Obesity and Appetite-Related Hormones

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Objective: *Alterations of hormones involved in food intake can lead to obesity and related-diseases. The aim of the present study was to measure plasma levels of appetite-related hormones: insulin, leptin, adiponectin, acylated ghrelin, and cortisol in connection with eating behaviors among obese and non-obese women.*
Material and Method: *The present study was performed in 53 non-obese and 33 obese Thai women (BMI < 23 and ≥ 25 kg/m^2 respectively), aged 25 to 45 years. Saliva and fasting blood samples were collected for hormone measurements. Subjects' eating behavior was evaluated using Thai version of the Three-factor eating questionnaire (TFEQ) and their stress status was assessed by the Thai stress test (TST).*
Results: *In comparison to non-obese individuals, obese women showed higher disinhibition eating, plasma glucose, insulin, HOMA insulin resistance index, leptin, and triglyceride levels but lesser plasma adiponectin and HDLC. Lower adiponectin was directly associated with higher disinhibition eating. Plasma leptin related positively to fat mass and insulin resistance but negatively to acylated ghrelin level. The trend towards increased acylated ghrelin after adjusted for age, obesity and eating behaviors was shown in stress women.*
Conclusion: *Increased insulin resistance, high leptin, and reduced adiponectin accompanied with disinhibition eating have been detected in obese women.*

Keywords: *Insulin, Leptin, Adiponectin, Cortisol, ACR, Acylated ghrelin, Eating behavior, Obese*

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Evidences indicate that alteration of hormones involved in appetite and energy homeostasis are associated with disturbances of eating behavior and obesity[1]. Moreover, Thai women as well as other nationalities had higher risk of becoming obese than men[2]. Resistance to insulin and leptin actions in reducing food intake frequently develops in obesity[3,4]. Total adiponectin, another adipocyte-secreting hormone, has been shown to be low and have an inverse relation with insulin and leptin levels in the obese condition[5,6]. Furthermore, a negative relationship between plasma adiponectin and disinhibition eating behavior has been demonstrated[7]. In addition, ghrelin, the only known stomach peptide that stimulates food intake in humans, has been shown to be elevated in obese individuals[8]. Acylated form of ghrelin basal levels is reported to be influenced positively by cortisol, leptin, and insulin in healthy women[9]. In addition, increased cortisol secretion is strongly correlated with insulin and leptin resistance[10]. Three dimensions of eating behaviors: dietary restraint, disinhibition eating and susceptibility to hunger are associated with obesity as well[11].

Although, metabolic disorders caused by alterations of these hormones is widely accepted, the roles of insulin, leptin, adiponectin, acylated ghrelin and cortisol regarding to food intake are still inconclusive and have never been examined in Thais. Therefore, the authors aimed to investigate the association between these appetite-related hormones, eating behaviors and obesity in Thai women.

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Material and Method

Subjects

Eighty-six healthy working women aged 25 to 45 years were recruited by intra-campus advertising. The exclusion criteria were hypertension (BP > 130/85 mmHg), having historical and biochemical criteria of diseases, as well as being a current smoker, current alcohol drinker, taking oral contraceptive or

any medication known to affect body weight and cortisol secretion. All subjects were separated into two groups, 53 non-obese women (BMI < 23 kg/m^2), and 33 obese women (BMI ≥ 25 kg/m^2), according to the appropriate BMI for Thai population[12].

Study protocol

Recruited women read participant information sheet and gave their consent. All were approved by the Human Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Then, they provided information about the health status and menstrual history, their general lifestyle including eating and food habits. Next, the routine physical examination was carried out.

On a working day in early to mid-follicular phase of individual menstrual cycle after 10 h overnight fast, subjects visited the laboratory. Approximately 15 to 30 min after arrival, fasting venous blood was drawn and dispensed into evacuated tubes contained the proper anticoagulant. Plasma was separated after centrifugation and kept frozen at -70°C until analyses of insulin, leptin, adiponectin, and cortisol. Acidified plasma by adding 50 µL of 1N hydrochloric acid and 10 µL of serine proteases inhibitor (phenylmethylsulfonyl fluoride at concentration of 10 mg/mL of methanol per 1 mL of plasma) was stored at -70ºC for acylated ghrelin assay. Awakening cortisol response (ACR) is a rise of free cortisol in saliva after wakening and resembles blood cortisol as an index of the adrenocortical activity. [13] Two saliva samples were collected at 0 and 30 min after awaking on the first and the second visits two-three days apart. Upon arrival at the laboratory room, saliva was centrifuged and the supernatant was kept at -70°C for measurement of cortisol. Smoking, caffeine and other factors known to affect salivary cortisol were eliminated from subjects during the study.

Anthropometric measurements were done using the Tetra-polar Body Composition Analyzer based on a bioelectrical impedance analysis system. (TANITA, TBF-410GS, Tanita Corporation, Japan). Body weight, height, waist, and hip circumferences were measured. Waist-to-hip ratio was calculated. Later, subjects were asked to complete 24 items of the Thai Stress Test and 51 items of the Thai version of Three-factor eating questionnaire.

Hormone assays

The commercial radioimmunoassay kits (Linco research, USA) were used to measure plasma insulin, leptin, adiponectin, and acylated ghrelin. Cortisol in plasma and in saliva was assessed by solid-phase radioimmunoassay method (CIS Bio International, France). Intra- and inter-assay variability of plasma hormone within our laboratory were less than 10%, while inter-assay variability of cortisol measured in saliva was less than 20%. ACR was calculated by subtracting the cortisol value at 30 min by value immediately after wakening. A homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin concentrations[14].

Three-factor eating questionnaire

The Three-Factor Eating Questionnaire (TFEQ), originally developed by Stunkard and Messick[15], consists of 36 true/false-answer items and 15 possible-question items. It was used to measure three categories of eating behavior, including restraint, disinhibition, and susceptibility to hunger. The original TFEQ version was translated back and forth between English-Thai with the permission of the publisher (Harcourt Assessment Inc.) to reduce potential semantic problems. The Thai version of TFEQ used to evaluate subjects' eating behaviors in the present study showed good internal consistency and test-retest reliability[16].

Psychological stress test

Self-reported data revealed 98% of subjects having work stress, 90% having general life (non-work) stress, and none having neither work stress nor daily life stress. Daily life stress of the subjects was measured using the stress inventory called Thai Stress Test[17]. The questionnaire is composed of 24 items that divided into equal items of positive and negative effects. Subjects chose their feel frequency (*i.e.* often, sometimes, or never) for each item. Individual's stress level was calculated from the affect balance score. Obtained levels of stress were subsequently divided into four categories (1 = excellent mental health, 2 = normal mental health, 3 = mild stress, and 4 = stressful).

Statistical analysis

SPSS version 13.0 was used for statistical analysis. Unpaired t-test or Mann-Whitney U test was used for two-group comparison. ANOVA followed by Bonferroni/Dunn test or Kruskal Wallis test was used for comparing more than two groups. The relationship between two continuous variables was tested by both simple and multiple linear regression analyses. A logistic regression analysis was used to determine the association among low-high tertiles of each

eating behavior, obesity-related parameters, hormones, and biochemical levels. Data are presented as mean ± standard error of mean (SEM) and significance was set at p-value less than 0.05.

Results

The general characteristics of studied subjects are shown in Table 1. Subjects were separated into non-obese and obese groups, then divided into non-stress (stress score < 3, n = 42) and stress (stress score ≥ 3, n = 44) subgroups. Not only parameters indicating obesity, but also the cardiovascular risk factors such as age, systolic and diastolic blood pressure were higher in obese than non-obese women. However, mean stress score in non-obese women (2.47 ± 0.07) did not differ from obese women (2.52 ± 0.10). Other studied characteristics were not different between stressed and non-stressed women as well.

Appetite-affecting hormones, eating behaviors and obesity

Values of studied hormones, blood chemistry and eating behavior scores in non-obese and obese women were compared and tabulated in Table 2. Obese women had significantly higher plasma insulin, glucose, HOMA-IR, leptin, triglycerides, and disinhibition eating behavior; but had lower plasma adiponectin and HDLC than non-obese women. Acylated ghrelin, plasma cortisol, and salivary ACR were not different between obese and non-obese women. Odds ratio with 95% CI of increased plasma acylated ghrelin in stressed women was more than non-stressed women, even after controlling for age, obesity and eating behaviors (Table 3). However, other measured hormones, ACR, blood chemistries, and eating behaviors did not differ between stress and non-stress women in the present study.

Table 4 shows the statistically significant associations by univariate and multivariate analyses. Plasma leptin was associated positively with insulin resistance index but negatively with acylated ghrelin level. Salivary ACR was correlated inversely with plasma adiponectin but directly with plasma cortisol. Disinhibition eating was related positively to hunger but negatively to plasma adiponectin. Simple linear relationship between fat mass and leptin was observed as well ($r = 0.63$, $p < 0.0001$).

There was an increased risk of becoming obese, having higher fasting blood glucose, insulin, HOMA-IR, and leptin, but having lesser HDLC and adiponectin in women with high disinhibition eating in comparison to women with low disinhibition (Table 5).

Discussion

The current findings confirm that enhanced insulin resistance, hyperleptinemia, hypoadiponectinemia and high disinhibition eating, are involved in obesity in women. A direct relationship between fasting leptin levels and insulin resistance was obtained in the present study. The corresponding result that fasting plasma leptin level correlated positively with BMI but negatively with insulin sensitivity was reported previously[18]. Reduced insulin sensitivity in different

Table 1. Characteristics of studied women[1]

	Non-obese (BMI < 23 kg/m^2)			Obese (BMI ≥ 25 kg/m^2)		
	Non-stress (n = 31)	Stress (n = 22)	Total[2] (n = 53)	Non-stress (n = 11)	Stress (n = 22)	Total[2] (n = 33)
Age (y)	29.68 ± 0.90	30.68 ± 1.48	30.09 ± 0.80[2]	33.00 ± 2.12	33.95 ± 1.29	33.64 ± 1.10[2]
BMI (kg/m^2)	20.40 ± 0.39	21.10 ± 0.45	20.69 ± 0.30[2]	30.00 ± 1.15	29.14 ± 0.76	29.42 ± 0.63[2]
Waist (cm)	64.31 ± 0.96	65.73 ± 1.18	64.90 ± 0.74[2]	83.68 ± 1.99	82.04 ± 8.91	82.59 ± 1.42[2]
WHR	0.73 ± 0.008	0.73 ± 0.010	0.73 ± 0.006[2]	0.79 ± 0.011	0.80 ± 0.009	0.80 ± 0.007[2]
Body fat (%)	25.40 ± 0.83	27.24 ± 1.04	26.16 ± 0.66[2]	39.00 ± 1.80	39.76 ± 1.23	39.51 ± 1.00[2]
Fat mass (kg)	12.94 ± 0.67	14.61 ± 0.81	13.63 ± 0.53[2]	29.96 ± 2.39	28.53 ± 1.75	29.01 ± 1.40[2]
Fat free mass (kg)	37.15 ± 0.50	38.28 ± 0.58	37.62 ± 0.39[2]	45.81 ± 1.74	42.03 ± 0.73	43.29 ± 0.81[2]
Systolic BP (mmHg)	106.95 ± 1.86	104.57 ± 1.29	105.96 ± 1.21[2]	115.82 ± 2.74	112.91 ± 1.92	113.88 ± 1.57[2]
Diastolic BP (mmHg)	71.55 ± 1.26	67.73 ± 1.12	69.96 ± 0.90[2]	77.59 ± 1.74	75.32 ± 1.21	76.08 ± 1.00[2]

[1] All values are mean ± SEM

[2] Significant differences between non-obese and obese groups

Table 2. Values of studied hormones, blood chemistry and eating behaviors in obese and non-obese women[1]

	Non-obese (n = 53)	Obese (n = 33)	p-value
Hormones			
Insulin (pmol/L)	65.35 ± 3.80	104.78 ± 10.34	0.0001
HOMA-IR	2.04 ± 0.13	3.51 ± 0.36	<0.0001
Leptin (pmol/L)	407.97 ± 27.71	1,016.80 ± 56.37	<0.0001
Adiponectin (µg/mL)	10.28 ± 0.73	5.53 ± 0.48	<0.0001
Acylated ghrelin (pmol/L)	264.24 ± 14.10	223.37 ± 15.40	0.062
Plasma cortisol (nmol/L)	246.39 ± 14.94	223.24 ± 18.81	0.338
Salivary ACR (nmol/L)	5.10 ± 0.87	5.11 ± 1.12	0.923
Blood chemistry			
Glucose (mmol/L)	4.82 ± 0.06	5.20 ± 0.07	<0.0001
Triglycerides (mmol/L)	1.93 ± 0.11	2.31 ± 0.14	0.011
Total cholesterol (mmol/L)	4.63 ± 0.09	4.62 ± 0.10	0.938
LDLC (mmol/L)	2.82 ± 0.08	2.99 ± 0.08	0.175
HDLC (mmol/L)	1.62 ± 0.05	1.37 ± 0.04	0.001
Eating behaviors			
TFEQ-restraint	8.59 ± 0.59	9.73 ± 0.65	0.699
TFEQ-disinhibition	6.79 ± 0.42	8.51 ± 0.53	0.001
TFEQ-hunger	5.64 ± 0.35	6.76 ± 0.47	0.087

[1] All values are mean ± SEM

Table 3. Odds of increased acylated ghrelin in stress women in comparison to non-stress women

	OR[1] (95% CI)	p-value
Non-adjusted	4.22 (1.41-12.66)	0.010
Adjusted for age	4.39 (1.43-13.39)	0.009
Adjusted for obese	6.37 (1.78-22.82)	0.004
Adjusted for obese, restraint, disinhibition and hunger	7.55 (1.98-28.83)	0.003
Adjusted for age, obese, restraint, disinhibition and hunger	7.57 (1.98-28.91)	0.003

[1] OR was calculated by logistic regression and its value in non-stress women was equal to 1

Table 4. Relationship among hormones and eating behaviors determined by univariate and multivariate analyses[1]

		Univariate analysis		Multivariate analysis	
		R[2]	p-value	R[3]	p-value
Leptin	vs. HOMA-IR	0.523	<0.0001	0.355	0.002
	vs. acylated ghrelin	-0.330	0.002	-0.316	0.005
ACR	vs. adiponectin	-0.231	0.032	-0.301	0.008
	vs. plasma cortisol	0.260	0.016	0.259	0.024
Disinhibition	vs. hunger	0.589	<0.0001	0.563	<0.0001
	vs. adiponectin	-0.412	<0.0001	-0.263	0.022

[1] Only the data of significant association by multivariate analysis are shown
[2] Pearson correlation coefficient
[3] Coefficient of partial correlation adjusted for age, BMI, waist circumference, fat mass, total cholesterol, triglycerides, HDLC, LDLC, and stress score

Table 5. Odds ratios (OR) calculated by logistic regression among low and high tertiles of obesity-related parameters, hormones and blood chemistry of women grouped by low and high disinhition habit[1]

	Number		OR	95% CI	p-value
	High disinhibition (score > 10)	Low disinhibition (score < 5)			
BMI (kg/m^2)					
< 23	13	21	1		0.007
> 29	15	4	6.06	1.65-22.27	
Waist (cm)					
< 65	6	12	1		0.032
> 76	12	5	4.80	1.15-20.09	
WHR					
< 0.72	7	11	1		0.037
> 0.79	14	5	4.40	1.09-17.72	
Fat mass (kg)					
< 13.9	5	13	1		0.004
> 21.3	14	4	9.10	1.99-41.45	
Glucose (mmol/L)					
< 4.72	7	14	1		0.019
> 5.16	13	5	5.20	1.32-20.54	
Insulin (pmol/L)					
< 59.18	6	14	1		0.005
> 85.60	14	4	8.17	1.85-33.22	
HOMA-IR					
< 1.76	5	14	1		0.005
> 2.86	14	5	7.84	1.85-33.22	
Leptin (pmol/L)					
< 368	10	20	1		0.002
> 773	18	5	7.20	2.07-25.08	
Adiponectin (µg/ml)					
< 5.77	4	4	1		0.004
> 9.30	11	15	0.10	0.02-0.47	
Acylated ghrelin (pmol/L)					
< 56.94	8	8	1		0.666
> 83.82	12	9	1.33	0.36-4.92	
Plasma cortisol (nmol/L)					
< 176.53	10	6	1		0.373
> 266.75	9	10	0.54	0.14-2.09	
Salivary ACR (nmol/L)					
< 1.97	11	8	1		1.000
> 7.54	11	8	1	0.28-3.62	
Triglycerides (mmol/L)					
< 0.68	5	12	1		0.125
> 1.04	8	6	3.20	0.72-14.14	
Total cholesterol (mmol/L)					
< 4.30	8	6	1		0.797
> 4.79	10	9	0.83	0.21-3.34	
LDLC (mmol/L)					
< 2.69	7	11	1		0.241
> 3.08	10	7	2.24	0.58-8.69	
HDLC (mmol/L)					
< 1.35	5	13	1		0.007
> 1.67	11	3	0.11	0.02-0.54	

[1] OR of woman with low disinhibition = 1

organs such as liver and adipose tissue can explain an impaired triglyceride clearance in insulin resistance patients[19]. In addition, triglycerides inhibit the transport of leptin across blood brain barrier. Therefore, may provide a mechanism for leptin resistance[20]. Increased plasma triglycerides and leptin were detected in obese women in the present study as well.

Adiponectin has been suggested to accelerate HDLC synthesis in the liver[21]. A recent meta-analysis showed that low serum adiponectin was associated with increased incidence of the first cardiovascular disease[22]. In addition, high HOMA-IR, TG/HDLC ratio and circulating leptin increased the risk of developing cardiovascular disease[23,24]. Therefore, data from Thai women supports an augmented risk of cardiovascular disease among obese women as a result of reduced adiponectin and HDLC as well as increased circulating triglycerides and insulin resistance.

A negative correlation of fasting plasma leptin with acylated ghrelin was also observed in the present study. Intracerebroventricular injection of ghrelin reversed leptin-induced inhibition of food intake in animals[25], and clinical evidences support the reverse relationship between ghrelin and leptin releases in humans[26]. Accordingly, leptin may act in opposition to acylated ghrelin in the regulation of energy balance. Though direct relationship between plasma cortisol and salivary ACR was shown in the presented subjects, the discrepancy of stress score and indices of adrenocortical activity between obese and non-obese women was not detected. Adaptation within HPA axis during repeated episodes of stress may explain the authors' observations. However, a negative correlation between adiponectin and free cortisol index was shown in our and another studies[27]. This observation is consistent with the inhibition effect of glucocorticoids in physiological dose or supra-physiological dose on adiponectin expression *in vivo* and *in vitro* using rats[28].

It has been recommended that the physiological role of ghrelin is to increase the incentive motivation for natural rewards such as food[29] and increased ghrelin levels were suggested to protect against stress-induced anxiety and depression in humans and in animals[30]. In the present study, a higher chance of having elevated plasma acylated ghrelin in women with daily life stress than in those without stress regardless of age, obesity or eating behaviors was detected. Further investigation to better understand the exact roles of acylated ghrelin in stress and obesity is required.

High disinhibition eating behavior was reported to be a major determinant of weight gain and higher risk of obesity in both cross-sectional and longitudinal studies[31,32]. In the present study, women with high disinhibition had higher obesity indices, fasting blood glucose, insulin, insulin resistance and leptin but had a lesser amount of HDLC and adiponectin levels when compared to those with low disinhibition. In addition, an inverse relationship between disinhibition and adiponectin together with a direct association between disinhibition and hunger were shown in our subjects as in another previous study[7]. Thus, disinhibition eating put women more at risk of obesity.

In conclusion, the abnormal eating behavior, especially disinhibition, and the changes in appetite-affecting hormones, insulin, leptin, adiponectin with other biochemical indices was demonstrated in obese Thai women. Hence, obese women would have higher possibility to develop cardiovascular disease in comparison to non-obese women.

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Potential conflicts of interest

None.

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ความอ้วนและฮอร์โมนที่เกี่ยวข้องกับความอยากอาหาร

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วัตถุประสงค์: *การเปลี่ยนแปลงของฮอร์โมนที่มีผลต่อการรับประทานอาหารนำไปสู่ความอ้วนและโรคที่เกี่ยวข้อง การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อตรวจวัดระดับฮอร์โมนที่เกี่ยวข้องกับความอยากอาหาร: อินซูลิน เลปติน อะดิโพเนกติน เอซิลกรีลิน และคอร์ติซอล ร่วมกับพฤติกรรมการบริโภคในหญิงอ้วนและไม่อ้วน*

วัสดุและวิธีการ: *ศึกษาในหญิงไทยไม่อ้วน 53 ราย และอ้วน 33 ราย (ดัชนีมวลกาย < 23 และ ≥ 25 กก./ม.^{2}ตามลำดับ) อายุ 25-45 ปี อาสาสมัครเก็บตัวอย่างน้ำลายหลังตื่นนอน และได้รับการเจาะเลือดตอนเช้าขณะอดอาหารเพื่อวัดระดับฮอร์โมน หลังจากนั้นจึงตอบแบบสอบถามเพื่อประเมินพฤติกรรมการบริโภคและแบบทดสอบความเครียดสำหรับคนไทย*

ผลการศึกษา: *หญิงอ้วนมีพฤติกรรมการบริโภคอย่างขาดความยับยั้งมากกว่า มีระดับกลูโคส อินซูลิน ดัชนีความดื้ออินซูลิน เลปติน และไตรกลีเซอไรด์ในเลือดสูงกว่า แต่มีระดับอะดิโพเนกติน และไลโปโปรตีนคอเลสเตอรอลชนิดความหนาแน่นสูงน้อยกว่า เมื่อเทียบกับหญิงไม่อ้วน ระดับอะดิโพเนกตินลดลงตามกันกับการเพิ่มขึ้นของการบริโภคแบบขาดความยับยั้ง ระดับเลปตินสัมพันธ์ตามกันกับมวลไขมันและภาวะดื้ออินซูลิน แต่สัมพันธ์ตรงข้ามกับระดับเอซิลกรีลิน ระดับเอซิลกรีลินหลังปรับด้วยอายุ ความอ้วน และพฤติกรรมการบริโภค ในหญิงกลุ่มเครียดมีแนวโน้มที่จะเพิ่มขึ้นเมื่อเทียบกับหญิงกลุ่มไม่เครียด*

สรุป: *พบภาวะดื้ออินซูลิน เลปตินสูง อะดิโพเนกตินต่ำ และพฤติกรรมการบริโภคอย่างขาดความยับยั้งในหญิงอ้วน*