Hyperthyroidism Induces Glucose Intolerance by Lowering Both Insulin Secretion and Peripheral Insulin Sensitivity

Weranuj Roubsanthisuk MD*, Praneet Watanakejorn PN*,
Monchaya Tunlakit BPH*, Sutin Sriussadaporn MD*

** Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University*

Objective: *The objectives of this study were to examine the effects of hyperthyroidism on glucose tolerance, insulin secretion, and insulin sensitivity.*

Material and Method: *Thirty-eight patients with hyperthyroidism and twenty-six healthy volunteers with matching age and body mass index were included. Patients with conditions known to affect glucose metabolism were excluded. An oral glucose tolerance test was performed after the diagnosis of hyperthyroidism and again when they achieved euthyroid state. Areas under the glucose and insulin curves were used to assess plasma glucose and insulin responses, respectively. β-cell function was determined by the corrected insulin response (CIR) and homostatic model assessment model 2 (HOMA2-%B). Peripheral insulin sensitivity was determined by the insulin activity (IA) and HOMA2-%S.*

Result: *The prevalence of glucose intolerance in hyperthyroid state was 39.4% [impaired glucose tolerance (IGT) 31.5% and diabetes mellitus (DM) 7.9%]. This was significantly higher than that of 30.7% [IGT 19.2% and DM 11.5%] in healthy volunteers ($p < 0.05$). Glucose intolerance was associated with higher systolic blood pressure, higher mean arterial pressure, lower CIR, and higher T_4 levels but not with the levels of T_3. IA and HOMA2-%S significantly improved when achieving a euthyroid state despite the increase in body mass index.*

Conclusion: *In conclusion, glucose intolerance is common in hyperthyroidism. Both impaired insulin secretion and decreased peripheral insulin sensitivity are the factors contributing to the development of abnormal glucose tolerance in the hyperthyroid state.*

Keywords: *Hyperthyroidism, Oral glucose tolerance, Diabetes mellitus, Insulin resistance*

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The association between glucose intolerance and hyperthyroidism has been recognized for a long time. Some studies have shown that glucose intolerance in hyperthyroidism is common with a prevalence of as high as 44-65%[1,2] and may reverse to normal glucose tolerance after achieving euthyroid status[2]. However, the mechanism of abnormal glucose metabolism in hyperthyroidism is not fully understood. A number of mechanisms underlying glucose intolerance in hyperthyroidism have been proposed in different studies including derangement in peripheral insulin sensitivity, insulin and glucagon secretion, hepatic glucose metabolism, intestinal glucose absorption, and glucoregulatory response to catecholamines[3-8]. The differences in the mechanism of glucose intolerance observed in theses studies might be owing to several factors such as ethnicity, sample size, study design, and different methods in the assessment of glucose metabolic status. The present study was therefore carried out to examine the prevalence of glucose intolerance in hyperthyroidism and to determine

Correspondence to : Sriussadaporn S, Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Prannok Rd, Bangkoknoi, Bangkok 10700, Thailand. Phone: 0-2419-7799, Fax: 0-2419-7792, E-mail: sisdp@mahidol.ac.th

factor(s) associated with the development of glucose intolerance in hyperthyroidism.

Material and Method

Subjects

Patients with untreated newly diagnosed or recurrent Graves' hyperthyroidism and healthy volunteers who had matching age and body mass index (BMI) were studied. The diagnosis of Graves' hyperthyroidism was established based on clinical and biochemical features including diffuse enlargement of the thyroid gland, presence of signs and symptoms of thyrotoxicosis, presence of elevated serum thyroid hormones in conjunction with suppressed serum TSH levels, and absence of other common causes of thyrotoxicosis (i.e., toxic multinodular goiter, toxic adenoma, and thyroiditis). Hyperthyroid patients and healthy volunteers who had the following conditions were excluded: concomitant medications known to interfere with glucose and thyroid hormone metabolism (i.e., thyroxine, β-adrenergic blocking agents, lithium, amiodarone, glucocorticoids, oral contraceptive pills, and other oestrogen containing agents), known diabetes mellitus (DM), family history of DM, medical illnesses including diarrhoea and malabsorption that might affect glucose absorption and metabolism, pregnancy, and thyroid storm. This study was approved by the Ethical Committee of Human Research, Faculty of Medicine, Siriraj Hospital. All patients and healthy volunteers agreed to participate in this study and gave their informed consent.

Study design

After the diagnosis of hyperthyroidism was established, all patients were assigned to have a standard oral glucose tolerance test (OGTT), designated as hyperthyroid-OGTT, according to the method described by the World Health Organization (WHO) 1985[9]. The test was performed in the morning after an overnight fast. Each patient drank a 250 ml glucose solution containing 75 g anhydrous glucose within five minutes. Venous blood samples were obtained before (at 0 minute) and at 30, 60, 90, and 120 minutes after drinking the glucose solution. The blood samples were immediately sent to our laboratory for separation of plasma and serum. The plasma samples were then immediately proceeded to plasma glucose measurement and the serum samples were stored at -20° C for subsequent insulin assay. After finishing the hyperthyroid-OGTT, the patients were then treated with an appropriate dosage of an antithyroid drug (either methimazole or propylthiouracil). Propranolol, a β-adrenergic blocking agent, was concomitantly administered in patients who had tachycardia and/or overt sympathetic symptoms. Clinical symptoms and signs of thyrotoxicosis and thyroid function test were assessed every 4 weeks during the treatment. The dosages of antithyroid drugs and propranolol were adjusted according to the clinical symptoms and signs of thyrotoxicosis and results of thyroid function. If prescribed, propranolol was stopped as soon as the symptoms and signs of thyrotoxicosis improved. Patients who achieved euthyroid status (defined as the presence of normal serum total T_3, total T_4 and free T_4 levels) and stopped propranolol for at least 2 weeks, were assigned to repeat standard OGTT, designated as euthyroid-OGTT. Healthy volunteers were studied as a control group.

Biochemical analyses and calculation methods

Serum total T_4 and TSH levels were measured by chemiluminometric assay (Kodak Clinical Diagnostics, Amersham, UK) and serum total T_3 levels were measured by radioimmunoassay (Kodak Clinical Diagnostics, Amersham, UK). Plasma glucose level was measured by the glucose oxidase method using an autoanalyser (Hitachi, Japan). Plasma insulin level was measured by radioimmunoassay (Diagnostic Products Corporation, USA). Glycaemic and glucose tolerance status were determined according to the criteria introduced by the WHO 1998[9] and American Diabetes Association 2005[10] using plasma glucose levels at fasting (FPG) and 2-hour post glucose load (2-h-PG) as follows: normal; FPG < 100 mg/dl and 2-h-PG < 140 mg/dl, impaired fasting glucose (IFG); FPG 100-125 mg/dl and 2-h-PG < 140 mg/dl, impaired glucose tolerance (IGT); FPG < 126 mg/dl and 2-h-PG 140-199 mg/dl, and DM; FPG ≥ 126 mg/dl and/or 2-h-PG ≥ 200 mg/dl. Plasma glucose response and insulin secretory response during OGTT were assessed by area under the glucose and insulin curves, respectively. Beta-cell function was assessed by homostatic model assessment model 2 (HOMA2-%B) during the fast state[11] and by calculation of corrected insulin response (CIR) during OGTT according to the formula: CIR = [plasma insulin at the glucose peak (μU/ml) x 100] / peak glucose (mg/dl) x [peak glucose (mg/dl) -70][12]. Insulin sensitivity was assessed by haemostatic model assessment model 2 (HOMA2-%S) during the fast state[11]. Peripheral insulin activity (IA) during OGTT was assessed using the formula: IA = 10^4 / [peak plasma glucose (mg/dl) x plasma insulin at the glucose peak (μU/ml)][13]. HOMA2-%B and HOMA2-%S were calculated from fasting plasma glucose and serum insulin levels using a computer

program available from www.OCDEM.ox.ac.uk[14].

Statistical analysis

Data were demonstrated as mean ± SD or percent as appropriate. In the hyperthyroid state, an unpaired t-test was used to examine factor(s) possibly associated with the occurrence of glucose intolerance. A paired t-test was applied to compare variables between hyperthyroid and euthyroid states in patients who completed the study. A p-value of ≤ 0.05 was considered statistically significant.

Results

There were 38 hyperthyroid patients (32 females and 6 males) aged 16-56 years (32.0 ± 10.2) and 26 healthy volunteers that matched their age and BMI (20 females and 6 males) aged 19-45 years, (36.1 ± 7.7) included in the study. The patients' clinical and biochemical characteristics at baseline are shown in Table 1. Results of OGTT performed during hyperthyroidism in all 38 patients showed that 22 cases (57.9%) had normal glucose tolerance, 1 case (2.6%) had IFG, 11 cases (28.9%) had IGT, 1 case (2.6%) had IFG and IGT, and 3 cases (7.9%) had DM. None of the patients with and without abnormal glucose tolerance had an FPG of ≥ 126 mg/dl. The prevalence of abnormal glucose tolerance (IGT and DM) during hyperthyroidism increased with age as follows: 0%, 29.4%, 33.3%, 75%, and 100% in patients aged < 21, 21-30, 31-40, 41-50, and > 50 years, respectively. The patients with abnormal glucose tolerance (15 cases) had systolic blood pressure, mean blood pressure, and serum total T_4 levels significantly higher than those with normal glucose tolerance (23 cases). There was no significant difference in age, BMI, diastolic blood pressure, pulse rate, and serum total T_3 levels between patients with normal and abnormal glucose tolerance. Patients with abnormal glucose tolerance had plasma glucose responses to an oral glucose load as determined by the area under the glucose curves significantly higher than those with normal glucose tolerance (Fig. 1A), whereas there was no significant difference in insulin secretory responses as determined by the area under the insulin curves between both groups (Fig. 1B). Patients with abnormal glucose tolerance had a CIR significantly lower than those with normal glucose tolerance. There was no difference in IA, HOMA2-%B, and HOMA2-%S between both groups.

There were 30 out of 38 patients (79%) who were followed-up until they achieved a euthyroid state and OGTT was repeated. Eight cases (21%) were lost to follow-up. Clinical and biochemical characteristics before treatment and after achieving euthyroid status of these 30 patients who had completed the study are shown in Table 2. After achieving euthyroid status, the patients had a significant increase in BMI (21.1 ± 2.9

Table 1. Clinical and laboratory data of all subjects in a hyperthyroid state divided into 2 groups according to glucose tolerance status

	Normal glucose tolerance group (n = 23)	Abnormal glucose tolerance group (n = 15)	p-value
Age (years)	29.39 ± 8.07	36.00 ± 11.98	0.074
Systolic blood pressure (mmHg)	116.70 ± 17.72	131.07 ± 20.97	0.029
Diastolic blood pressure (mmHg)	65.57 ± 11.53	71.87 ± 13.38	0.131
Mean blood pressure (mmHg)	82.61 ± 11.89	91.60 ± 14.21	0.042
Pulse (beats/min)	102.96 ± 13.90	108.87 ± 12.64	0.185
Body mass index (kg/m^2)	20.75 ± 2.43	20.67 ± 3.46	0.938
Serum T_3 (ng/dl)	458.65 ± 216.16	539.0 ± 215.48	0.270
Serum T_4 (μg/dl)	20.40 ± 6.03	25.15 ± 7.70	0.041
Fasting plasma glucose (mg/dl)	86.87 ± 7.19	86.67 ± 11.40	0.947
Fasting serum insulin (μU/ml)	11.38 ± 6.18	13.12 ± 14.45	0.664
Area under glucose curve (min mg/dl)	267.52 ± 31.39	348.82 ± 73.42	0.001
Area under insulin curve (min μU/ml)	105.40 ± 47.90	116.17 ± 61.01	0.547
Corrected insulin response	0.57 ± 0.39	0.32 ± 0.22	0.017
Insulin activity	0.97 ± 0.41	0.77 ± 0.40	0.152
HOMA2-%B	134.39 ± 59.08	114.17 ± 38.08	0.208
HOMA2-%S	86.64 ± 43.47	108.20 ± 48.91	0.177

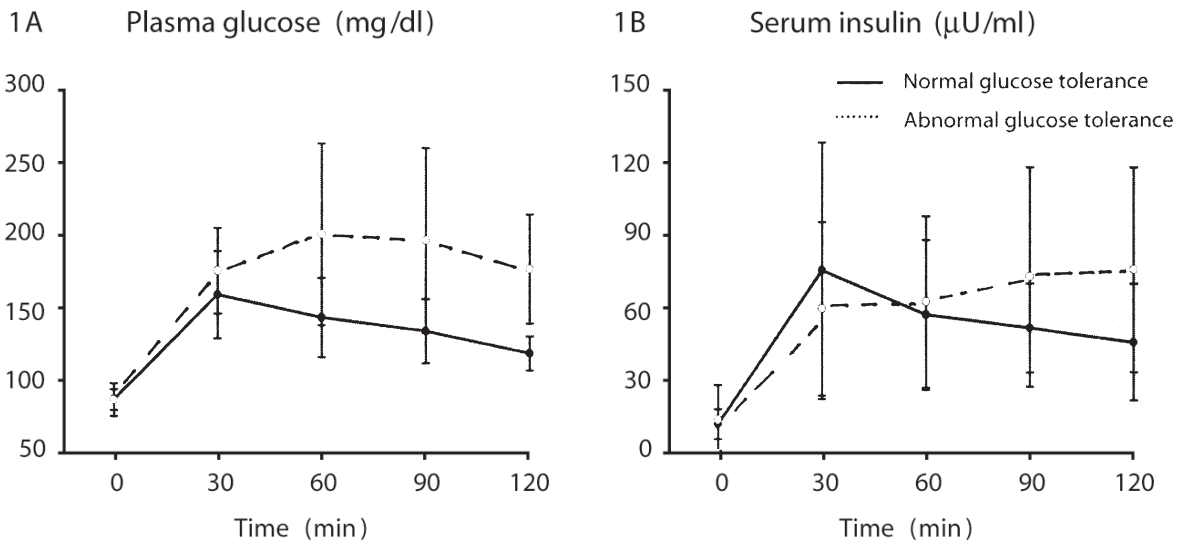

Fig. 1 Mean ± SD of plasma glucose (1A) and serum insulin (1B) levels during OGTT of all subjects in hyperthyroid states divided into normal and abnormal glucose tolerance groups

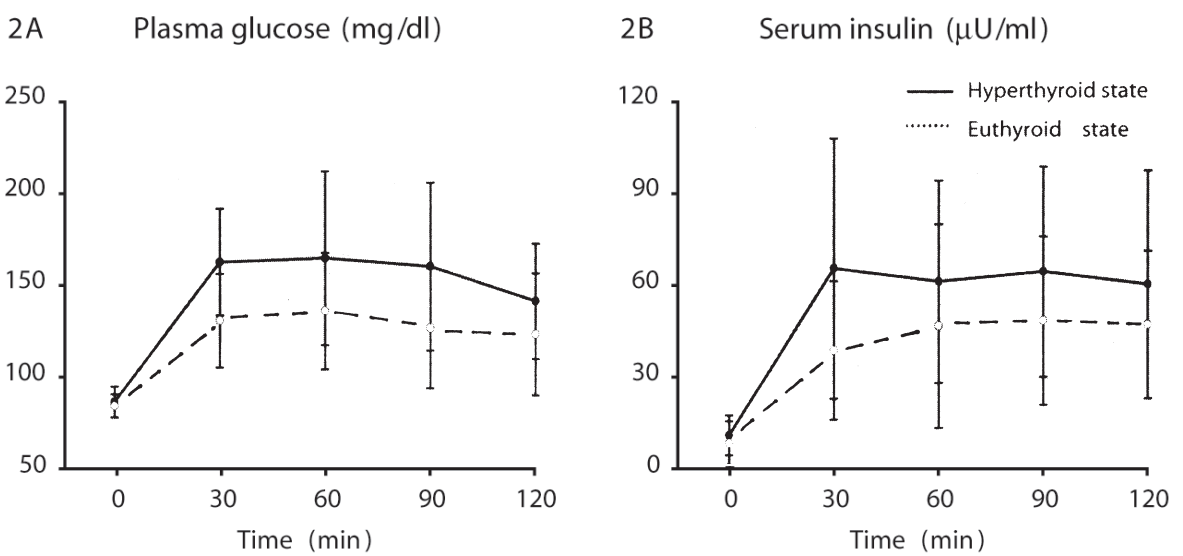

Fig. 2 Mean ± SD of plasma glucose (2A) and serum insulin (2B) levels during OGTT in the hyperthyroid compared with euthyroid state in 30 subjects who had completed the study

vs. 22.7 ± 2.8 kg/m^2, $p < 0.001$), decrease in systolic blood pressure (123.2 ± 21.9 vs. 111.3 ± 11.8 mmHg, $p = 0.003$), and changes in glucose tolerance status as compared to the hyperthyroid state. Eight cases (26.7%) had improved glucose tolerance status with six of them (20%) turned from IGT to normal and the other two (6.7%) turned from DM to IGT. Sixteen cases (53.3%) had no change in glucose tolerance status including 11 cases (36.7%) with normal glucose tolerance status and 5 cases (16.6%) with IGT. Six cases (20%) had glucose tolerance status changed from normal to IGT, however their average 2-h-PG level was 150 mg/dl, which was slightly higher than the cut off value of 140 mg/dl, 3 of them had improved IA and 4 of them had

Table 2. Compared clinical and laboratory data between hyperthyroid and euthyroid states of 30 subjects who had completed the study

	Hyperthyroid (n = 30)	Euthyroid (n = 30)	p-value
Systolic blood pressure (mmHg)	123.23 ± 21.85	111.33 ± 11.80	0.003
Diastolic blood pressure (mmHg)	67.90 ± 13.23	71.43 ± 8.16	0.127
Mean blood pressure (mmHg)	86.34 ± 14.51	84.73 ± 8.26	0.519
Pulse (beats/min)	106.64 ± 14.37	72.16 ± 8.91	<0.001
Body mass index (kg/m^2)	21.10 ± 2.92	22.68 ± 2.83	<0.001
Serum T_3 (ng/dl)	472.16 ± 191.80	111.46 ± 28.82	<0.001
Serum T_4 (μg/dl)	21.19 ± 5.62	7.89 ± 1.71	<0.001
Fasting plasma glucose (mg/dl)	85.76 ± 8.52	83.53 ± 6.33	0.142
Fasting serum insulin (μU/ml)	10.49 ± 6.55	7.78 ± 7.24	0.130
Area under glucose curve (min mg/dl)	296.43 ± 57.16	248.77 ± 45.8	<0.001
Area under insulin curve (min μU/ml)	111.50 ± 56.34	79.46 ± 40.89	0.001
Corrected insulin response	0.46 ± 0.32	0.55 ± 0.37	0.188
Insulin activity	0.90 ± 0.41	1.64 ± 0.99	<0.001
HOMA2-%B	131.05 ± 56.40	111.71 ± 52.26	0.131
HOMA2-%S	96.12 ± 47.34	129.90 ± 68.26	0.030

increased HOMA2-%S. There were significant decreases in area under the glucose (Fig. 2A) and insulin curves (Fig. 2B) and significant increases in IA and HOMA2-%S but no change in CIR and HOMA2-%B as compared with the hyperthyroid state.

The healthy volunteers had a BMI of 15-24.9 kg/m^2 (21.8 ± 2.2), which was not significantly different from hyperthyroid patients**.** Of the 26 cases, 18 cases (69.2%) had normal glucose tolerance, 5 cases (19.2%) had IGT, and 3 cases (11.5%) had DM. The prevalence of abnormal glucose tolerance was significantly lower than that of patients with the hyperthyroid state ($p < 0.05$).

Discussion

The present study has shown that the prevalence of abnormal glucose tolerance including IGT and DM in 38 patients with the hyperthyroid state was 39.4% which was significantly higher than that of 30.7% in 26 age and BMI matched healthy controls who were enrolled in the study under the same criteria that both groups had no factors that might interfere with their glucose metabolism. In addition, the high prevalence of abnormal glucose tolerance in patients with the hyperthyroid state observed in this study was higher than that in the general Thai population. Studies in the north-eastern part of Thailand have shown that the prevalence of IGT and DM in the general population aged 30-74 years was ~11-18% and 6-12%, respectively[15,16]. A recent study by the InterASIA Collaborative Group in 5,105 participants older than 35 years in Bangkok and all main regions of Thailand has shown that the national prevalence of DM was 9.6%[17]. In the Thai population with risk factors of glucose intolerance including obesity, first degree relative of patients with DM, hypertension, dyslipidemia, premature atherosclerosis, history of gestational DM, and delivery of macrosomic babies, the prevalence of IGT and DM were 23.7% and 13.6%, respectively[18]. These observations indicate that the hyperthyroid state plays a role in the development of abnormal glucose tolerance and individuals with the hyperthyroid state and those with known risk factors for glucose intolerance are at comparable risk for the development of glucose intolerance. However, the high prevalence of abnormal glucose tolerance observed in this study was lower than that of 44-65% shown in previous studies[1,2]. This difference might be attributable to the different criteria used in classifying glucose tolerance status and the absence of risk factors interfering with glucose metabolism in our hyperthyroid patients.

The present study has found that hyperthyroid patients with abnormal glucose tolerance had sys-tolic blood pressure, mean blood pressure, and serum total T_4 levels higher than, and CIR lower than hyperthyroid patients with normal glucose tolerance. Higher blood pressure was a common clinical characteristic found in individuals prone to develop glucose intolerance. The association of higher blood pressure with the occurrence of glucose intolerance found in

this study may be due either to the cardiovascular effect of excess thyroid hormones or to the presence of more risk factors in subjects inclined to be glucose intolerant. Since mean systolic blood pressure in the abnormal glucose tolerance group was 131.07 mmHg, which was not in the hypertensive range, and systolic blood pressure significantly decreased when the subjects achieved a euthyroid state, these favoured the assumption that excess thyroid hormones caused elevated systolic blood pressure. Hyperthyroidism tends to increase systolic blood pressure but decrease diastolic blood pressure[19,20]. The pattern of blood pressure changes after the treatment also supported the cardiovascular effects of excess thyroid hormones. When achieving a euthyroid state, mean systolic blood pressure was lower but diastolic blood pressure was higher, though not statistically significant, than in the hyperthyroid state. Although age is another well-established factor related with the deterioration of glucose tolerance like higher blood pressure, the mean age of the subjects in the normal compared with that in the abnormal glucose tolerance group in this study was not significantly different. This was in contrast with the findings from two previous studies indicating that age-related glucose intolerance was magnified by hyperthyroidism[7,21]. This may be due to a small number of participants and the young age of most subjects. However, the prevalence of abnormal glucose tolerance tended to increase with age, from 0% in subjects younger than 21 years old to 100% in those who were older than 50 years old.

In normal physiology, pancreatic β-cells should secrete more insulin to maintain euglycemia when plasma glucose increases. Individuals in the abnormal glucose tolerance group had an area under the glucose curve but not an area under the insulin curve significantly higher than subjects in the normal group. In contrast with normal physiologic response, participants in the abnormal group had significantly lower CIR than those in the normal group. CIR has an advantage over other parameters of β-cell response after an oral glucose load such as serum insulin level, serum insulin/plasma glucose ratio, etc. in that it is independent of plasma glucose level[12]. Therefore, this indicated that subjects with impaired β-cell response had more chance to develop glucose intolerance when triggered by hyperthyroidism. Subjects who developed glucose intolerance in the hyperthyroid state might have more hyperthyroidism than those with normal glucose tolerance as supported by significantly higher serum total T_4. However, there was no association between T_3 levels, which is an active thyroid hormone, and the occurrence of glucose intolerance. This finding is in accordance with the study of Krienes, et al[2]. T_3 and T_4 might have different effects on glucose metabolism. It has been shown that tissue glucose uptake in rats in response to T_3 administration was stimulated at a physiologic dose but was inhibited at a higher pharmacologic dose[22]. In the other studies in rats, exogenous T_4 treatment has been shown to acutely increase the rate of β-cell apoptosis[23] and increase glucose transporter 2 (GLUT-2) levels in hepatocyte plasma membranes[24] resulting in the increase in glucose efflux across the hepatocyte plasma membrane in the final step of hepatic glucose production. Accordingly, the higher T_4 levels in hyperthyroid patients with abnormal glucose tolerance in this study might induce more β-cell death causing lower CIR in the hyperthyroid state as compared with those in the normal glucose tolerance group. However, further study on the magnitude of contribution of thyroid hormones, either T_3 or T_4, to the development of glucose intolerance is needed.

After the treatment of hyperthyroidism till achieving a euthyroid state, the majority of subjects had improved IA despite the increment in BMI indicating that another mechanism of glucose intolerance in hyperthyroidism was peripheral insulin resistance. In the hyperthyroid state, subjects whose β-cells cannot compensate for the increased demand of insulin might then turn out to be glucose intolerant as shown above that lower CIR was a factor associated with the presence of glucose intolerance. On the other hand, hyperthyroidism could be viewed as a triggering event initiating glucose intolerance in subjects likely to be. Although there was a minimal increment in the prevalence of glucose intolerance from 39.4% in the hyperthyroid state to 43.3% when achieving a euthyroid state, most subjects had an improvement or no change in glucose tolerance status. This slightly higher prevalence of glucose intolerance in the euthyroid state was partly due to those 6 cases that deteriorated from normal to borderline IGT. However, the mean of 2-h-PG in these cases was 150 mg/dl, which was just slightly higher than the cut off value of 140 mg/dl as compared with the higher average of 2-h-PG of 161 mg/dl in patients who had IGT in the hyperthyroid state. In addition, 3 of them had improved IA and 4 of them had increased HOMA2-%S. If we consider these 6 cases to be normal, the prevalence of glucose intolerance in the euthyroid state would have been 23%, which is much lower than that of 39.4% in the hyperthyroid state. The long-term

prognosis of individuals with IGT even when achieving the euthyroid state is not clearly known. However, subjects with abnormal glucose tolerance at the end of this study should be carefully monitored according to the following reasons. Firstly, individuals with IGT are at significant risk of developing DM and also at increased risk of cardiovascular morbidity and mortality[25]. Secondly, the most common cause of hyperthyroidism is Graves' disease, which usually has a high relapse rate varying from 40-60% after an antithyroid drug discontinuation[26]. Thirdly, Maxon, et al had observed long-term prognosis of thyrotoxic patients and revealed that 40% and 25% of subjects remained glucose intolerant at 9 months and 12 years, respectively[27]. An appropriate management of hyperthyroid relapse and lifestyle modification to prevent insulin resistance such as body weight control might interrupt a deterioration of glucose tolerance status in the future. The findings in this study can therefore be applied clinically. Glucose intolerance should be looked for in hyperthyroid subjects, particularly in those who have higher blood pressure or who are in an older age group. In subjects with known DM, diabetic control may be worse during hyperthyroidism and modification of diabetic treatment may be needed in different states of hyperthyroidism.

In conclusion, hyperthyroidism can frequently induce glucose intolerance. The mechanism responsible for glucose intolerance in hyperthyroidism is impaired insulin secretion in combination with decreased peripheral insulin sensitivity.

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ภาวะฮัยเปอร์ไทรอยด์ดิซึมลดความทนกลูโคสโดยลดการหลั่งอินซูลินและลดความไวต่ออินซูลิน

วีรนุช รอบสันติสุข, ปราณีต วัฒนเขจร, มนชยา ทันละกิจ, สุทิน ศรีอัษฎาพร

คณะผู้วิจัยได้ทำการศึกษาผลของภาวะฮัยเปอร์ไทรอยด์ดิซึมต่อความทนกลูโคส การหลั่งอินซูลิน และความไวต่ออินซูลิน ผู้เข้าร่วมการศึกษาประกอบด้วยผู้ป่วยฮัยเปอร์ไทรอยด์ดิซึมที่ไม่มีปัจจัยอื่นที่มีผลกระทบต่อความทนกลูโคสจำนวน 38 ราย และอาสาสมัครปกติที่มีอายุและดัชนีมวลกายใกล้เคียงกับผู้ป่วยฮัยเปอร์ไทรอยด์ดิซึมจำนวน 26 ราย ผู้ป่วยแต่ละรายได้รับการทดสอบความทนกลูโคสทั้งก่อนและหลังได้รับการรักษาภาวะฮัยเปอร์ไทรอยด์ดิซึม ใช้การคำนวณ corrected insulin response (CIR) และ HOMA2-%B เพื่อประเมินการหลั่งอินซูลินจากบีต้าเซลล์ของตับอ่อน และใช้การคำนวณ insulin activity (IA) และ HOMA2-%S เพื่อประเมินความไวต่ออินซูลิน พบว่าในขณะมีภาวะฮัยเปอร์ไทรอยด์ดิซึมร้อยละ 39.4 ของผู้ป่วยมีความทนกลูโคสผิดปกติ โดยร้อยละ 31.5 มีความทนกลูโคสบกพร่อง และร้อยละ 7.9 เป็นเบาหวาน ในขณะที่พบความทนกลูโคสผิดปกติร้อยละ 30.7 ในอาสาสมัครปกติ โดยร้อยละ 19.2 มีความทนกลูโคสบกพร่อง และร้อยละ 11.5 เป็นเบาหวาน ซึ่งความแตกต่างดังกล่าวมีนัยสำคัญทางสถิติ ($p < 0.05$) ผู้ป่วยที่มีความดันเลือดซิสโตลิค ความดันเลือดเฉลี่ย ระดับซีรัม T_4 ที่สูงกว่า หรือมีค่า CIR ที่ต่ำกว่ามีแนวโน้มที่จะเกิดความทนกลูโคสผิดปกติ ในขณะที่การเกิดความทนกลูโคสผิดปกติไม่มีความสัมพันธ์กับระดับซีรัม T_3 ความไวต่ออินซูลินทั้งจากการประเมินด้วย IA และ HOMA2-%S ดีขึ้นหลังได้รับการรักษาจนระดับไทรอยด์ฮอร์โมนลดลงเป็นปกติแม้ดัชนีมวลกายจะเพิ่มขึ้น โดยสรุปความทนกลูโคสผิดปกติพบได้บ่อยในภาวะฮัยเปอร์ไทรอยด์ดิซึม ความบกพร่องในการหลั่งอินซูลินและการลดลงของความไวต่ออินซูลินเป็นกลไกที่ทำให้เกิดความทนกลูโคสผิดปกติ