocyte/macrophage cell lines and human peripheral blood mononuclear cells are generated through an alternative splicing mechanism. Eur J Immunol 1994;24:1945-8.
[37] Müllberg J, Oberthür W, Lottspeich F, et al. The soluble human IL-6 receptor. Mutational characterization of the proteolytic cleavage site. J Immunol 1994;152:4958-68.
[38] Peters M, Jacobs S, Ehlers M, et al. The function of the soluble interleukin 6 (IL-6) receptor in vivo: sensitization of human soluble IL-6 receptor transgenic mice towards IL-6 and prolongation of the plasma half-life of IL-6. J Exp Med 1996;183:1399-406.
[39] Bank U, Kupper B, Ansorge S. Inactivation of interleukin-6 by neutrophil proteases at sites of inflammation. Protective effects of soluble IL-6 receptor chains. Adv Exp Med Biol 2000;477:431-7.
[40] Schöbitz B, Pezeshki G, Pohl T, et al. Soluble interleukin-6 (IL-6) receptor augments central effects of IL-6 in vivo. FASEB J 1995;9: 659-64.
[41] Pecoits-Filho R, Barany P, Lindholm B, Heimburger O, Stenvinkel P. Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. Nephrol Dial Transplant 2002;17:1684-8.
[42] You TJ, Berman DM, Ryan AS, Nicklas BJ. Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. J Clin Endocrinol Metab 2004;89: 1739-46.
[43] Nelson TL, Hickey MS. Acute changes in dietary omega-3 fatty acid intake lowers soluble interleukin-6 receptor in healthy adult normal weight and overweight males. Cytokine 2004;26:195-201.