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AssociationbetweenBodyMass IndexandSeverityAccordingofClassification ofThyroid Cancer

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1. Abstract

Purpose: Obesity is associated with aggressive pathological featuresandpoorclinicaloutcomesinbreastandprostatecancers. However, the associations between excess weight and prognostic factorsforthyroidcancerareuncertain.Thisstudyaimedtoevaluatetheassociationsbetweenbodymassindex(BMI)andseverity according of classification of thyroid cancer.

Methods: Retrospective analysis of 4485 patients with thy- roid cancer was performed. Patients were grouped according to BMI(underweight,normalweight,overweightandobesity)-based WorldHealthOrganizationstandardizedcategories.Clinicopathological factors were analyzed and compared between normal and other groups.

Results:According to the results, 3789 patients were women (84.5%)andmeanagewas47.1years.4338patients(96.7%)were diagnosedwithPTC.FTCwere115(2.6%),MTAware24(0.5%), ATC were 5(0.1%). There were no significant associations be- tween BMI quartiles and Multifocality, cervical lymph node me- tastasis, or distant metastasis. Higher BMI were significantly as- sociated with extrathyroidal extension of PTC ($P < 0.001$). And higher BMI were significantly associated with advanced TNM stage ($P=0.005$).

Conclusion:IncreasedBMImightelevatetherisksofaggres- sive clinicopathological features of PTC, such as extrathyroidal invasionandadvancedTNMstage.However,therewerefewcases exceptforPTC,whichmadeitdifficulttofindstatisticallysignificantresults.Toconfirmthisresult,furtherstudieswithlong-term follow-upandmorepatientsarerequired.

2. Introduction

Recently,theincidenceofthyroidcancerhasbeengrowingworld- wide[1].Higherprevalenceofthyroidcancercanbeexplainedin partbythefactthatdevelopmentanduseofneckultrasonography andultrasound-guidedfine-needleaspirationhaveledtoincreased diagnosticrateforasymptomaticthyroidcancer[2].Additionalas- pects, such as changes in exposure to environmental factors, may also play a role in explaining such increase in prevalence.

However,consideringthatincreaseinprevalenceofthyroidcancer coincidedwithincreasednumberofearlycancerwithsmalltumor size, aswell asvarioustumor sizesand stages, it issuspected that thereareotherunidentifiedfactorsbesidesadvancesindiagnostic tools [3].The main risk factors for thyroid cancer are exposure to ionizingradiation,ahistoryofbenignthyroiddisease,andafamily history of thyroid cancer [4, 5, 6]. Overweight and obesity, ex- pressedasa highBMI,are possibleriskfactorsforthyroid cancer

Obesityisassociatedwithonsetandprogressionofmanycancers, including those of esophagus, colon, kidney, breast, skin, rectum, and gallbladder [7]. Obesity is the second most common, pre- ventable, and modifiable cause of carcinogenesis, after smoking, thereisworldwidevariationthatisdependentonthedifferentinci- dences of obesity [8].Although obesity is a known risk factor for carcinogenesis it does not seem to equally impact on all types of cancer.However,therearefewreportsontherelationshipbetween obesityandthyroidcancerandtheunderlyingmechanismislarge- ly unknown [9 -12].

A review of studies on the association between thyroid cancer and BMI showed that recent studies are reporting that obesity is one of the factors considered to cause increase in thyroid cancer [13,14].Inaddition,someretrospectivestudieshavereportedthat increase in BMI is associated with aggressive clinicopathological featuresinpatientswithpapillarythyroidcarcinoma[15].However,therelationshipbetweenobesityandpoorprognosisassociated with thyroid cancer is still controversial [16], and while the basis for the correlation between excessive weight and malignant thyroid tumor has not yet been completely identified, the traditional riskfactorsofthyroidcancerstillremainradiationexposure,high iodine intake, and family history of thyroid cancer [17]. For future evident on the potential negative effect of obesity on thyroid cancer,itisdeterminedthatclinicalinterventionincludingweight lossprogramsforoverweightandobesepeopleandthyroidcancer screening guidelines would play an important role. Accordingly, the present study aimed to investigate the correlation between clinicopathological parameters and being overweight in relationtothyroidcancertousethefindingstoidentifythecorrelationbetweenBMIandcanceraggressivenessinrelationtothyroidcancer.

3. Methods

Thestudypopulationincluded4,485patientswhoreceivedsurgicaltreatmentatKosinUniversityGospelHospitalbetweenJanuary 2005 and December 2015 and were subsequently diagnosed with thyroidcancer.Allmedicalrecordsofthesepatients,includinghistopathologicalresults,wereretrospectivelyanalyzed.BMIofeach patientwascalculatedusingtheheightandweightmeasuredatthe timeofadmissionforthesurgery.UsingthestandardBMIcategoriesfromtheWorldHealthOrganization(WHO),thepatientswere dividedintofourgroups:underweight(18.5),normal(18.5∼24.9), overweight(25.0∼29.9),andobese(≥30.0).[18].Theclinicopathological factors of the normal group were compared to those of other groups, while tumor size, multifocality, lymph node (LN) metastasis, advancedTNM staging, and recurrence were compared asfactorssuggestingaggressivenessofthetumor.AdvancedTNM staging was divided according to the classification system given

by the American Joint Committee on Cancer (AJCC; 8th edition) [19], and stages 1 and 2 were compared and analyzed against stages 3 and 4, representing advanced cancer. Recurrence was defined as new pathologically confirmed lesion in a patient who had been determined to be in remission during the follow-up observation period. Univariate analyses including chi-square test and one-way analysis of variance (ANOVA) were performed to determine the significance between BMI and the variables, while multivariate analysis was performed on the factors suggesting cancer aggressiveness. A logistic regression model was used to estimate the odds ratio (OR) and 95% confidence interval (CI), while adjusted OR was calculated by adjusting for age, gender, and TSH value. All statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) with statistical significance set to P-value <0.05.

4. Results

Among a total of 4,485 patients, there were 3,789 females (84.5%) and 696 males (15.5%). The mean age was 47.1 years (14~82 years) and mean BMI was 24.0±3.3 (15.0~41.2). Based on BMI categories, the patients were divided into the underweight (n=112, 2.5%), normal (n=2,824, 63.0%), overweight (n=1,341, 29.9%), and obese (n=208, 4.6%) groups.

Based on Pathology, There were 4,338 (96.7%) patients with papillary thyroid cancer, 115 (2.6%) patients with Follicular thyroid carcinoma, 24 (0.5%) patients with Medullary thyroid carcinoma, 5 (0.1%) patients with Anaplastic thyroid carcinoma.

The mean tumor size was 12.1 mm (2~72mm), there were 2,602 cases (58.0%) with tumor size ≤1cm and 1,470 cases (32.8%) had multifocality. Extrathyroid invasion and LN metastasis was found in 2,100 cases (46.8%) and 1,824 cases (40.7%), respectively, where LN metastasis involved the central neck LN in 1,430 cases (31.9%) and lateral neck LN in 394 cases (8.8%). In advanced TNM staging, the number of cases classified as stage 1, 2, 3, and 4 was 2,768 (61.7%), 84 (1.9%), 1,435 (32.0%), and 197 (4.4%), respectively, while in adjusted TNM staging for statistical analysis, there were 2,853 cases (63.6%) of stages 1 and 2 and 1,632 cases (36.4%) of stages 3 and 4. The mean follow-up period was 1,721±464.2 days, and during the follow-up period, there were 88 cases (2.0%) of recurrences. Of those cases, recurrence found in the central neck LN, lateral neck LN, and contralateral thyroid in 3 cases (3.4%), 62 cases (70.5%), and 23 cases (26.1%), respectively (Table 1).

There were few cases except for PTC, which made it difficult to find statistically significant results (Table 2).

1) Normal group versus underweight group

The mean BMI in the normal and underweight group was 22.3 ± 1.6 and 17.7 ± 0.7, respectively (Table 2), while there were no significant differences between the two groups with respect to tumor size, multifocality, extrathyroid invasion, LN metastasis, recurrence, and thyroiditis. However, in the univariate analysis, the normal and underweight groups showed differences based on TNM staging (P=0.000), but such differences were not found in the multivariate analysis (OR 0.255 [0.062~1.049], P=0.058) (Tables 3, 4).

2) Normal group versus overweight group

The mean BMI in the overweight group was 26.8 ± 1.3 (Table2), while there were no significant differences between the two groups with respect to LN metastasis, TNM staging, recurrence, and thyroiditis. However, as compared to the normal group, the overweight groups showed differences in tumor size (12.0mm±8.7, p=0.024), multifocality (30.5% vs 36.7%, p=0.000), extrathyroid invasion (44.3% vs 51.6%, p=0.000), and TNM stage (p=0.000) in

the univariate analysis and statistically significant differences in multifocality(OR1.300[1.127~1.499],P=0.000)andextrathyroid invasion (OR 1.322 [1.152~1.517], P=0.000) in the multivariate analysis (Tables 3, 4).

3) Normalgroupversusobesegroup

ThemeanBMIintheobesegroupwas32.2±2.2(Table2), while therewerenosignificantdifferencesbetweenthetwogroupswith respect to tumor size, LN metastasis, TNM staging, and recurrence.However,ascomparedtothenormalgroup,theobesegroup showed differences in multifocality (OR 1.671 [1.241~2.251], P=0.001), extrathyroid invasion (OR 1.630 [1.206~2.202], P=0.001), and thyroiditis (OR 0.642 [0.449~0.919], P=0.016) in both univariate and multivariate analyses (Tables 3, 4).

Table1: Baselineclinicopathologicalcharacteristicsofpatientsdiagnosedwiththyroidcarcinoma

Characteristic	Total**(N=4485)**
Gender	
Female	3789 (84.5%)
Male	696 (15.5%)
MeanAge (years)	47.1 ±11.5
<55	1888 (42.1%)
≥55	2597 (57.9%)
BMI(kg/m2)	24.0 ±3.3
Pathology	
Papillary thyroid carcinoma	4338 (96.7%)
Follicular thyroid carcinoma	115(2.6%)
Medullary thyroid carcinoma	24 (0.5%)
Anaplastic thyroid carcinoma	5 (0.1%)
Etc.	3 (0.1%)
Tumorsize(mm)	12.1 ±9.0
≤10	2602 (58.0%)
> 10	1883 (42.0%)
Multifocality	1470 (32.8%)
Extrathyroidal invasion	2100 (46.8%)
LN metastasis	1824 (40.7%)
Central LN	1430 (31.9%)
Lateral LN	394 (8.8%)
TNMstage	
1	2768 (61.7%)
2	85 (1.9%)
3	1435 (32.0%)
4	197 (4.4%)
Recurrence	88(2.0%)
central LN	3 (3.4%)
lateral LN	62 (70.5%)
opposite gland	23 (26.1%)
Thyroditis	1174(26.2%)

Table2: Clinicopathologicalcharacteristicsofpatientsdiagnosedwiththyroidcarcinoma

	Underweight (N=112)	**Normal (N=2824)**	**Overweight (N=1341)**	**Obese (N=208)**	**p**
Gender					0
Female	109 (97.3%)	2457 (87.0%)	1052 (78.4%)	171 (82.2%)	
Male	3 (2.7%)	367 (13.0%)	289 (21.6%)	37 (17.8%)	
Mean age (years)	40.1 ±13.0	46.3 ±11.3	49.7 ±11.2	46.2 ±11.9	0
< 55	78 (69.6%)	1264 (44.8%)	446 (33.3%)	100 (48.1%)	
≥55	34 (30.4%)	1560 (55.2%)	895 (66.7%)	108 (51.9%)	
BMI(kg/m2)	17.7 ±0.7	22.3 ±1.6	26.8 ±1.3	32.2 ±2.2	0
Pathology					0.564
PTC	109 (97.3%)	2741 (97.1%)	1288 (96.0%)	200 (96.2%)	
FTC	3 (2.7%)	64 (2.3%)	42 (3.1%)	6 (2.9%)	
MTC	0 (0.0%)	14 (0.5%)	9 (0.7%)	1 (0.5%)	
ATC	0 (0.0%)	4 (0.1%)	1 (0.1%)	0 (0.0%)	
Etc.	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	
Tumorsize(mm)	12.4 ±9.2	11.8±8.7	12.5 ±9.5	13.0 ±10.0	0.036
≤10	65 (58.0%)	1653 (58.5%)	772 (57.6%)	112(53.8%)	0.592
> 10	47 (42.0%)	1171(41.5%)	529 (41.1%)	96 (46.2%)	
Multifocality	32 (28.6%)	859 (30.4%)	491 (36.6%)	88 (42.3%)	0
Extrathyroidal invasion	46 (41.1%)	1248 (44.2%)	687 (51.2%)	119(57.2%)	0
LymphnodeMets	46 (41.1%)	46 (41.1%)	543 (40.5%)	87 (41.8%)	0.987

Central LN	35 (31.2%)	904 (32.0%)	423 (31.5%)	68 (32.7%)	0.998
Lateral LN	11(9.8%)	244 (8.6%)	120 (8.9%)	19 (9.1%)	
TNMstage					0
1	93 (83.0%)	1814 (64.2%)	724 (54.0%)	137 (65.9%)	
2	2 (1.8%)	55 (1.9%)	27 (2.0%)	1 (0.5%)	
3	13 (11.6%)	847 (30.0%)	513 (38.3%)	62 (29.8%)	
4	4 (3.6%)	108 (3.8%)	77 (5.7%)	5 (2.4%))	
Recurrence	3 (2.7%)	50 (1.8%)	30 (2.2%)	3 (1.5%)	0.665
central LN	0 (0.0%)	2 (4.0%)	0 (0.0%)	1 (20.0%)	0.282
lateral LN	3 (100.0%)	35 (70.0%)	22 (73.3%)	2 (40.0%)	
opposite gland	0 (0.0%)	13 (26.0%)	8 (26.7%)	2 (40.0%)	
Thyroditis	35 (31.2%)	770 (27.3%)	327 (24.4%)	42 (20.2%)	0.025

Table3: Univariateanalysisofparametersaccordingtobodymassindex

	Underweight (N=109, 2.5%**)**	**Normal (N=2741,** 63.2%**)**	**Overweight (N=1288,** 29.7%**)**	**Obese (N=200,** 4.6%**)**
Tumorsize(mm)	11.9±8.5	11.3±8.0	12.0 ±8.7	12.1 ±8.3
Pvalue	0.46	Reference	0.024	0.19
Multifocality	30 (27.5%)	837 (30.5%)	473 (36.7%)	86 (43.0%)
Pvalue	0.572	Reference	0	0
Extrathyroid invasion	44 (40.4%)	1214 (44.3%)	664 (51.6%)	115(57.5%)
Pvalue	0.477	Reference	0	0
LN metastasis	46 (42.2%)	1132(41.3%)	535 (41.5%)	87 (43.5%)
Pvalue	0.929	Reference	0.913	0.592
TNMstaging				
1	91 (83.5%)	1764 (64.4%)	697 (54.1%)	132 (66.0%)
2	2 (1.8%)	50 (1.8%)	22 (1.7%)	0 (0.0%)
3	12 (11.0%)	826 (30.1%)	496 (38.5%)	60 (30.0%)
4	4 (3.7%)	101 (3.7%)	73 (5.7%)	8 (4.0%)
Pvalue	0	Reference	0	0.287
Recurrence	3 (2.8%)	45 (1.6%)	27 (2.1%)	3 (1.5%)
Pvalue	0.614	Reference	0.374	1
Thyroditis	34 (31.2%)	757 (27.6%)	321 (24.9%)	40 (20.0%)
Pvalue	0.479	Reference	0.078	0.024

Table4: Multivariateanalysiswithoddsratio(OR)and95%confidenceinterval(CI)

	Underweight (N=109, 2.5%**)**	**Normal (N=2741,** 63.2%**)**	**Overweight (N=1288,** 29.7%**)**	**Obese (N=200,** 4.6%**)**
Tumorsize(mm)				
OR (95% CI)	1.01 (0.985~1.035)	1	1.007 (0.998~1.017)	1.012 (0.994~1.031)
Pvalue	0.455	Reference	0.113	1.198
Multifocality				
OR (95% CI)	0.862 (0.558~1.331)	1	1.3 (1.127~1.499)	1.671 (1.241~2.251)
Pvalue	0.502	Reference	0	0.001
Extrathyroid invasion				
OR (95% CI)	0.846 (0.565~1.267)	1	1.322 (1.152~1.517)	1.63 (1.206~2.202)
Pvalue	0.417	Reference	0	0.001
LN metastasis				
OR (95% CI)	1.098 (0.733~1.644)	1	0.898 (0.780~1.034)	0.885 (0.653~1.198)
Pvalue	0.651	Reference	0.135	0.428
AdvancedTNM staging				
OR (95% CI)	0.255 (0.062~1.049)	1	0.775 (0.476~1.261)	0.763 (0.277~2.097)
Pvalue	0.058	Reference	0.304	0.599
Recurrence				
OR (95% CI)	1.727 (0.525~5.675)	1	1.239 (0.762~2.012)	0.835 (0.256~2.727)
Pvalue	0.368	Reference	0.387	0.765
Thyroditis				
OR (95% CI)	1.197 (0.790~1.813)	1	0.863 (0.741~1.005)	0.642 (0.449~0.919)
Pvalue	0.396	Reference	0.058	0.016

5. Discussion

IncreasedBMIhasbeenassociatedwithahighercancerincidence forseveralmalignancies,includingthyroidcancer[9].Inaddition, obesity has been reported to be associated with poor pathological prognostic correlates and the development of recurrence and metastases for several cancer types, including breast, prostate, and colon cancers [7]. Obesity can cause impairment in the metabolic processwithinthebodyandalsocauseabroadrangeofendocrine abnormalities involving the pituitary, pancreas, gonad, adrenal glands, and thyroid glands [20].

Recent studies are also reporting that obesity is associated with increased incidence of thyroid cancer [21]. Kim et al. [21]. Performed a case–control study in which the authors hypothesized that overweight and obesity would be associated with higher risk of PTC in an adolescent Korean population (BMI≥25 at age 18 years). They included 1549 cases and selected 15 490 controls matched 1: 10 for age (±5 years) and sex who were all more than 20 years age. After adjustment for potential confounders, a BMI at least 25 at the age of 18 was associated with a higher risk of developing PTC compared with those with BMI less than 23 [hazard ratios 4.31 (3.57–5.22)], both in men [hazard ratios 6.65 (4.76–9.27)] and women [hazard ratios 3.49 (2.74–4.43)] [22]. In an analysis conducted in the US, increase in the incidence of thyroid cancer according to increase in BMI was observed in both malesandfemales,whileastudyconductedintheFrenchPolynesian region with relatively high prevalence of thyroid cancer also confirmed such correlation. Especially in the study from French Polynesian region, BMI ≥25 in those aged 18 years or older, the periodwhentheyareenteringadulthood,showedhighprobability of thyroid cancer (OR 6.2, P < 0.01) [23].

OtherreportshavealsoindicatedthathigherBMImanifestsmore aggressive forms of cancer, including breast cancer. [21]According to Harari et al. [21], in terms of thyroid cancer, obese patients showed higher stage and more aggressive form of PTC. In their study,thepercentageofthoseinstage3or4amongnormal,overweight, obese, and morbidly obese groups was 13.2%, 22.7%, 24.3%, and 35.7%, respectively, while the relative risk in overweight, obese, and morbidly obese groups was 1.94, 2.11, and 3.67, respectively (P=0.04) [24].

According to a report by Feng et al. [24] of 417 papillary thy-roid cancer patients, 31.6% were overweight and 6% were obese. After adjusting for clinicopathological features, overweight was associatedwithvascularinvasion[hazardratios3.9(1.06–14.31)], while obesity was associated with ETE [hazard ratios 6.14 (1.81–0.89)] and vascular invasion [hazard ratios 9.19 (1.73–51.71)], when compared with those who were normal weight. No statistically significant differences were reported in PTC recurrence among the BMI groups [25]. In an analysis by Kim et al. [25] BMIatleast25atage18yearswaspositivelyassociatedwithETE [hazard ratios 1.5 (1.06–2.12)] and tumor stage at least 2 [hazard ratios1.94(1.03–3.65)],butnotwithlymphnodestageatleast 1 or BRAF V600E mutation positivity compared with those with BMI less than 23. [22]. Similar results were reported by Grani et al. [22], who investigated the association between overweight or obesity and aggressive features of DTC among 432 patients in Italy [n=154 (35.6%) overweight and n=86 (19.9%) obese]. Obese patientsweresignificantlymorefrequentlymaleandoldage.Most PTCs were at low-risk (67.8%) and the majority had never been treated with 131I (69.2%). In their analysis, BMI as a categorical variable was not associated with aggressive DTC features, while patientswithETEhadasignificantlyhigherBMIwhenevaluated as a continuous variable [26].

Inthisstudy,theresultsdemonstratedthatBMIwascloselyasso- ciated with aggressive oncologic features of PTC, such as tumor multiplicityandextrathyroidinvasion.Tumormultiplicityisnota strongprognosticatorofPTC,butbasedonthis,itwasdetermined that obesity can affect the aggressive tendency of PTC (invasive metastasis) and cancer susceptibility of patients, such as multifocality. Moreover, the univariate and multivariate analyses results inthepresentstudyconfirmedthattheobesegrouphadhigherrate of multifocality and extrathyroid invasion than the normal group, whiletherateofthyroiditiswasactuallylower.Inthecomparison between the overweight and normal groups, the univariate analysis results also confirmed higher rate of multifocality, extrathyroid invasion, and advanced TNM staging, while the multivariate analysis results confirmed higher rate of only multifocality and extrathyroidinvasion.Inthecomparisonbetweentheunderweight and normal groups, there were no factors that showed significant differences.

Thyroiditisbeinglowerintheobesegrouphasnotbeenmentioned in existing reports, and thus, additional studies on this topic are needed.Thepresentstudyhadthelimitationsofbeingaretrospec- tive study with relatively short follow-up period. Moreover, the studydidnotfullyaccountforconfoundingfactors,suchassmok- ing, drinking, activity level, and diabetes. However, a major significance of the study can be found in the fact that it analyzed the correlationbetweenobesityandaggressivenessofPTC,including recurrence,usingahighnumberofcasesandconfirmedthatBMI is closely associated with aggressive oncologic features, such as multifocality and extrathyroid invasion.

6. Conclusions

RetrospectiveanalysisoftheassociationbetweenBMIandcancer aggressiveness in patients with PTC showed that the obese group showedhigherrateofmultifocalityandextrathyroidinvasionthan the normal group.Although various cause may play a role in the onset of PTC, maintaining BMI at an appropriate level may be a methodforpreventingtheonsetofPTCwithmoreaggressiveten- dencies,suchasmultifocalityandextrathyroidinvasion.However,

there were few cases except for PTC, which made it difficult to find statistically significant results.To confirm this result, further studies with long-term follow-up and more patients are required.

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