Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2022.18218

Glucose tolerance status in patients with newly diagnosed papillary thyroid carcinoma

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Received 10 Sep. 2020
Accepted 19 Nov. 2020
Published online 30 Nov. 2020

Keywords: Papillary thyroid cancer, Insulin resistance, Oral glucose tolerance test

Abstract

Introduction: Thyroid cancer is one of the most common endocrine system malignancies with 9 out of 100,000 estimated annual incidence and papillary carcinoma is the most common type of thyroid cancer. Papillary thyroid cancer (PTC) increases blood insulin levels by creating insulin resistance. Many studies have suggested the role of insulin resistance in the prognosis of PTC.
Objectives: The aim of the present study was to determine the prevalence of impaired glucose tolerance in patients with PTC and to compare the relationship between insulin resistance and disease severity, lymph node involvement and distant metastasis.
Patients and Methods: In this cross-sectional study, 68 patients with PTC diagnosis examined for metastasis by whole body scan and cervical lymph nodes by ultrasound were included in this study. A 75 g oral glucose tolerance test was also performed on subjects.
Results: In this study 68 patients (76.5% female and 23.5% male) were enrolled. The mean age of the patients was 44.2 ± 13.8 years. The mean serum level of fasting blood glucose (FBG in patients was 103.14 ± 21.8 mg/dL and the mean 2 hours past-prandial was 145.12 ± 22.37 mg/dL. Statistically significant lymphatic involvement was observed in 25% of patients between insulin resistance and nodal involvement ($P = 0.03$). A significantly higher metastasis was also observed in 16.2% of patients with glucose intolerance ($P < 0.05$).
Conclusion: The results indicated that the rate of insulin resistance in PTC patients is significantly higher and glucose intolerance in these patients is associated with increased lymphatic involvement and increased risk of metastasis and poor prognosis.

Citation: Aghamohammadzadeh N, Fadayi Haghi T, Houshyar J, Najafipour F. Glucose tolerance status in patients with newly diagnosed papillary thyroid carcinoma. Immunopathol Persa. 2022;x(x):e18218. DOI:10.34172/ipp.2022.18218.

Introduction

Thyroid cancer is the most common malignancy of endocrine system, affecting approximately 9 out of 100 000 people per year (1). Many thyroid cancers initially present as asymptomatic nodules, and papillary thyroid cancer (PTC) is the most common thyroid malignancy, which accounts for about 70 to 90% of thyroid cancers. The average age of diagnosis is 45 years and the onset of the disease occurrs in childhood and incidence increases with age (2). PTC originates from epithelial follicular cell which responses to TSH stimulation like normal epithelium tissue (3). In general, cancers cause insulin resistance by multiple mechanisms such as impaired glucose tolerance and diabetes (4). Glucose tolerance test is one of the most effective methods to predict the incidence of diabetes in patients. In some cases blood glucose level between 140 to 200 mg/dL is considered as impaired glucose control two hours after 75 g glucose consumption and the patient needs serious control and attention regarding diabetes (5).

Key point

Insulin resistance and impaired glucose tolerance are associated with increased incidence of nodal lymph involvement and metastasis and decreased papillary thyroid cancer prognosis.

PTC is one of the most common cancers causing increased blood insulin level by insulin resistance induction. Insulin as an anabolic hormone stimulates cell growth. Similar properties are also observed regarding the thyroid gland which in turn increases the volume of the cancerous mass, the volume of the thyroid gland, and the number of thyroid nodules. Recent studies suggest that insulin resistance is associated with increased resistance to PTC treatment. In addition, due to the larger mass size of the nodule, patients with insulin resistance have a poor prognosis and the recurrence rate is higher compared

to the other patients (6,7). Several studies suggest the role of insulin resistance in the severity of PTC; however, the higher prevalence of insulin resistance in these patients is debated. The determination of the insulin resistance prevalence and impaired glucose tolerance is a prelude to overt diabetes. In case with higher insulin resistance prevalence, urgent decision making is necessary; because accurate control of blood sugar and improvement of insulin resistance with common treatments can be effective in the prognosis of the underlying disease and additionally reduces the underlying problems which are developed with prolonged diabetes (3,8). Measurement of the fasting blood glucose (FBG) and glucose tolerance test is the simplest method to assess insulin resistance. In this regard, when the blood glucose level is between blood glucose is between 140 to 200 mg/dL, the glucose control is impaired and more severe diabetic control is needed (5).

Objectives

According to above mentioned information and the need for accurate assessment of glucose metabolism in PTC patients, we decided to determine the prevalence of impaired glucose tolerance in PTC patients, compare blood glucose changing with thyroid mass volume and the likelihood of metastasis.

Patients and Methods

Study design

This cross-sectional study was performed on patients with newly diagnosed PTC referred to Imam Reza hospital at Tabriz University of Medical Sciences from September 2016 to September 2017. The minimum estimated sample size for this study with 95% confidence level and 80% power was 68. Histopathologically confirmed PTC patients which were respectively assessed by whole-body scan and ultrasound regarding the metastasis and cervical lymph nodes status were enrolled in this study. Then, glucose tolerance test was done by using 75 g of oral glucose to assess insulin resistance. Glucose was measured based on enzymatic and colorimetric methods. Glucose is first hydrolyzed by glucose oxidase with gluconic acid and hydrogen peroxide, and then hydrogen peroxidase reacts with 4-hydroxy benzoic acid and 4-aminoantipyrine in the presence of peroxidase to form a red color that concentrates the color intensity with concentration. Available in the sample and the measurable wavelength for glucose is 546 nm. In the present study, blood glucose levels were determined using a Pars Azmoun kit and an autoanalyzer (Alcyon 300).

Inclusion criteria were patients with PTC referring to the endocrine clinic with a pathological diagnosis. History of diabetes, malignancy treatment at the same time or previous history of another malignancy, thyroid gland surgery, pregnancy, and carbohydrate cycle disorders were also considered as exclusion criteria.

FBG, glucose tolerance test, the presence of distant metastases, existence of nodal involvement (lymphadenopathy), the size of the lymph nodes involved in the presence of lymphadenopathy, and diagnosed variant of carcinoma were then evaluated. Thyroid mass size, metastasis to distant areas and nodal involvement, which play a key role in determining the outcomes of the disease in these patients were also evaluated.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study was approved by the ethics committee of Tabriz University of Medical Sciences (code: IR.GUMS.REC.1398.076). Accordingly, informed consent was obtained from all the patients. This work has been done as part of the internal medicine specialty dissertation by Taghi Fadayi Haghi. This study was supported by Endocrine Research Center at Tabriz University of Medical Sciences, Iran (Grant No. 62248).

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) software 23.0. Chi-square test was used for comparing mean values between two groups. $P<0.05$ was also considered as statistically significant.

Results

76.5% and 23.5% of patients were female and male, respectively. Mean age of individuals was 44.24 ± 13.8 years. Metastasis was observed in 16.2% with a significantly higher frequency in patients with glucose intolerance ($P<0.05$). Mean serum level of FBG and 2-hour post-prandial (2hpp) were 103.21 ± 14.8 mg/dL and 145.12 ± 22.37 mg/dL, respectively. The mean tumor size in all subjects was 24.8 ± 10.07 mm. According to the pathological reports, classic type was the most common type of tumor with a frequency of 67.65%. The frequencies of follicular and tall cell variants were also 17.65% and 7.35%, respectively. Other uncommon variants of tumors including columnar, trabecular, hobnail, multifocal and oncocytic, also shared 7.35% of frequency (Table 1).

No significant relationship was found between the tumor variant and patients' gender ($P=0.09$). Regarding the mean age of patients with each of the PTC variants, a significant relationship was also found between the group with tall cell variant and other groups ($P=0.002$; Table 2).

Considering the GTT >140 mg/dL as glucose intolerance, 37 patients (54.4%) had glucose intolerance and were considered as insulin resistant. No significant correlation was found between GTT results between the groups with different PTC variants ($P>0.05$). The mean tumor size in patients with insulin resistance was also clinically larger than that of non-insulin resistant patients; however, this difference was not statistically significant ($P=0.096$). The mean dimensions of tumor in two groups with and without insulin resistant were 26.10 ± 7.2 and 22.6±9.6 mm, respectively ($P=0.088$) (Table 3). Moreover, 25%

Table 1. General characteristics of the patients

Parameter	Values
Gender (% female)	76.5
Age (y)	44.24±13.8
Metastasis (%)	16.2
FBG (mg/dL)	103.21±14.8
2hpp	145.12±22.37
Tumor size (mm)	24.8±10.07
Tumor Type, (%)	
Classic type	67.65
Follicular variant	17.65
Tall cell variant	7.35
Other	7.35

Data are presented as mean ± standard division (SD) or percent.

Table 2. Mean age of patients with each of the PTC variants.

PTC variants	Mean age
Classic type	43.72±13.45
Follicular variant	42.17±8.79
Tall cell variant	64.6±8.23
Other types	33.6±14.7
Total	43.24±13.8

of patients had lymph node involvement, which was significantly correlated with the presence of insulin resistance ($P=0.03$).

Discussion

Comparison of the present results with global statistics shows that the percentage of insulin resistance is significantly higher in PTC patients. As in our study, insulin resistance was observed in more than 50% of the patients; according to statistics, only about 10-25% of the population is reported to have insulin resistance regarding the racial differences (9-13). The results of this study also showed that not only the percentage of insulin resistance in patients with PTC is higher than normal population, but also disease complications and lymph node involvement and distant metastasis have a significant correlation with insulin resistance. Since the prognosis of PTC is directly related to the presence of lymphadenopathy and the presence or absence of distant metastasis and regarding the fact that the patient's survival severely is reduced in the presence of metastasis; therefore, it can be concluded that the existence of insulin resistance is directly correlated with reduced PTC prognosis (14). Pitoia et al(6) showed that insulin resistance is significantly associated with increased PTC resistance to therapy. In addition, patients with insulin resistance had a worse prognosis compared to other patients. Sahin et al (7) also reported a higher insulin resistance rate in PTC patients than that of the average

Table 3. Tumor size, tumor dimension and lymph node involvement in insulin resistant and non-insulin resistant patients

Parameters	Insulin resistant	Non-insulin resistant	*P*
Number (%)	35 (54.4)	31 (45.6)	0.6
Tumor size (mm)	26.7±10.2	22.6±9.6	0.096
Tumor dimension (mm)	26.1±7.2	22.6±9.6	0.088
Lymph node involvement (%)	25	75	0.03

Data are presented as mean±standard division (SD) or percent. $P<0.05$ was considered as statistically significant.

population which was directly correlated with tumor size. Bae et al (15) in a study on 1272 individuals (PTC patients and controls) also reported similar results. However, no association was observed between the presence of insulin resistance and the severity of PTC symptoms and complications which may be due to study on only female population, and different sample size. Paulus et al (3) also found that the prevalence of diabetes in new diagnosed PTC patients is significantly higher.

The results of the above mentioned studies are in line with our results; since all of them suggest the higher insulin resistance rate in PTC patients. Additionally, previous studies have also indicated the association of decreased PTC prognosis and insulin resistance which are in line with our findings. Balkan et al (16) in a study compared 41 patients with thyroid cancer and 41 patients with nodular goiter. Data revealed that despite the effect of insulin resistance on increased thyroid cells growth and increased thyroid nodules prevalence, it does not have a higher prevalence in patients with thyroid cancer.

Bae et al (15) in their study also compared two groups of patients with thyroid tissue defects. Therefore, the different findings in their study may be due to different modeling of their study with the present study.

In a cohort study by Shi et al (17) on different variants of 6282 PTC patients, it has been reported that 74.8%, 17.9%, and 8.3% of patients were classic, follicular and tall cell variants, respectively. Similar results have also been reported by Nath et al (18) study, regarding the different PTC variants prevalence, which are consistent with our findings.

Regarding the size of the primary tumor in PTC patients, different findings have also been reported by studies. Based on these studies, the average size of these tumors varies from 8.2 mm to 40 mm depending on the gender, variant and the presence of co-morbidities (19-22). The average size of the tumor in our study was 24.8 mm.

Conclusion

The results of the present study indicate that the rate of insulin resistance in PTC patients is significantly higher than the other individuals. Additionally, insulin resistance and impaired glucose tolerance are associated with increased incidence of nodal lymph involvement and

metastasis and decreased PTC prognosis.

Limitations of the study

The major limitation of this study is small sample size due to the rarity of the disease.

Acknowledgments

This work has been done as part of the Internal Medicine Specialty Dissertation for Taghi Fadayi Haghi. The authors would like to acknowledge Endocrine Research Center and Department of Internal Medicine at Tabriz University of Medical Sciences (Iran) for their great help.

Authors' contribution

Naser Aghamohammadzadeh and Taghi Fadayi Haghi designed the research. Farzad Najafipour conducted the study and prepared the final draft of the manuscript. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission and redundancy) have been completely observed by the authors.

Funding/Support

This study was supported by Endocrine Research Center at Tabriz University of Medical Sciences, Iran (Grant # 62248).

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