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CORRELATION BETWEEN TSH, T3, T4 AND HISTOLOGICAL TYPES OF THYROID CARCINOMA

Hilda Fitriyani, T. Ibnu Alferraly, Lidya Imelda Laksmi

Department of Anatomical Pathology, Faculty of Medicine, University of Sumatera Utara/Adam Malik Hospital, Sumatera, Indonesia. E-mail: fitriyanihilda@yahoo.co.id

ABSTRACT

Thyroid carcinoma is a malignancy of the thyroid gland derived from follicular or parafollicular cells. Thyroid carcinoma is the most common endocrine gland malignancy and accounts for approximately 1% of all malignancies. Thyroid carcinoma ranked ninth of 10 most common carcinomas in Indonesia. It may occur at any age but is usually diagnosed between the 3rd and 6th decade. The incidence is three or four times higher in females than in males. Based on histological features thyroid carcinoma is classified into four major types: papillary, follicular, anaplastic and medullary carcinoma. Thyroid Stimulating Hormone (TSH), Triiodothyronine (T_3), Thyroxine (T_4) are thyroid gland hormones. Low T_3 and T_4 accompanied with high TSH levels are associated with malignancy in thyroid carcinoma. This study aimed to determine the correlation between TSH, T_3, T_4 hormone levels, and histological type of thyroid carcinoma at the Adam Malik Hospital Medan between 2013 and 2015. The study was a cross-sectional analytical study. The sample was be obtained using consecutive sampling method. Data were collected from medical records of thyroid carcinoma patients that had undergone pathological examination and thyroid function test at the Adam Malik Hospital Medan between 2013 and 2015. Based on the Chi-Square analysis, there was a significant difference between T3 hormone level with the histopathological type of thyroid carcinoma ($p<0.001$), however it did not apply to the level of T4 ($p = 0.120$) and TSH ($p = 0.328$).

Key words: Endocrine gland, thyroid carcinoma, TSH, T_3, T_4

INTRODUCTION

Thyroid nodule constitutes a common clinical problem; therefore, it is considered essential to remove thyroid carcinoma from it.[1] Thyroid carcinoma is a malignant tumor of the thyroid gland which comes from follicular cells or parafollicular cells. Thyroid gland is a part of the body which rarely undergoes malignancy. However, among the endocrine glands, thyroid carcinoma belongs to the malignant type of endocrine gland which is most commonly found; it represents in about 1% of all malignancies in the whole body.[2-6]

It seems that the incidence of thyroid cancer is gradually increasing. In England and Wales, there are 900 new cases and 250 deaths caused by thyroid carcinoma each year. In 2001, the data from Cancer Research, UK, revealed that there were 1,200 new cases of thyroid carcinoma in England and Wales with a yearly incidence of 3.5 per 100,000 females and 1.3 per 100,000 males.[7] Up to the present, thyroid carcinoma has not been found in Indonesia even though in the Pathology Registration in 2010, it ranked the ninth of ten most common malignant diseases.[8]

Thyroid carcinoma can attack any person at any age although children are rarely affected by it. Most tumors are diagnosed in the third decade up to the sixth decade of age. The incidence of this disease is three to four times more frequently undergone by females rather than by males.[9] The average age when it is diagnosed is in the middle of 40 years old up to the beginning of 50 years old for the papillary type, 50 years old for follicular and medullary types and 60 years old for poorly differentiated and undifferentiated types.[2] The age when it is diagnosed is one of the most consistent prognostic factors in patients with papillary and follicular thyroid carcinoma. The risk for recurrence and death increase, along with the growing older, especially when one is 40 years old. Children below 10 years old have a higher risk of recurrence than the older children or adolescents.

Histopathologically, thyroid carcinoma is divided into four main types: papillary carcinoma, follicular carcinoma, anaplastic carcinoma which comes from epithelial follicle thyroid and medullar carcinoma which comes from parafollicular cells as calcitonin (C cell) thyroid secretion.[3,9] Besides carcinoma, the malignancy of non-epithelial and metastatic components of the other organs can also be found in thyroid.[3] The case of papillary carcinoma is the most common form of thyroid cancer (85%-90%), followed by follicular carcinoma (5%-10%), medullary carcinoma (about 2%) and anaplastic carcinoma (less than 2%) of thyroid cancer, especially in elderly patients.[9]

Many researches point out that the higher concentration of thyroid stimulating hormone (TSH) is even in a normal threshold, concerning thyroid carcinoma diagnosis in patients with nodule thyroid.[10-12] The patients who became the research subjects of Jonklaas in 2008 had higher TSH content (mean = 1.50 mIU/L, CI 1.22-1.78mIU/L, p= 0.0017) than that of the patients with benign diseases (mean= 1.01 mIU/mL, CI 0.84-1.18 mIU/L). Jonklaas divided TSH values into four quartiles: quartile one (0.34-1.1 mIU/L), quartile two (1.2-2.0 mIU/L), quartile three (2.1-2.8 mIU/L), and quartile four (2.9-3.7 mIU/L). The serum content of the three upper quartiles (quartile 2-4) is used as a filtering test for differentiated thyroid carcinoma. There is more risk for suffering from thyroid carcinoma in patients with TSH content in the three upper quartiles of TSH value, compared to patients with TSH concentration in lower quartile of TSH value (odds ratio = 8.7, CI 2.2-33.7).[10]

Haymart *et al.* revealed that there was a correlation between the higher serum content of TSH with the last stage of thyroid carcinoma.[13] The result of this research gave the impression that TSH content might play its role in the development of thyroid carcinoma.[12]

Jonklaas was also the first person who found lower triiodothyronine (T_3) in patients with thyroid carcinoma (mean = 112.6 ng/dL, CI 103.8-121.4 ng/dL, p= 0.015), compared to patients with benign diseases (mean = 129.9 ng/dL, CI l121.4-138.4 ng/dL). There was no difference between the two groups in free thyroxine (FT_4) (p = 0.78).[10]

However, Jonklaas' research was contrary to the research done by Ye *et al.* who retrospectively studied 2,052 patients with nodule thyroid who were suspected of suffering from malignancy of thyroid based on *Sibajah* (cytological biopsy of fine needle) or ultra-sonography; they were patients with nodules which rapidly developed or nodule fixed to the adjacent structure and underwent thyroidectomy from June 2006 until August 2008. From their researches, it was found that TSH serum content (>4.94 mIU/L) was not related to the number of risks for the incidence of thyroid carcinoma. Besides that, free triiodothyronine (FT_3) and FT_4 statistically were not different from the two groups of patients who underwent thyroid carcinoma (p = 0.306 and p = 0.337).[14]

Based on the explanation of the background and the problems above, the researchers wanted to find out 'whether there was a correlation of the increasing TSH serum content and the decreasing T_3 and T_4 with histological types of thyroid carcinoma at the Department of Anatomical Pathology, Faculty of Medicine, USU/ Adam Malik Hospital, in the period of 2013-2015.

The objective of the research was to find out the correlation of serum content of TSH, T_3, and T_4 with the histopathological types of thyroid carcinoma at the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, during the period of 2013-2015.

METHODS

This cross-sectional study was conducted in the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015. The purpose of this study was to find the relationship between TSH, T3, and T4 serum levels with thyroid carcinoma histopathological types. Clinical data from thyroid carcinoma patients and TSH, T3, and T4 serum levels were obtained from patients medical records. After that, the researcher collected and re-evaluated the histopathological slides. Slides that were adequate to be re-evaluated were included in the inclusion criteria, but inadequate slides were reprocessed. After being reprocessed, adequate slides were included in the inclusion criteria, but the inadequate slides were excluded. Complete data and adequate slides were made as study samples. Complete data were grouped based on TSH, T3, and T4 hormone levels. Adequate slides were double-blind re-evaluated by the researcher with the assistance of two pathologists. Each slide determined the type of histopathology based on WHO classification 2004, which was a papillary carcinoma, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma. Then, the histopathology slide evaluation results were processed based on a statistical programme and reported in tables. To statistically analyze the relationship between TSH, T3, and T4 hormone levels with the type of thyroid carcinoma histopathology, the researcher used the Chi-Square test to identify the relationship between variables.

RESULT AND DISCUSSION

During the period of January 1st, 2013 – December 31th, 2015, the data from medical records of patients histopathologically diagnosed as thyroid carcinoma showed that there were 44 samples with the following characteristics:

Table 1. Distribution of characteristic of thyroid carcinoma patients

Characteristic of patients (n=44)	Total (n)	Percentage (%)
Age (year)		
< 14	1	2.3
15 - 29	9	20.5
30 - 44	9	20.5
45 - 59	19	43.2
60 - 74	6	13.5
Gender		
Male	11	25
Female	33	75
Hormone content		
TSH (µIU/mL)		
< 0,35	10	22.7
0.35 – 1.17	11	25.0
1.18 – 1.96	8	18.2
1.97 – 4.94	8	18.2
> 4.94	7	15.9
T_3		
0.58-1.59	33	75
< 0.58	4	9.1
> 1.59	7	15.9
T_4		
4.87-11.72	27	61.4
< 4.87	12	27.3
> 11.72	5	11.3
Histopathological type		
Papillary carcinoma	32	72.7
Follicular carcinoma	10	22.7
Medullary carcinoma	0	0
Anaplastic cacinoma	2	4.6

Distribution of thyroid carcinoma patients based on age at the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period from 2013 to 2015 showed that the patients average age was 42.42 years. It was also found that 19 respondents (43.2%) were in the age group of 45-59 years and only one respondent (2.3%) was below 14 years old. This finding was in accordance with the research done by Ye et al. who stated that the majority of thyroid carcinoma patients were in the age group of 30-44 years (n = 449 patients, 43.8%). Nevertheless, the high rate of the incidence of tumor in the age group of 45-60 years (n = 370 patients, 36.1%) should not be ignored.14 However, this result was not consistent with the research done by Polyzos who found that 22.2% of thyroid carcinoma patients were ≥ 70 years old and the fewest patients (5.9%) were 50-59 years old. Statistically, this difference was significant (p = 0.022).[11]

The distribution of thyroid carcinoma patients based on gender at the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 1) showed that of the 44 thyroid carcinoma patients, 33 of them (75%) were females and 11 of them (25%) were males. This finding was in accordance with the research done by Ye *et al.* who found that the significant level of malignancy increased in female patients (82.3%) (p= 0.014).[14] However, it was contrary to the research

done by Polyzos who stated that male patients significantly had a higher level of malignancy (28.3%) than female patients (6.8%, p<0.001).[11]

Distribution of thyroid carcinoma patients based on the category of TSH, T_3, and T_4 hormone content at the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 1) showed that the majority of thyroid carcinoma patients (n= 11 patients, 25%) had TSH hormone content of 0.35-1.17µIU/mL T_3 normal hormone content (75%) and T_4 normal hormone content (61.4%).

Distribution of thyroid carcinoma patients based on histopathological types at the Department of Anatomical Pathology, the Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 1) showed that 32 patients (72.7%) suffered from papillary carcinoma, 10 patients (22.7%) suffered from follicular carcinoma, 2 patients (4.6%) suffered from anaplastic carcinoma and no patient suffered from medullary carcinoma. The incidence of papillary thyroid carcinoma was probably caused by the increasing use of early detection method through USG examination and FNAB. Another reason was the change in specific core to become the morphological criteria of papillary thyroid carcinoma.[2,4] This finding was in accordance with the researches done by Fiore *et al.* who found that most of the cases of thyroid malignancy (98.05%) were papillary thyroid carcinoma.[14,15]

In the categorical correlation between TSH hormone content and histopathological types of thyroid carcinoma examined at the Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 2), using Chi-Square test, it was found that there was no significant difference between TSH hormone content and histopathological types of thyroid carcinoma (p = 0.328). According to Ye *et al.* there was an increase in the risk for thyroid cancer, along with the increase in TSH serum content even though in the normal threshold. The higher the TSH content, the higher the chance for the incidence and the last stage of the malignant tumor. Anaplastic thyroid carcinoma is the most malignant carcinoma, compared with papillary and follicular thyroid carcinoma. From this research, it was found that TSH serum content (>4.94 µIU/mL) was not related to malignant thyroid cancer like anaplastic thyroid carcinoma. This result was supported by the research done by Ye *et al.* who found that TSH serum content (>4.94 µIU/mL) was not related to the high risk for thyroid cancer.[14] The reason was that the size of the group samples with TSH serum content (>4.94 µIU/mL), and anaplastic carcinoma sample were smaller than those in the other groups. However, it was contrary to the research done by Haymart *et al.* who found that the frequency of malignancy in thyroid increased, along with the increase in TSH serum content (16% when TSH < 0.06 mIU/L vs. 52% when TSH ≥ 5 mIU/L). The mean of TSH content was higher in the last stage of cancer (4.9± 1.5 mIU/L in stage III/ IV vs. 2.1± 0.2 mIU/L in stage I/II).[13]

Categorical correlation between T_3 hormone content and histopathological types of thyroid carcinoma at the Anatomical Pathology Department, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 3) showed that the majority of the patients with papillary and follicular thyroid had normal T_3 content (27 patients and 6 patients respectively). However, all the patients with anaplastic thyroid carcinoma (2 patients) had lower T_3 hormone content. The result of Chi-Square test showed that there was a significant difference in the categorical correlation between T_3 hormone content and histopathological types of thyroid carcinoma (p< 0.001). This finding was supported by the research done by Jonklaas who found that T_3 content was lower in thyroid carcinoma patients (mean= 112.6ng/dL, CI 103.8-121.4 ng/dL, p=0,015) than benign diseases (mean= 129.9 ng/ dL, CI 121.4-138.4 ng/dL).[10]

Table 2. Categorical correlation between TSH hormone content and histopathological types of thyroid carcinoma

Categorical TSH hormone	Histopathological type			Total
	Papillary carcinoma	Follicular carcinoma	Anaplastic carcinoma	
< 0.35	7	3	0	10
0.35 – 1.17	7	4	0	11
1.18 – 1.96	7	1	0	8
1.97 – 4.94	7	2	0	8
> 4.94	4	0	2	7
Total	32	10	2	44

Table 3. Categorical correlation between T3 hormone content and histopathological types of thyroid carcinoma

T_3 categorical hormone	Histopathological type			Total
	Papillary carcinoma	Follicular carcinoma	Anaplastic carcinoma	
Normal	27	6	0	33
Lower	2	0	2	4
High	2	5	0	7
Total	32	10	2	44

Table 4. Categorical correlation between T_4 hormone content and histopathological types of thyroid carcinoma

T_4 categorical hormone	Histopathological type			Total
	Papillary carcinoma	Follicular carcinoma	Anaplastic carcinoma	
Normal	28	3	0	31
Lower	2	0	2	4
High	2	7	0	9
Total	32	10	2	44

Categorical correlation between T4 hormone content and histopathological types of thyroid carcinoma at Department of Anatomical Pathology, Faculty of Medicine, USU/Adam Malik Hospital, in the period of 2013-2015 (Table 4) showed that the majority of patients with papillary and follicular thyroid had normal T4 content (28 patients and 3 patients respectively). However, all of the patients with anaplastic thyroid carcinoma (2 patients) had a lower T3 hormone content. The result of Chi-Square test showed that there was no significant difference in the categorical correlation between T4 hormone content and histopathological types of thyroid carcinoma ($p = 0.021$). In some literature, it was found that T4 serum content which had been examined was free T4 serum (free T4/FT4). Jonklaas and Ye et al. found that FT4 content had no significant difference in thyroid and thyroid carcinoma benign disease.10,14

CONCLUSION AND SUGGESTION

Based on the Chi-Square analysis, there was a significant difference between T3 hormone level with the histopathological type of thyroid carcinoma ($p<0.001$) however, it did not apply to T4 ($p = 0.120$) and TSH level ($p = 0.328$).

This research only found that T3 hormone level was significantly correlated with thyroid carcinoma thus the researcher suggested that further researches were needed with a longer time and larger samples.

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