Cardiometabolic Risk in Thai Adults with Type 2 Diabetes Mellitus: Obese versus Non-Obese

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Background: *Adiposity is an inflammatory condition contributing to the morbidity and mortality of several disorders, including type 2 diabetes mellitus (T2DM) and cardiovascular disease.*
Objective: *To compare cardiometabolic risk factors between obese and non-obese Thai patients with T2DM.*
Material and Method: *The cross-sectional study was done in 20 obese (BMI ≥25 kg/m^2) and 20 non-obese (BMI ≤23 kg/m^2) T2DM. Researchers measured fasting plasma glucose and lipids, serum levels of insulin, leptin, adiponectin, and soluble tumor necrosis factor-alpha receptors type 1 and 2 (sTNF-R1 and sTNF-R2). Insulin sensitivity check index (QUICIKI) and insulin resistance index (HOMA-IR) were calculated.*
Results: *Thai obese adults with T2DM had greater amounts of sTNF-R2 and HOMA-IR, higher ratios of leptin/adiponectin, and more incidences of hypertension and hypertriglyceridemia in comparison to non-obese counterparts. Additionally, HOMA-IR values in non-obese T2DM were greater than those reported among non-diabetic Thai adults. A reverse association between inflammatory markers (both sTNF-Rs) and HDLC was detected. Leptin/adiponectin ratios correlated directly with HOMA-IR, serum insulin, plasma triglycerides and BMI, whereas HOMA-IR did not relate to any studied plasma lipid.*
Conclusion: *The present study demonstrated an increased cardiometabolic risk in obese T2DM adults than non-obese T2DM adults among the Thai population. The leptin/adiponectin ratio may be more relevant to predict the risk of cardiovascular events in T2DM patients than HOMA-IR.*

Keywords: *Obesity, Type 2 diabetes mellitus (T2DM), Insulin resistance, Leptin/adiponectin ratio, sTNF-R*

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The prevalence of type 2 diabetes mellitus (T2DM) in Thailand is rising like other countries in the world[1,2]. Among T2DM patients, 90% have excess body weight[3]. Obesity-induced dysregulation of adipokine could contribute to metabolic disturbances, such as, insulin resistance (IR) and T2DM[4]. Adipokine profiles in obesity could increase the risk of cardiovascular disease[5]. Tumor necrosis factor-alpha (TNF-α), an adipokine and marker of inflammation, is a suggested link between obesity, IR, and type 2 diabetes[6]. TNF-α acts via two different surface receptors, TNF-R1 and TNF-R2. Circulating level of these truncated receptors accurately reflect the TNF-α activity[7]. Besides TNF-α, abnormal secretion of other adipocyte-derived hormones such as leptin and adiponectin were found to induce IR[8].

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Cardiometabolic risk factors include obesity, especially central obesity, hyperglycemia, hypertension, abnormal lipid metabolism and IR[9]. Thus, cardiovascular complications are common in obesity-associated diabetes mellitus[10]. In Thailand, over 70% of T2DM patients were reportedly overweight or obese in the 2009 national survey and approximately 50% of mortality among these patients was due to cardiovascular disease[11]. Consequently, the present study aims to compare the cardiometabolic risk status between obese and non-obese Thai T2DM patients. We measured TNF-R1 and TNF-R2, IR and adipokines related to IR (leptin, adiponectin), as well as blood lipids and blood pressure. Findings obtained may point toward more suitable management of patients' health status.

Material and Method

Subjects

After obtaining patients' informed consent, we performed a cross-sectional study of 20 non-obese

(BMI ≤23 kg/m^2) and 20 obese (BMI ≥25 kg/m^2) adults, according to WHO's redefined criteria for obesity in Asian populations[12]. All studied patients were within five years of their diagnosis of type 2 diabetes mellitus. Subjects were 26 to 70 years of age and had normal blood tests for liver and kidney functions on their most recent follow-up visit. They had stable levels of HbA_{1C} (5.2 -8.0%) and body weight for at least three months. Drugs were excluded except sulfonylurea and metformin. The research proposal was approved by the Human Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Data collection and measurements

Visceral fat level was obtained using a bioelectrical impedance analysis (Tanita BC 532). Fasting plasma glucose and lipids were promptly assessed by automated enzymatic calorimetric method at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, the central laboratory certified by ISO 15189, on the day that venous blood sample was taken. Aliquots of serum were stored frozen at -20°C for analytical determinations. Serum levels of insulin, leptin, and adiponectin were measured using a ^{125}I-labeled radioimmunoassay technique (Linco research, USA) while sTNF-R1 and sTNF-R2 levels were assessed by the sandwich enzyme immunoassay procedure (R&D System, USA). All procedures were performed according to the manufacturers' instructions. The intra- and inter-assay variations in our laboratory (Endocrine Unit, Faculty of Medicine Siriraj Hospital, Mahidol University) were within the acceptable limits (less than 5%). Insulin sensitivity was estimated using the quantitative insulin sensitivity check index (QUICIKI = 1/log fasting insulin value + log fasting glucose value). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting serum insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5.

Statistical analysis

All statistical analyses were carried out using SPSS version 18.0. The unpaired student t-test was used for comparing variables in obese and non-obese patients. Relationships between two variables were tested by partial correlation analyses. Binary logistic regression analysis was performed to determine an association between obesity and the measured parameters. A p-value of <0.05 was considered statistically significant.

Results

Characteristics and biochemical data of non-obese and obese T2DM patients were compared as shown in Table 1. The obese group exhibited elevated systolic and diastolic blood pressures, hypertriglyceridemia, hyperinsulinemia, more IR/less insulin sensitivity, a higher leptin/adiponectin ratio, higher circulating levels of leptin, and greater amounts of sTNF-R2 than the non-obese group. No significant differences in fasting plasma glucose, HbA_{1C}, and other measured lipids were found between the two patient groups. T2DM patients who were obese had significantly higher cardiometabolic risk from increased serum insulin, leptin, leptin/adiponectin ratio, and HOMA-IR as well as plasma triglycerides in comparison to the non-obese patients (see Table 2). Serum levels of sTNF-R1 and sTNF-R2 were related to each other, while both were negatively related to HDLC levels (Table 3). No significant relationship was found between HOMA-IR and blood pressure, lipid profiles, or sTNF-R. On the other hand, leptin/adiponectin ratios showed a statistically significant direct association with body mass index (BMI), triglyceride, insulin, and HOMA-IR levels.

Discussion

The present study had detected greater amounts of cardiometabolic risk factors, such as, larger waist circumference, more visceral fat, hypertriglyceridemia, hypertension, and higher insulin resistance in obese T2DM patients compared to non-obese T2DM patients. Additionally, obese diabetic patients had higher blood levels of sTNF-R2 than their non-obese counterparts. The results obtained from this small sample of Thai T2DM patients were consistent with the findings from large-scale population based studies[10]. Bringing together these data may imply abdominal adiposity had the capacity to intensify inflammatory response and to impair insulin signaling in diabetes mellitus. Notably, Thai non-obese diabetic patients with a mean HOMA-IR of 7.9 in the present study still had raised level of IR when compared to Thai non-diabetic individuals (IR 1.21-2.16 in males and 1.07-1.63 in females)[13]. Our result was inconsistent with the previous study in which the insulin resistance was not detected by insulin clamp technique in Thai lean T2DM[14]. However, our result was compatible with reports of defects in the insulin

Table 1. Characteristics of non-obese and obese patients with type 2 diabetes mellitus

	Non-obese T2DM (n = 20)	Obese T2DM (n = 20)	*p*-value*
Age (years)	51.06±12.25	52.61±10.33	0.659
Male:female	7:13	10:10	
Years of diabetes diagnosis	3.76±3.99	3.80±3.28	0.942
Body weight (kg)	53.86±5.53	78.03±10.84	<0.0001
BMI (kg/m^2)	21.76±1.09	28.56±3.08	<0.0001
Waist circumference (cm)	78.77±6.37	96.14±9.37	<0.0001
Waist-to-hip ratio	0.87±0.06	0.93±0.07	0.002
Total body fat (%)	27.79±9.98	32.56±9.07	0.109
Visceral fat level	6.55±2.63	12.73±3.25	<0.0001
Systolic blood pressure (mmHg)	121.30±15.63	143.09±16.32	<0.0001
Diastolic blood pressure (mmHg)	76.40±10.83	85.76±8.44	0.003
HbA_{1C} (%)	6.78±0.66	6.77±0.69	0.981
Fasting plasma glucose (mg/dL)	137.40±30.46	134.65±26.67	0.754
Total cholesterol (mg/dL)	171.82±30.87	171.70±26.56	0.989
LDLcholesterol (mg/dL)	103.72±31.10	94.73±22.95	0.299
HDL cholesterol (mg/dL)	53.12±12.12	50.36±12.13	0.481
Triglycerides (mg/dL)	99.06±52.90	139.00±45.88	0.015
sTNFR-1 (pg/mL)	1,127.92±250.96	1,380.82±541.39	0.067
sTNFR-2 (pg/mL)	2,179.82±538.27	2,656.03±860.40	0.043
Insulin (μU/mL)	23.64±9.87	38.97±18.48	0.001
HOMA-IR index	7.89±3.25	12.79±6.11	0.003
QUICKI index	2.88±0.13	2.78±0.11	0.004
Leptin (ng/mL)	7.01±4.41	14.45±8.93	0.002
Adiponectin (ng/mL)	10.64±5.75	10.15±7.14	0.805
Leptin/adiponectin ratio	0.97±1.14	1.89±1.34	0.024

T2DM = type 2 diabetes mellitus; BMI = body mass index; HbA_{1C} = glycated hemoglobin A1c; HDL = high density lipoprotein; LDL = low density lipoprotein; sTNFR-1 and sTNFR-2 = soluble tumor necrosis factor-alpha receptors type 1 and 2; HOMA-IR = homeostasis model assessment of insulin resistance; QUICKI = quantitative insulin sensitivity check index
* Significant different at *p*-value less than 0.05
Non-obese T2DM = BMI ≤23 kg/m^2, Obese T2DM = BMI ≥25 kg/m^2

signaling pathway and good beta-cell reserve in non-obese T2DM[15,16]. As waist circumference and waist-hip ratio (WHR) of non-obese diabetic patients were within the normal range for Thai population (waist circumference 82-85 cm and WHR 0.85 for men and 0.89 for women)[17], central adiposity would not explain IR in our patients. Recently, a genetic predisposition to reduced tissue sensitivity to insulin was suggested to increase the risk of developing T2DM in normal weight individuals[18]. Expression of IR-related genes among Thai population causing a resistance to insulin and T2DM in individuals with low-BMI, is awaiting further investigation. Besides, the former study has documented the existence of beta-cell dysfunction that is possibly due to genetic factors, abnormal immune response, or intrauterine programming in non-obese as well as in obese T2DM[19].

Apart from more sTNF-R2 and over-intense IR, increased blood leptin and a higher leptin/adiponectin ratio in obese versus non-obese diabetic patients was shown in this group of Thai patients. sTNF-R2, the main receptor type mediating an adipokine TNF-α action in human obesity, is preferential shedding and more stable in blood in comparison to sTNF-R1[20]. This may explain a different concentration of sTNF-R2 but not sTNF-R1 between non-obese and

Table 2. Significant cardiometabolic risk factors in obese type 2 diabetes mellitus

	OR (95% CI)	*p*-value
Increased		
Insulin	37.39 (3.31, 422.16)	0.003
HOMA-IR index	14.20 (1.83, 110.07)	0.011
Leptin	16.75 (1.63, 172.16)	0.018
Leptin/adiponectin ratio	16.03 (1.63, 169.19)	0.018
Triglycerides	5.44 (1.12, 26.42)	0.036
Decreased		
QUICKI index	0.13 (0.02, 0.71)	0.019

Logistic regression analysis stratified by low and high tertile values of parameters
OR with adjustment for sex and equal to 1 in non-obese group

Table 3. Partial correlation analysis between studied parameters

		r	*p*-value
Leptin/adiponectin	vs. insulin	0.565	0.001
	vs. HOMA-IR	0.513	0.004
	vs. triglycerides	0.434	0.016
sTNFR1	vs. sTNFR2	0.878	<0.0001
	vs. HDLC	-0.411	0.024
sTNFR2	vs. HDLC	-0.472	0.008

Only significant relationships were shown in Table
r coefficient of partial correlation adjusted for sex, BMI, waist to hip ratio, % body fat, and visceral fat level

obese T2DM observed in our study. In addition, the sTNF-R2 is strongly associated with the risk of coronary heart diseases among diabetic women[21].

Leptin is an adipokine that reflects existing fat mass and negatively regulates insulin action in adipose tissue[8]. Leptin increases TNF-α production[22], inhibits insulin release[23], and impairs insulin signaling[24]. Moreover, increased amounts of plasma leptin are an independent risk factor for coronary heart disease according to the large prospective study[25]. Adiponectin, an adipokine with unique metabolic properties, yields the insulin-sensitizing action by decreasing hepatic gluconeogenesis, increasing muscle glucose transport, and enhancing fatty acid oxidation in peripheral tissues[26]. Additionally, adiponectin attenuates leptin-induced TNF-α production[27] and promotes HDLC formation[28]. Increased IR together with a reverse association of sTNF-α receptor levels and HDLC obtained in the present study may point to a contribution of IR and TNF-α in suppressing HDLC[29,30]. A lack of difference in adiponectin levels between non-obese and obese T2DM in the present study may due to the multifactorial involvement, i.e. genetic, body fat distribution, insulin and other hormones, in regulation of its secretion. Besides, the significant positive relationship between the leptin/adiponectin ratio and BMI, triglycerides, and blood insulin as well as HOMA-IR were detected in diabetic patients, whereas, HOMA-IR did not show any association with blood pressure, lipid profiles, or sTNF-R. These suggest that the leptin/adiponectin ratio is a good marker of IR and may be more relevant than HOMA-IR in predicting adverse cardiometabolic outcomes among T2DM as studies have previously shown[31,32].

Conclusion

In conclusion, the study supported findings that obesity intensifies cardiometabolic risk in T2DM patients. Choosing proper antidiabetic drugs along with weight reduction regimens could be beneficial in preventing and reducing the cardiovascular complications in obese T2DM. The study also suggested an advantage of using the leptin/adiponectin ratio as another cardiometabolic risk factor in obese T2DM.

What is already known on this topic?

T2DM may occur in both lean and obese individuals. In Thailand, over 70% of Thai patients with T2DM are overweight or obese and half of them died from cardiovascular disease. In addition, evidences show that cardiovascular disease risk factors are significantly greater in the overweight/obese individuals who are also insulin resistant. In contrast, a higher mortality in lean than obese T2DM patients has been reported from other Asian population. While IR was shown in both lean and obese patients in other nations, contradictory findings of only beta-cell dysfunction without significant IR were reported among Thai T2DM patients who were non-obese. Conflicting about pathophysiology and prognosis of non-obese and obese T2DM needs more investigation.

What this study adds?

Our data support that obesity aggravated an inflammatory response and heightened cardiometabolic risk factors in Thai T2DM patients. Nonetheless, IR was observed in this group of non-obese Thai T2DM, though less severe than in obese group. Reduction of IR and body weight would be required for cardiovascular disease prevention in both obese and non-obese T2DM. Leptin/adiponectin ratio may have complementary role

for the prediction of cardiometabolic risks in obese T2DM.

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Potential conflicts of interest

None.

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ภาวะเสี่ยงโรคหัวใจและเมแทบอลิกในผู้ป่วยไทยโรคเบาหวานชนิดที่สองซึ่งอ้วนเทียบกับไม่อ้วน

สุพรพิมพ์ เจียสกุล, อภิรดี ศรีวิจิตรกมล, สุวัฒณี คุปติวุฒิ, สมาน อ่อนเรียบร้อย, มาลิกา ชุรินทรพรรณ, น้ำอ้อย เสมประเสริฐ

ภูมิหลัง: ความอ้วนเป็นภาวะอักเสบที่ก่อความผิดปกติและตายได้จากโรคหลายชนิดซึ่งรวมโรคเบาหวานชนิดที่ 2 และโรคหัวใจและหลอดเลือด

วัตถุประสงค์: ทำการเปรียบเทียบปัจจัยเสี่ยงโรคหัวใจและเมแทบอลิก ระหว่างผู้ป่วยไทยโรคเบาหวานชนิดที่ 2 ที่อ้วนและไม่อ้วน

วัสดุและวิธีการ: ศึกษาแบบตัดขวางในคนอ้วน (ดัชนีมวลกาย ≥25 กก./ม.^{2}) 20 ราย และคนไม่อ้วน (ดัชนีมวลกาย ≤23 กก./ม.^{2}) 20 ราย ที่เป็นโรคเบาหวานชนิดที่ 2 ผู้นิพนธ์ทำการวัดระดับน้ำตาลและไขมันในพลาสมาหลังอดอาหาร ระดับอินซูลิน เลปติน อะดิโพเนกติน และตัวรับทูเมอร์โครซิสแฟคเตอร์-อัลฟาชนิด 1 และ 2 (sTNF-R1 และ sTNF-R2) ในซีรัม คำนวณค่าดัชนีวัดความไวต่ออินซูลิน (QUICIKI) และดัชนีความดื้อต่ออินซูลิน (HOMA-IR)

ผลการศึกษา: ผู้ป่วยไทยโรคเบาหวานชนิดที่ 2 ที่อ้วนมีค่า sTNF-R2, HOMA-IR, อัตราส่วนเลปติน/อะดิโพเนกติน, ความดันเลือดและไขมันในเลือด มากกว่าผู้ป่วยโรคเดียวกันที่ไม่อ้วน อีกทั้งค่า HOMA-IR ในผู้ป่วยไทยโรคเบาหวานชนิดที่ 2 ที่ไม่อ้วนยังสูงกว่าค่าที่มีผู้รายงานไว้ในคนไม่เป็นโรคเบาหวาน ตัวบ่งชี้การอักเสบ (sTNF-R ทั้ง 2 ชนิด) มีระดับสัมพันธ์ตรงข้ามกับ HDL คอเลสเตอรอล อัตราส่วนเลปติน/อะดิโพเนกตินสัมพันธ์โดยตรงกับ HOMA-IR, ซีรัมอินซูลิน, พลาสมาไตรกลีเซอไรด์ และดัชนีมวลกาย ในขณะที่ HOMA-IR ไม่สัมพันธ์กับระดับไขมันทุกชนิดที่ศึกษา

สรุป: การศึกษาครั้งนี้พบว่าผู้ป่วยไทยซึ่งเป็นโรคเบาหวานชนิดที่ 2 ที่อ้วน เสี่ยงต่อการเกิดโรคหัวใจและเมแทบอลิกมากกว่าผู้ที่ไม่อ้วน อัตราส่วนเลปติน/อะดิโพเนกตินอาจเหมาะสมกว่า HOMA-IR ในการทำนายภาวะเสี่ยงต่อโรคหัวใจและหลอดเลือดในผู้ป่วยโรคเบาหวานชนิดที่ 2