

## Thyroid Dysfunction in Type 2 Diabetes Mellitus Patients

Imam Subekti<sup>1</sup>, Laurentius A. Pramono<sup>2</sup>, Esthika Dewiasty<sup>1</sup>, Dante S. Harbuwono<sup>1</sup>

<sup>1</sup> Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

<sup>2</sup> Department of Internal Medicine, St. Carolus Hospital, Jakarta, Indonesia.

### Corresponding Author:

Imam Subekti, MD., PhD. Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. email: isubekti@yahoo.com.

### ABSTRAK

**Latar belakang:** disfungsi tiroid lebih banyak terjadi pada pasien diabetes dibandingkan populasi umum. Sampai saat ini belum ada penelitian yang menemukan prevalensi hipotiroidisme dan hipertiroidisme pada pasien diabetes mellitus di Indonesia. Tujuan penelitian ini adalah menemukan proporsi dan karakteristik disfungsi tiroid pada pasien diabetes melitus tipe 2 di Indonesia. **Metode:** penelitian potong lintang dilakukan di Poliklinik Endokrin dan Diabetes Departemen Ilmu Penyakit Dalam Rumah Sakit Cipto Mangunkusumo pada bulan Juli hingga September 2015. Penelitian ini mengikutsertakan pasien diabetes melitus tipe 2, usia di atas 18 tahun, dan bersedia melakukan pemeriksaan laboratorium fungsi tiroid. Dalam penelitian ini, hipotiroidisme didefinisikan TSH lebih dari 4,0 mIU/L, sementara hipertiroidisme didefinisikan TSH kurang dari 0,4 mIU/L menggunakan metode eCLIA. **Hasil:** dari 364 subjek yang direkrut di Poliklinik Endokrin dan Diabetes Rumah Sakit Cipto Mangunkusumo, sebanyak 303 subjek mengikuti penelitian hingga analisis. Dua ratus tujuh puluh tiga (273) (90,1%) subjek eutiroidisme, 7 (2,31%) subjek hipertiroidisme, dan 23 (7,59%) subjek hipotiroidisme. Sebagian besar subjek termasuk hipotiroidisme subklinis (56,5% berdasarkan Index Zulewski dan Billewicz, 65,2% berdasarkan pemeriksaan fT4), sementara 42,9% dan 71,4% subjek termasuk kategori hipertiroidisme klinis masing-masing berdasarkan tampilan klinis dan pemeriksaan fT4. **Kesimpulan:** pada pasien diabetes melitus tipe 2, proporsi hipotiroidisme adalah 7.59% dan proporsi hipertiroidisme adalah 2.31% sehingga secara total, disfungsi tiroid memiliki proporsi sebesar 9.9%. Disarankan skrining fungsi tiroid dilakukan pada pasien risiko tinggi sebagai manajemen komprehensif pasien diabetes melitus tipe 2.

**Kata kunci:** disfungsi tiroid, hipotiroidisme, hipertiroidisme, diabetes melitus tipe 2.

### ABSTRACT

**Background:** thyroid dysfunction is more likely to occur in diabetes mellitus patients than general population. Until now, no study has been done to find prevalence of hypothyroidism and hyperthyroidism in Indonesian diabetics. This study aimed to find the proportion and characteristics of thyroid dysfunction in Indonesian type 2 diabetes mellitus patients. **Methods:** a cross-sectional study was conducted in Endocrine and Diabetes Polyclinic, Department of Internal Medicine, Cipto Mangunkusumo Hospital from July to September 2015. This study include type 2 diabetes mellitus patients, age  $\geq 18$  year-old, willing to undergo thyroid laboratory testing. In this study, hypothyroidism defined as TSH more than 4.0 mIU/L, while hyperthyroidism is defined as TSH less than 0.4 mIU/L with eCLIA. **Results:** from 364 subjects who were recruited from Endocrine and Diabetes Polyclinic, Cipto Mangunkusumo Hospital, 303 subjects underwent this study until analysis. Two hundred and three (273) subjects (90.1%) were euthyroid, 7 subjects (2.31%) were hyperthyroid, and 23 subjects (7.59%) were

*hypothyroid. Majority of the patients had subclinical hypothyroidism (56.5% based on Zulewski and Billewicz Score and 65.2% based on fT4 laboratory result), while 42.9% and 71.4% subjects had clinical hyperthyroidism based on clinical appearance and fT4 laboratory result respectively. **Conclusion:** proportion of hypothyroidism was 7.59% and hyperthyroidism was 2.31%, while the proportion of total thyroid dysfunction was 9.9% among diabetics. It is suggested that screening for thyroid dysfunction can be done in high risk condition as a part of comprehensive management in type 2 diabetes mellitus patients.*

**Keywords:** thyroid dysfunction, hypothyroidism, hyperthyroidism, type 2 diabetes mellitus.

## INTRODUCTION

Prevalence of thyroid dysfunction is greater in diabetes patients compared to the general population.<sup>1-3</sup> Prevalence of thyroid dysfunction in general population is around 6.6-13.4%, while in diabetes population around 10-24%.<sup>1</sup> Studies found that subclinical hypothyroidism is the most common thyroid dysfunction in diabetic population. Study from Pasupathi et al<sup>4</sup> found that the prevalence of hypothyroidism and hyperthyroidism in diabetes patients reach 28% and 17%, respectively. Studies and several organizations recommend thyroid screening test for diabetic patients.

Connection between thyroid dysfunction especially hypothyroidism and type-1 diabetes mellitus is well-established since the autoimmune mechanism in type-1 diabetes correlates with thyroid autoimmunity.<sup>5,6</sup> Meanwhile, explanation of the correlation between type 2 diabetes and thyroid dysfunction is unclear as the mechanism is very complex and involves many variables such as synthesis of thyrotropin releasing hormone (TRH), circadian rhythm of thyroid stimulating hormone (TSH), insulin resistance, autoimmunity, and the use of metformin.<sup>7,8</sup> The co-existence of thyroid dysfunction in type 2 diabetes mellitus patients will worsen the macrovascular and microvascular complications, morbidity, mortality, and quality of life.<sup>7</sup> Detecting thyroid dysfunction in type 2 diabetes patients will inform clinicians to give optimal treatment for metabolic conditions since thyroid condition such as hypothyroidism will delicate achievement of glycemic target and other comorbidities.<sup>9</sup>

Although thyroid dysfunction in diabetic population had been studied by many researchers around the world, until recently, there is no

study about thyroid dysfunction in type-2 diabetes mellitus patients in Indonesia. The aim of this study was to find the proportion and characteristics of thyroid dysfunction in Indonesian type 2 diabetes mellitus patients. Hopefully the study will complete the database of thyroid dysfunction in different populations around the world.

## METHODS

A cross-sectional study was conducted in Endocrine and Diabetes Polyclinic, Department of Internal Medicine, Cipto Mangunkusumo Hospital from July to September 2015. The inclusion criterias of the subjects were type-2 diabetes mellitus patients, aged  $\geq 18$  years old and willing to undergo thyroid laboratory testing. Exclusion criterias were pregnant women, on antithyroid or thyroid hormone medication, on medication which impaired thyroid function, history of neck radiation, thyroidectomy, and known history of thyroid disorders (e.g. Graves' disease or goiter) previously.

Study subjects were obtained from the polyclinic through consecutive sampling method with a minimum study subjects calculated using previous study by prevalence 24% (using prevalence from Devi MA et al<sup>10</sup> study which has the closest similarity with our study),  $\alpha$  5% ( $Z_{\alpha}$  1.96), precision (d) 10%. Based on that calculation, we got 292 subjects as minimum samples for our study. Type-2 diabetes mellitus patients from polyclinic were screened for inclusion and exclusion criterias. If suitable for becoming our study subjects, patients were asked for informed consent before undergo study. Study subjects must fill all test starting with history taking, physical examination, thyroid laboratory testing, and thyroid ultrasound if needed.

**Clinical and Laboratory Parameters**

In this study, hypothyroidism was defined as TSH more than 4.0 mIU/L detected using eCLIA (electro-chemiluminescence immunoassay) method from Cobas 6000 (Roche Diagnostics). Hypothyroidism was classified based on clinical signs and symptoms according to Zulewski and Billewicz Index as clinical and subclinical hypothyroidism, and based on free-T4 (fT4) laboratory result as clinical hypothyroidism (fT4 <0.93 µg/L) and subclinical (mild) hypothyroidism (normal fT4). Hyperthyroidism was defined as TSH less than 0.4 mIU/L with eCLIA. Further, hyperthyroidism was classified based on free-T4 (fT4) laboratory result as clinical hyperthyroidism (fT4 > 1.7 µg/L) and subclinical (mild) hyperthyroidism (normal fT4).

**Statistical Analysis**

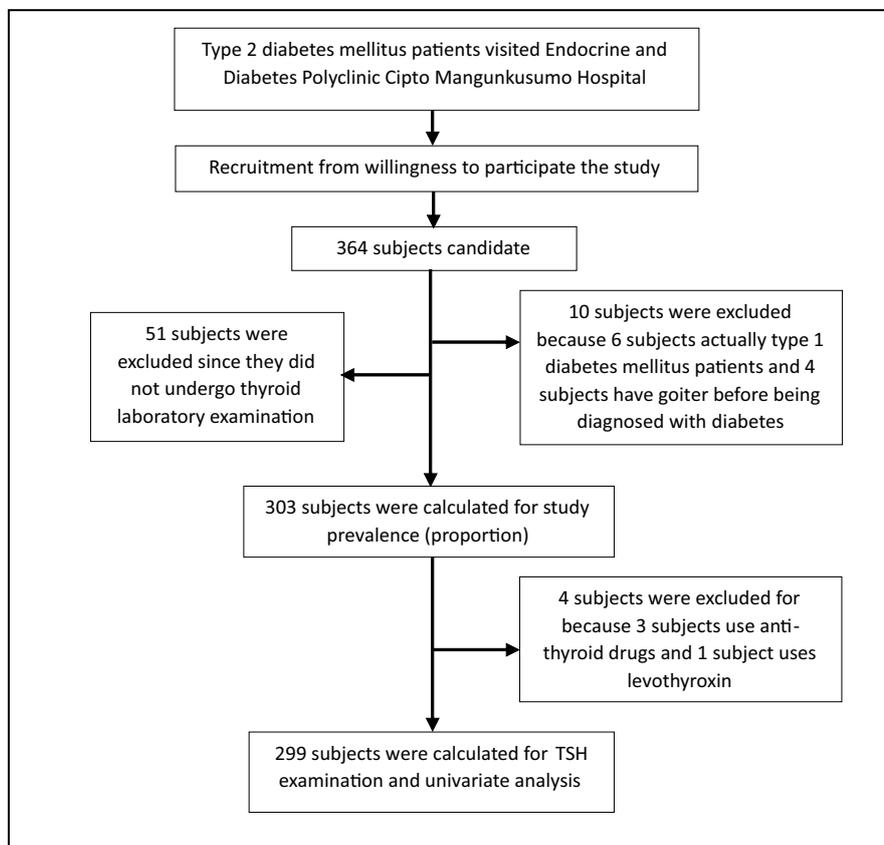
Data editing was done before entering data to Microsoft Excell 2013 and SPSS Statistics 17.0. Descriptive data analysis was done to obtain proportion and characteristics of thyroid dysfunction in type 2 diabetes mellitus patients.

**Ethical Clearance**

This study had been ethically approved by Research Ethic Committee from Faculty of Medicine Universitas Indonesia (715/UN2.F1/ETIK/2015).

**RESULTS**

A total of 364 subjects were recruited from Endocrine and Diabetes Polyclinic, Department of Internal Medicine, Cipto Mangunkusumo Hospital. Out of those subjects, 51 subjects were excluded since they did not undergo thyroid function test procedure and 10 subjects were excluded because 6 subjects were actually type 1 diabetes mellitus patients after in-depth history taking and 4 subjects had goiter before being diagnosed with type-2 diabetes mellitus. Later, 4 subjects were excluded because 3 subjects were in anti-thyroid medication and 1 subjects was in levothyroxine therapy. At the end, 299 subjects were included for univariate analysis. **Figure 1** shows subject’s profile.



**Figure 1.** Flowchart of study subject recruitment

**Table 1.** Socio-demography and clinical characteristics of the study subjects (n=299)

Characteristics	Category	Frequency (n, %)
Gender	Male	128 (42.8%)
	Female	171 (57.2%)
Age, Median (Range; year)		60 (37-86)
Education background	Uneducated	2 (0.7%)
	Elementary school	56 (18.7%)
	Junior high school	39 (13%)
	Senior high school	108 (36.1%)
	Academy	35 (11.7%)
	Bachelor	59 (19.7%)
Job/Employment	Unemployed	9 (3%)
	Retired	97 (32.4%)
	Housewife	123 (41.1%)
	Labour	15 (5%)
	Government sector	12 (4%)
	Private sector	29 (9.6%)
	Profesional	14 (4.6%)
Diabetes duration	1-5 years	109 (36.5%)
	5-10 years	62 (20.7%)
	> 10 years	128 (42.8%)
	Median (Range; year)	10 (1-45)
Diabetes therapy	Dietary	1 (0.3%)
	Oral anti-diabetes	145 (48.4%)
	Insulin	62 (20.7%)
	Combination (oral and insulin)	91 (30.4%)
Body mass index (BMI)	< 18,5 Kg/m <sup>2</sup> (underweight)	10 (3.3%)
	18,5-22,9 Kg/m <sup>2</sup> (normoweight)	82 (27.4%)
	23-24,9 Kg/m <sup>2</sup> (overweight)	68 (22.7%)
	25-30 Kg/m <sup>2</sup> (grade 1 obesity)	97 (32.4%)
	> 30 Kg/m <sup>2</sup> (grade 2 obesity)	42 (14%)
	Median (Range; Kg/m <sup>2</sup> )	24.7 (16.7-37.2)
Diabetes complication	Cerebrovascular disease	31 (10.4%)
	Coronary artery disease	68 (22.7%)
	Diabetic nephropathy	169 (56.5%)
	Diabetic retinopathy	68 (22.7%)
	Diabetic neuropathy	147 (49.2%)
	Peripheral arterial disease	11 (3.7%)
	Diabetic foot	53 (17.7%)
Clinical manifestation of thyroid dysfunction (based on Billewicz and Zulewski Index)	No clinical manifestation of thyroid dysfunction	78 (26.1%)
	Query clinical manifestation of thyroid dysfunction	190 (63.5%)
	Positive clinical manifestation of thyroid dysfunction	31 (10.4%)
Thyroid status (n=303 for prevalence or proportion study)	Euthyroidism	273 (90.1%)
	Hyperthyroidism	7 (2.31%)
	Hypothyroidism	23 (7.59%)

**Table 2.** Classification of hypothyroidism in diabetes subjects (n=23)

Methods	Diagnosis	Frequency (n, %)
Zulewski Index Score > 5 or Billewicz Index Score > 25	Clinical hypothyroidism	10 (43.5%)
	Subclinical hypothyroidism	13 (56.5%)
fT4 < 0.93 µg/dL	Clinical hypothyroidism	8 (34.8%)
	Subclinical hypothyroidism	15 (65.2%)

**Table 3.** Classification of hypothyroidism in diabetes subjects (n=23)

Methods	Diagnosis	Frequency (n, %)
Clinical appearance	Toxic (clinical hyperthyroidism)	3 (42.9%)
	Non-toxic (subclinical hyperthyroidism)	4 (57.1%)
fT4 > 1.7 µg/dL	Clinical hyperthyroidism	5 (71.4%)
	Subclinical hyperthyroidism	2 (28.6%)

Based on thyroid status, 273 subjects (90.1%) were euthyroid, 7 subjects (2.31%) were hyperthyroid, and 23 subjects (7.59%) were hypothyroid. In total, 30 subjects (9.9%) have thyroid dysfunction in this study. **Table 2** and **Table 3** show the classification of hypothyroidism and hyperthyroidism based on clinical appearance and fT4 laboratory result.

Hypothyroid patients were classified to clinical and subclinical hypothyroidism based on clinical appearance using Zulewski and Billewicz Score and based on laboratory result (fT4). According to these two methods, majority of the patients had subclinical hypothyroidism (56.5% based on Zulewski and Billewicz Score and 65.2% based on fT4 laboratory result), while 42.9% and 71.4% subjects were clinical hyperthyroidism based on clinical appearance and fT4 laboratory result.

## DISCUSSION

Prevalence of thyroid dysfunction in type 2 diabetes mellitus patients become an attention in epidemiological studies in the field of endocrinology in the last decade.<sup>7,11</sup> Several studies with various design and aim were held to find out prevalence and determinants of thyroid dysfunction in type-2 diabetes patients.<sup>11,12</sup> The focus of these studies were prevalence of hypothyroidism which has connection with pathophysiology, pathogenesis, comorbidities, and complications of type-2 diabetes mellitus.<sup>12,13</sup>

This study obtained proportion of hypothyroidism and hyperthyroidism in type-2

diabetes population. About 23 subjects (7.59%) have hypothyroidism and 7 subjects (2.3%) have hyperthyroidism. Proportion of thyroid dysfunction in this cross-sectional – Indonesian population was 9.9%. Further, it was paradoxically seen that subclinical hypothyroidism was higher than clinical hypothyroidism (based on clinical presentation and laboratory result), but clinical hyperthyroidism was more than twice number of subclinical hyperthyroidism.

Other interesting finding was that the clinical appearance of hypothyroidism was more lucid in diabetic patients since the proportion based on clinical appearance score (e.g. Zulewski and Billewicz Index) for clinical hypothyroidism more higher than the proportion obtained by actual laboratory result (43.5% versus 34.8%). This condition can be caused by overlapping clinical condition between hypothyroidism and diabetes.<sup>7</sup> Contrariwise, in hyperthyroid subjects, the proportion of clinical hyperthyroidism was higher based on laboratory result than based on clinical appearance, although we did not calculate the Wayne's Index clinical score for hyperthyroidism. Based upon retrospective history taking (i.e. sign and symptom in the past), 3 subjects who use anti-thyroid drug had experienced toxic thyroid condition but remained non-toxic after the use of anti-thyroid drug. Again, this condition may be related to diabetes which can mask signs and symptoms of thyrotoxicosis. It is known that uncontrolled diabetes can influence assessment of thyroid toxic condition by falsely decreasing the blood

levels of thyroxine and triiodothyronine.<sup>14</sup>

The proportion of hypothyroidism in type 2 diabetes mellitus patients was 7.59% which was lower than previous studies in other populations. (Table 4 shows resume of the studies on thyroid dysfunction in diabetes patients from different populations around the world). Based on the meta-analysis which held by Han C et al.<sup>11</sup>, the prevalence of subclinical hypothyroidism (pooled adjusted) in type-2 diabetes mellitus patients was 10.2%. This number was obtained from 36 studies with the range of prevalence between 4.69% to 18.86%. Type-2 diabetes mellitus population which has the highest prevalence of subclinical hypothyroidism was Indian population who had prevalence above 20%. Studies done by Vikhe VB et al.,<sup>15</sup> Singh G et al.,<sup>16</sup> Devi MA et al.,<sup>10</sup> Demitrost L et al.,<sup>17</sup> and Uppal V et al.<sup>18</sup> obtained prevalence of subclinical hypothyroidism of 22%, 23.75%, 24%, 27.7%, and 17%, respectively. These five studies done in Indian population showed how big the burden of hypothyroidism in type 2 diabetes patients in India.

Han C<sup>11</sup> meta-analysis collected studies from Chinese population. Studies done by Liu W et al., Zhang NY et al., Deng X et al., Zang SF et al., Zhang MY et al., and Shi YS et al., that mentioned six studies held in 2007-2012, had a prevalence of subclinical hypothyroidism in type 2 diabetes mellitus of 10.85%, 12.02%, 12.81%, 12.31%, 12.5%, and 9.69%.<sup>11</sup> Compared to Indian and Chinese population, Indonesian population had lower proportion of hypothyroidism among diabetics. It can be caused by the high prevalence of iodine deficiency in China and India compared to Indonesian population.<sup>19,20</sup>

Explanation of variability in hypothyroidism prevalence in different diabetes populations can be made by several parameters such as adequacy of iodine intake which can affect the baseline thyroid status of population and presence of goiter, metabolic determinants like population glycemic achievement, metabolic syndrome, several comorbidities which related to thyroid dysfunction, and in epidemiology perspective, the total prevalence of diabetes in the population. In other words, studies about comorbidities of diabetes and thyroid dysfunction is population specific. Therefore, although it has been studied many times in other populations, data from

Indonesian population is still highly needed. In fact, this is the first study about thyroid dysfunction in Indonesian diabetics population.

While hypothyroidism has several mechanisms related to type-2 diabetes mellitus, the presence of hyperthyroidism can be back and forth since the established basic mechanism was the hypermetabolism in hyperthyroidism, affecting glucose intolerance (referring to impaired glucose tolerance or type 2 diabetes mellitus),<sup>21,22</sup> not contrariwise. It is also known that hyperthyroidism induces glucose intolerance by lowering both insulin secretion and peripheral insulin sensitivity.<sup>23</sup> On the other hand, there is also a hypothesis that both hyperthyroidism and diabetes are immune-related disorders which can be cross-linked and happen in the same individual. Whatsoever the mechanism and time-temporality, this two conditions must be treated separately with their own target respectively.

This study collected patients from tertiary hospital who received the state of the art treatment with many resources. They are treated ideally by endocrinology consultants, fellow endocrinologists, and internal medicine residents rotating in endocrinology division. This condition made the characteristics of the patients quite different from general population. It assumed that the prevalence of thyroid dysfunction was higher in general population who do not achieve diabetes treatment, education, and awareness like our study subjects got in Cipto Mangunkusumo Hospital.

Our study was set in a hospital-based population (i.e. outpatient polyclinic) which can be different from other community studies on thyroid disorders done in the past, such as Colorado Thyroid Disease Study,<sup>24</sup> Whickham Study,<sup>25</sup> and NHANES III<sup>26</sup> which was done nationally in the United States. In Indonesia, community survey in thyroidology field is still sparse except studies about iodine deficiency.<sup>27</sup> Similar to our study, many studies about thyroid dysfunction in type-2 diabetes mellitus patients was hospital-based studies.<sup>11</sup> The implication was that generalization of the studies can be made to patients in clinical practice setting, not in the community. Therefore, thyroid dysfunction screening was only recommended in patients attending healthcare facilities.

**Table 4.** The summary of studies on thyroid dysfunction in type 2 diabetes mellitus patients

Study	Population	Prevalence and proportion
Palma CCSSV et al. <sup>1</sup>	Cross-sectional study of 386 type 1 and type 2 diabetes mellitus patients, adult (Brazil).	Thyroid dysfunction 14.7%. Subclinical hypothyroidism 13% (type 1 diabetes) and 12% (type 2 diabetes).
Pasupathi P et al. <sup>4</sup>	Comparative cross-sectional study of 100 diabetic patients and 100 non-diabetic patients, adult (India).	Thyroid dysfunction 45% (hypothyroidism 28%, hyperthyroidism 17%).
Manjunath SC et al. <sup>28</sup>	Cross-sectional study of 100 type 2 diabetes mellitus patients, adult (India).	Subclinical hypothyroidism 13%.
Vikhe VB et al. <sup>15</sup>	Comparative cross-sectional study of 50 diabetic patients and 50 non-diabetic patients, adult (India).	Hypothyroidism 8%, subclinical hypothyroidism 14%.
Singh G et al. <sup>16</sup>	Comparative cross-sectional study of 80 diabetic patients and 80 non-diabetic patients, adult (India).	Subclinical hypothyroidism 15%, overt hypothyroidism 8.75%.
Radaideh ARM et al. <sup>29</sup>	Comparative cross-sectional study of 908 diabetic patients and 304 non-diabetic patients, adult (Yordania).	Thyroid dysfunction 12.5% (subclinical hypothyroidism 4.1%).
Gopinath B et al. <sup>30</sup>	Cohort of 113 type 2 diabetes patients and 950 non-diabetic subjects, age > 49 year-old (Australia).	Subclinical hypothyroidism 3.5%, overt hypothyroidism 1.8%.
Devi MA et al. <sup>10</sup>	Comparative cross-sectional study of 80 type 2 diabetes mellitus patients and 80 healthy subjects (India).	Clinical and subclinical hypothyroidism 24%.
Islam S et al. <sup>31</sup>	Comparative cross-sectional study of 50 type 2 diabetes mellitus patients and 50 healthy subjects (Bangladesh).	Serum fT3 of diabetes subjects were lower compared to control group
Kameda H et al. <sup>32</sup>	Cross-sectional study of 106 type 2 diabetes mellitus patients, adult (Japan).	Subclinical hypothyroidism 15%.
Yang JK et al. <sup>33</sup>	Cross-sectional study of 1170 type 2 diabetes mellitus patients, adult (China).	Subclinical hypothyroidism 10.85%.
El-Eshmawy MM et al. <sup>34</sup>	Comparative cross-sectional study of 147 prediabetes patients and 150 healthy subjects, adult (Egypt).	Subclinical hypothyroidism 16.3%.
Demitrost L et al. <sup>17</sup>	Cross-sectional study of 202 type 2 diabetes mellitus patients, adult (India).	Overt hypothyroidism 11.4%, subclinical hypothyroidism 16.3%.
Al-Geffari M et al. <sup>35</sup>	Cross-sectional study of 411 type 2 diabetes mellitus patients, adult (Saudi Arabian).	Hypothyroidism 15.3%, subclinical hypothyroidism 9.5%, overt hypothyroidism 0.5%.
Alam MJ et al. <sup>36</sup>	Comparative cross-sectional study of 104 type 2 diabetes mellitus patients and 104 healthy subjects, adult (Bangladesh).	Hypothyroidism 18.6%.
Shashi A et al. <sup>37</sup>	Comparative cross-sectional study of 117 type 2 diabetes mellitus & hypothyroid patients and 100 healthy subjects, age 20-50 year-old (India).	
Guney E et al. <sup>38</sup>	Cross-sectional study of 802 diabetes mellitus patients, adult (Turkey).	Hypothyroidism 1.1%.
Diez JJ et al. <sup>39</sup>	Cross-sectional study of 828 type 2 diabetes mellitus patients, age > 60 year-old (Spain).	
Distiller LA et al. <sup>40</sup>	Cross-sectional study of 918 type 2 diabetes mellitus patients, adult (South Africa).	Hypothyroidism 11.8%.
Chubb SAP et al. <sup>41</sup>	Prospective cohort of 420 type 2 diabetes mellitus patients, women (Fremantle Diabetes Study, Australia).	Subclinical hypothyroidism 8.6%.
Akbar DH et al. <sup>42</sup>	Comparative cross-sectional study of 100 type 2 diabetes mellitus patients and 100 healthy subjects, adult (Saudi Arabian).	Subclinical hypothyroidism 23%, hypothyroidism 15.3% (LADA group), subclinical hypothyroidism 4%, hypothyroidism 2.72% (type 2 diabetes group).
Diez JJ et al. <sup>43</sup>	Comparative cross-sectional study of 1112 type 2 diabetes mellitus patients and 911 healthy subjects, adult (Spain).	Overt hypothyroidism 9.9%, subclinical hypothyroidism 8.5%.
Fournier JP et al. <sup>44</sup>	Prospective cohort of 5689 diabetes patients & hypothyroid and 59937 diabetes patients (UK).	

**Table 4.** The summary of studies on thyroid dysfunction in type 2 diabetes mellitus patients

Study	Population	Prevalence and proportion
Chen HS et al. <sup>45</sup>	Cross-sectional study of 588 type 2 diabetes mellitus patients, adult (Taiwan).	Overt hypothyroidism 3.1%, hypothyroidism 0.9%, dan subclinical hypothyroidism 6.3%.
Yasuda T et al. <sup>46</sup>	Cross-sectional study of 159 type 2 diabetes mellitus patients, adult (Japan).	Subclinical hypothyroidism 17%.
Furukawa S et al. <sup>47</sup>	Cross-sectional study of 414 type 2 diabetes mellitus patients, adult (Japan).	Subclinical hypothyroidism 8.7%.
Sathyapalan T et al. <sup>48</sup>	Prospective cohort of 472 type 2 diabetes & hypothyroid patients and 472 type 2 diabetes & euthyroid, adult (UK).	
Uppal V et al. <sup>18</sup>	Case control study of 120 type 2 diabetes mellitus patients and 117 healthy subjects, adult (India).	hypothyroidism 17%.
Lambadiari V et al. <sup>49</sup>	Quasi-experimental, 17 healthy subjects, 22 offspring of diabetes patients, 15 impaired glucose tolerance subjects, and 24 type 2 diabetes mellitus patients.	
Ghazali SM et al. <sup>50</sup>	Comparative cross-sectional study of 64 type 2 diabetes mellitus patients and 36 healthy subjects, adult (Nigeria).	Subclinical hypothyroidism 4.7%, hypothyroidism 23.4%.
Ueckermann V et al. <sup>51</sup>	Cross-sectional study of 563 diabetes mellitus patients, adult (South Africa).	Subclinical hypothyroidism 0.9% from total diabetes patients, subclinical hypothyroidism 1.6% from type 2 diabetes patients.
Kashi Z et al. <sup>52</sup>	Comparative cross-sectional study of 103 type 2 diabetes mellitus patients and 103 healthy subjects, adult (Iran).	Hypothyroidism 17.5%.
Witting V et al. <sup>53</sup>	Cross-sectional study of 1957 type 2 diabetes mellitus patients, adult (Germany).	Hypothyroidism 17.83%.
Tamez-Perez HE et al. <sup>54</sup>	Comparative cross-sectional study of 1848 type 2 diabetes mellitus patients and 3313 healthy subjects, adult (Mexico).	Hypothyroidism 5.7%.
Swamy RM et al. <sup>55</sup>	Cross-sectional study of 58 type 2 diabetes mellitus patients, adult (India).	Hypothyroidism 12.06%, subclinical hypothyroidism 31.03%.
Al-Shibani et al. <sup>56</sup>	Cross-sectional study of 415 diabetes mellitus patients, adult (Iraq).	Hypothyroidism 4.1%, subclinical hypothyroidism 6.8%.

## CONCLUSION

This study revealed a quite high proportion of thyroid dysfunction in type 2 diabetes mellitus patients attending Endocrine and Diabetes Outpatient Polyclinic in Cipto Mangunkusumo Hospital. The proportion of hypothyroidism was 7.59% and hyperthyroidism was 2.31% with total thyroid dysfunction proportion of 9.9%. According to recommendation from several endocrinology and thyroidology organizations, TSH screening should be done first in patients attending healthcare facilities, not as mass screening in the community. It was suggested that screening for thyroid dysfunction can be selectively done in high risk condition as a part of comprehensive management in type-2 diabetes mellitus patients.

## ACKNOWLEDGMENTS

Our team thank Directorate of Research, Cipto Mangunkusumo Hospital, Jakarta for supporting our study with research grant in 2016. We also thank Division of Endocrinology and Metabolism Department of Internal Medicine Faculty of Medicine Universitas Indonesia/ Cipto Mangunkusumo Hospital for supporting our study.

## CONFLICT OF INTEREST

Authors declare that there are no conflict of interest in conducting the study and writing this manuscript. This study was granted by Operational Research Award Cipto Mangunkusumo Hospital 2016.

## REFERENCES

1. Palma CCSSV, Pavesi M, Nogueira VG, et al. Prevalence of thyroid dysfunction in patients with diabetes mellitus. *Diab Met Syndr*. 2013;58(5):1-5.
2. Mouradian M, Abourizk N. Diabetes mellitus and thyroid disease. *Diabetes Care*. 1983;6(5):512-20.
3. Johnson JL. Diabetes control in thyroid disease. *Diabetes Spectrum*. 2006;19(3):148-53.
4. Pasupathi P, Bakthavathsalam G, Saravanan G, Sundaramoorthi R. Screening for thyroid dysfunction in the diabetic/non-diabetic population. *Thyroid Science*. 2008;3(8):CLS1-6.
5. Umpierrez GE, Latif KA, Murphy MB, et al. Thyroid dysfunction in patients with type 1 diabetes. *Diabetes Care*. 2003;26:1181-5.
6. Gonzales GC, Capel I, Rodriguez-Espinosa J, Mauricio D, Leiva A, Perez A. Thyroid autoimmunity at onset of type 1 diabetes as a predictor of thyroid dysfunction. *Diabetes Care*. 2007;30(6):1611-2.
7. Brenta G. Diabetes and thyroid disorders. *Br J Diabetes Vasc Dis*. 2010;10:172-7.
8. Wang C. The relationship between type 2 diabetes mellitus and related thyroid diseases. *J Diab Res*. 2013;ID390534:1-9.
9. Harbuwono DS, Pramono LA, Hendaro H, Subekti I. Levothyroxine therapy in type 2 diabetes patient with hypothyroidism successfully improve several metabolic parameters. *Acta Med Indones – Indones J Intern Med*. 2016;48(2):145-7.
10. Devi MA, Singh NS, Singh LS. Thyroid hormone dysfunction in type 2 diabetic patients in urban areas of Manipur. *Int J Pharm Sci Int*. 2013;2(10):7-9.
11. Han C, He X, Xia X, et al. Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. *PloS One*. 2015;10(8):1-22.
12. Duntas LH, Orgiazzi J, Brabant G. The interface between thyroid and diabetes mellitus. *Clin Endocrinol*. 2011;75:1-9.
13. Joffe BI, Distiller LA. Diabetes mellitus and hypothyroidism: strange bedfellows or mutual companions? *World J Diabetes*. 2014;5(6):901-4.
14. Kunishige M, Sekimoto E, Komatsu M, Bando Y. Thyrotoxicosis masked by diabetic ketoacidosis. *Diabetes Care*. 2001;24(1):171.
15. Vikhe VB, Kanitkar SA, Tamakuwala KK, Gaikwad AN, Kalyan M, Agarwal RR. Thyroid dysfunction in patients with type 2 diabetes mellitus at tertiary care centre. *Nat J Med Res*. 2013;3(4):377-80.
16. Singh G, Gupta V, Sharma AK, Gupta N. Evaluation of thyroid dysfunction among type 2 diabetic Punjabi population. *Adv Biores*. 2011;2(2):3-9.
17. Demitrost L, Ranabir S. Thyroid dysfunction in type 2 diabetes mellitus: a retrospective study. *Indian J Endocr Metab*. 2012;16:S334-5.
18. Uppal V, Vij C, Bedi GK, Vij A, Banerjee BD. Thyroid disorders in patients of type 2 diabetes mellitus. *Ind J Clin Biochem*. 2013;28(4):336-41.
19. Lewis K. Iodine deficiency disorders still prevalent in China. *CMAJ*. 2009;181(8):E151-2.
20. Pandav CS, Yadav K, Srivastava R, Pandav R, Karmarkar MG. Iodine deficiency disorders (IDD) control in India. *Indian J Med Res*. 2013;138(3):418-33.
21. Dimitriadis GD, Raptis SA. Thyroid hormone excess and glucose intolerance. *Exp Clin Endocrinol Diabetes*. 2001;109(Suppl2):S225-39.
22. Brenta G. Why can insulin resistance be a natural consequence of thyroid dysfunction? *J Thyroid Res*. 2011;ID152850:1-9.
23. Roubsanthisuk W, Watanakejorn P, Tunlakit M, Sriussadaporn S. Hyperthyroidism induces glucose intolerance by lowering both insulin secretion and peripheral insulin sensitivity. *J Med Assoc Thai*. 2006;86(Suppl5):S133-40.
24. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526-34.
25. Vanderpump MP, Tunbridge WM, French JM. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol*. 1995;43:55-6.
26. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988-1028.
27. Pramono LA. Gangguan akibat kekurangan iodium di Indonesia: tinjauan epidemiologis dan kebijakan kesehatan. *Jurnal Kesmas*. 2009;4(2):71-7.
28. Manjunath SC, Krishnamurthy V, Puttaswamy BK, Prabhu S, Vishwanathaiah PM. Prevalence of subclinical thyroid disorders in type 2 diabetes mellitus. *Int J Med Public Health*. 2013;3(4):330-4.
29. Radaideh ARM, Nusier MK, Amari FL, et al. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. *Saudi Med J*. 2004;25(8):1046-50.
30. Gopinath B, Wang JJ, Kifley A, Wall JR, Leeder SR, Mitchehell P. Type 2 diabetes does not predict incident thyroid dysfunction in the elderly. *Diab Res Clin Pract*. 2008;82:e11-3.
31. Islam S, Yesmine S, Khan SA, Alam NH, Islam S. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. *Southeast Asian J Trop Med Public*. 2008;39(5):913-6.
32. Kameda H, Nagai S, Shimizu C, et al. Study of the relation between subclinical hypothyroidism and diabetic complications (abstract). *Endocrine Abstracts*. 2011;26:393.
33. Yang JK, Liu W, Shi J, Li YB. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. *Diabetes Care*. 2010;33(5):1018-20.
34. El-Eshmawy MM, El-Hafez HAA, El Shabrawy WO, Abdel Aal IA. Subclinical hypothyroidism is

- independently associated with microalbuminuria in a cohort of prediabetic Egyptian adults. *Diabetes Metab J.* 2013;37:450-7.
35. Al-Geffari M, Ahmad NA, Al-Sharqawi AH, Youssef AM, Al-Naqeb D, Al-Rubeaan K. Risk factors for thyroid dysfunction among type 2 diabetic patients in a highly diabetes mellitus prevalent society. *Int J Endocrinol.* 2013;ID 417920:1-6.
  36. Alam MJ, Mukti MNM, Hoque MM, Ali MI, Kamal MMK, Mallik SC, et al. Cross-sectional evaluation of thyroid hormone levels in non-diabetic and diabetic patients in Bangladeshi population. *Asian J Biol Sci.* 2013;6(4):228-33.
  37. Shashi A, Devi U, Singla S. Association between hypothyroidism and metabolic syndrome in type 2 diabetic patients: a cross-sectional study. *Int J Basic App Med Sci.* 2013;3(1):98-109.
  38. Guney E, Efe B, Akalin A, Kebapci N, Erenoglu E. Thyroid disease in diabetes mellitus. *Turkish J Endocr Med.* 1999;3:119-22.
  39. Diez JJ, Igleas P. Relationship between serum thyrotropin concentrations and metformin therapy in euthyroid patients with type 2 diabetes. *Clin Endocrinol.* 2013;78:505-11.
  40. Distiller LA, Polakow ES, Joffe BI. Type 2 diabetes mellitus and hypothyroidism: the possible influence of metformin therapy. *Diabet Med.* 2014;31:172-5.
  41. Chubb SAP, Davis WA, Inman Z, Davis TME. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. *Clin Endocrinol.* 2005;62:480-6.
  42. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. *Acta Diabetol.* 2006;43:14-18.
  43. Diez JJ, Iglesias P. An analysis of the relative risk for hypothyroidism in patients with type 2 diabetes. *Diab Med.* 2012;29:1510-4.
  44. Fournier JP, Yin H, Yu OHY, Azoulay L. Metformin and low levels of thyroid-stimulating hormone in patients with type 2 diabetes mellitus. *CMAJ.* 2014;186(15):1138-45.
  45. Chen HS, Wu TEJ, Jap TS, et al. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in type 2 diabetic patients. *Diab Med.* 2007;24:1336-44.
  46. Yasuda T, Kaneto H, Kuroda A, et al. Subclinical hypothyroidism is independently associated with albuminuria in people with type 2 diabetes. *Diab Res Clin Pract.* 2011;94:e75-7.
  47. Furukawa S, Yamamoto S, Todo Y, et al. Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus. *Endocrin J.* 2014;61(10):1011-8.
  48. Sathyapalan T, Manuchehri AM, Rigby AS, Atkin SL. Subclinical hypothyroidism is associated with reduced all-cause mortality in patients with type 2 diabetes. *Diabetes Care.* 2010;33(3):e37.
  49. Lambadiari V, Mitrou P, Maratou E, et al. Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. *Endocr.* 2011;39:28-32.
  50. Ghazali SM, Abbiyesuku FM. Thyroid dysfunction in type 2 diabetics seem at the University College Hospital, Ibadan, Nigeria. *Nig J Physiol Sci.* 2010;25:173-9.
  51. Ueckermann V, Van Zyl DG. The prevalence of subclinical hypothyroidism among patients with diabetes mellitus at the Kalafong Hospital Diabetes Clinic: a cross-sectional study. *JEMDSA.* 2013;18(2):106-10.
  52. Kashi Z, Akha O, Boroumand M, Bahar A, Mobini M. The correlation between type 2 diabetes mellitus and hypothyroidism [Abstract]. *J Mazand Univ Med Sci.* 2010;20(79):9-14.
  53. Witting V, Bergis D, Sadet D, Badenhoop K. Thyroid disease in insulin-treated patients with type 2 diabetes: a retrospective study. *Thyroid Reseach.* 2014;7(2):1-6.
  54. Tamez-Perez HE, Martinez E, Quintanilla-Flores DL, Tamez-Pena AL, Gutierrez-Hermosillo H, Leon-Gonzalez ED. The rate of diagnosed primary hypothyroidism in diabetic patients is greater than in the non-diabetic population: an observational study. *Med Clin (Barc).* 2012;138(11):475-7.
  55. Smawy RM, Kumar N, Srinivasa K, Manjunath GN, Prasad BDS, Ventakesh G. Evaluation of hypothyroidism as a complication in type 2 diabetes mellitus. *Biomed Res.* 2012;23(2):170-2.
  56. Al-Shibani MZ. Diabetes mellitus and thyroid disorders. *Kufa Med. J.* 2010;13(1):60-7.