Comparative Sonographic Assessment of Thyroid Volume in Adult Diabetics and Nondiabetics in the University of Uyo Teaching Hospital, Uyo

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Abstract

Background: Diabetes mellitus and Thyroid disorders are known to mutually influence each other. Thyroid dysfunction especially when undiagnosed has a negative impact on metabolic control, likewise, increased levels of insulin in insulin resistance has a proliferative effect on thyroid tissue. **Aims:** The study aimed to sonographically measure and compare Thyroid gland volume (TV) in adults with diabetes and apparently healthy subjects, as well as determine the effect of thyroid stimulating hormone (TSH), glycosylated haemoglobin (HbA1c) and anthropometry on TV. **Patients, Materials and Methods:** This was a case-controlled study carried out over 6 months in the University of Uyo Teaching Hospital, from April to September 2019, among 70 adult diabetics and an equal number of non-diabetics. The thyroid volume was correlated with gender, age, height, weight, BMI, waist circumference, duration of diabetes, TSH and HbA1c. **Results:** The overall mean TV was higher in diabetics (6.8 ± 3.5cm3 versus 6.3 ± 2.9cm3). Among those with diabetes, TV was significantly higher in those with poor glycemic control (p=0.020). A positive correlation was found between TV and duration of diabetes and height. The mean thyroid volume was higher among the male population of both groups. An equal number of subjects had abnormal (high) TSH levels in both study arms. There was no correlation between TV and most of the anthropometric indices. **Conclusion:** Sonographic thyroid volume is higher among diabetics and it has a positive correlation with gender, height, duration of diabetes and HbA1c.

Keywords: Diabetes mellitus, Thyroid gland volume, Ultrasonography, Biochemical parameters

Introduction

Diabetes mellitus is a group of diseases characterized by persistently high blood glucose levels due to deficiency in insulin production, inactivity of insulin, or both.[1]

The diagnosis in adults is by a persistent fasting plasma glucose level >126 mg/dl (7.0 mmol/L), two-hour postprandial plasma glucose level of 200 mg/dl (11.1 mmol/L), or glycosylated hemoglobin (HbA1c) >6.5%.[1]

The mere presence of diabetes reduces a person's quality of life. Diabetes mellitus is a major public health problem in developed as well as developing countries. According to the International Diabetes Federation, one in every 11 adults has diabetes (415 million worldwide), and by 2040, it is estimated that one in 10 adults (642 million worldwide) will suffer from it.[2] In Africa, diabetes reportedly affects over 15.9 million adults.[3] Of the total global expenditure, 12% was spent on diabetes.[2]

Thyroid disease is common in the general population and a prevalence of 11% has been reported in Europe,[4] with several reports documenting higher prevalence in the diabetic

Access this article online

Quick Response Code:

Website: www.njmonline.org

DOI: 10.4103/NJM.NJM_192_21

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How to cite this article: Obasi UO, Akintomide AO. Comparative sonographic assessment of thyroid volume in adult diabetics and nondiabetics in the University of Uyo Teaching Hospital, Uyo. Niger J Med 2022;31:98-105.

Submitted: 13-Nov-2021 **Revised:** 04-Dec-2021
Accepted: 09-Dec-2021 **Published:** 22-Feb-2022

population.[5-7] In Calabar, Nigeria, a high incidence of abnormal thyroid hormone levels has been reported among people with diabetes, revealing a prevalence of 46.5%.[8]

Diabetes mellitus and thyroid disorders are known to influence each other mutually.[9] Hyperthyroidism leads to uncontrolled diabetes, while hypothyroidism may lead to recurrent attacks of hypoglycemia.[10] Increased levels of circulating insulin in insulin resistance have a proliferative effect on thyroid tissue with a resultant increase in thyroid volume (TV).[11] Therefore, early sonographic detection of changes in TV may help physicians anticipate possible deterioration in glycemic control and adjust treatment accordingly. Ultrasonography is a nonionizing imaging modality, which gives excellent anatomical detail of the thyroid gland. It is an easy, reproducible, affordable, and noninvasive method to evaluate the gland's morphology, volume, and lesions.[12] Studies on comparative sonographic evaluation of TV among adults with diabetes and nondiabetics abound outside Nigeria[13-17] but scanty locally. This study aims to sonographically assess the thyroid gland volume in adults with diabetes and the age- and gender-matched apparently healthy subjects living in an iodine-sufficient coastal city. We also want to determine the effect of biochemical parameters such as thyroid-stimulating hormone (TSH) and HbA1c, duration of diabetes, age, gender, and anthropometric parameters on TV, thereby increasing the body of knowledge on the thyroid gland in diabetic and healthy adults.

Patients, Materials and Methods

This was a case control study to sonographically evaluate the thyroid gland volume among 70 people with diabetes and 70 nondiabetic adults in the Ultrasound Unit of the Department of Radiology, University of Uyo Teaching Hospital (UUTH) over a six-month period from April to September 2019. Diabetic patients were recruited from the diabetes clinic, while the age and sex-matched nondiabetic adult volunteers were students and staffs of the hospital. Ethical clearance for this study was obtained from the Ethics and Research Committee of UUTH. Subjects were examined after written informed consent had been obtained. Subjects' names were not included in the datasheet to ensure confidentiality. Data analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA, 2011). Tables, bar charts, and line diagrams were used to present the results.

Statistical test of significance was done using the student t-test and Fisher's Exact Test where appropriate, while analysis of variance (ANOVA) was used for continuous variables. Pearson's chi square test was applied for categorical data.

At 95% confidence interval, two-tailed $P \leq 0.05$ were considered statistically significant.

Inclusion criteria for diabetic subjects

1. Consenting adults of both sexes who are 18 years and above
2. Subjects who are on treatment for diabetes.

Exclusion criteria for diabetic subjects

1. Subjects without diabetes (fasting plasma glucose <5.5 mmol/L)
2. Subjects <18 years of age.
3. Nonconsenting subjects
4. Subjects with anterior neck swelling or clinical evidence of thyroid disease such as exophthalmos
5. Pregnant diabetic patients
6. Subjects with previous history of neck trauma, surgery, or irradiation.

Inclusion criteria for nondiabetics

1. Subjects without clinically diagnosed diabetes mellitus (fasting plasma glucose <5.5 mmol/L)
2. Subjects without anterior neck swelling or clinical evidence of thyroid disease
3. Consenting subjects who are 18 years and above.

Exclusion criteria for nondiabetics

1. Subjects with clinically diagnosed diabetes mellitus
2. Subjects <18 years old
3. Nonconsenting subjects
4. Pregnant women
5. Subjects with anterior neck swelling or clinical evidence of thyroid disease
6. Subjects with previous history of neck trauma, surgery, or irradiation.

Technique

Subjects were consecutively recruited using the systematic sampling method with a sampling interval of three. The recruited subjects were asked to come the next day after fasting for at least eight hours.

Blood specimen samples were collected for fasting plasma glucose, HbA1c, and TSH. Thereafter, the subjects were sonographically examined to measure the TV using a real-time, grayscale 7.5 MHz linear transducer of a Mindray DC-30 (Shenzhen Mindray, Bio-medical Electronics Co. Ltd., China 2016) ultrasound machine.

Sonographic procedure

With the subject lying supine on the couch, a sandbag was placed under each shoulder to hyperextend the neck in a comfortable position. After applying coupling gel over the anterior aspect of the neck, the transducer was placed directly over the gel. Using the common carotid artery and the internal jugular vein as landmarks, the thyroid gland was identified. The normal gland has a medium-level homogeneous echotexture. The craniocaudal dimension (length) of each lobe was measured in the longitudinal plane, and the transverse and anteroposterior dimensions (width and thickness) were obtained in the transverse scanning plane, as depicted in Figures 1 and 2, respectively. To improve reproducibility and minimize intra-observer errors in the measurement, the mean of three values was obtained for each lobe, and the volume was calculated using the Ellipsoid formula:

Volume = Length × Width × Thickness × 0.479[18]

The total volume of the thyroid gland was obtained by the addition of the volume of each lobe. The isthmus contributes little to the total TV; hence, it was excluded from the calculation.[12] Other pathologies such as nodules were sought.

A flexible measuring tape was used to measure the waist circumference, calibrated weighing scale (Avery Co. Ltd, England) for the weight, and a clinic stadiometer for the height. These were recorded in centimeters (cm), kilograms (kg), and meters (m), respectively. The body mass index (BMI) was calculated using the formula:

BMI (kg/m^2) = weight/$height^2$[19]

A pretested, interviewer-administered questionnaire was used to document sociodemographic profile, past medical history/comorbidities, other clinical histories such as duration of diabetes and drug history, anthropometric measurements, as well as the biochemical and sonographic data of subjects.

The normal laboratory reference values for the measured biochemical parameters are as follows:

- FPG: 3.0–5.5 mmol/l
- TSH: 0.4–7.0 microinternational units/ml
- HbA1C: 4.0%–<5.7%.

According to the American Diabetes Association, good glycemic control in a nonpregnant adult with diabetes is defined by HbA1c levels <7.0%, 7.0% is borderline, while levels >7.0% indicate poor glycemic control.[20]

To the best of our knowledge, there is no agreed Nigerian normal TV range or an indigenous textbook on sonographic anatomy to provide a reference locally. However, research findings in other parts of the country revealed lower normal values than the 10–15 ml and 12–18 ml in adult females and males, respectively, documented in foreign textbooks for the Western population.[21]

Results

Table 1 shows the sociodemographic characteristics of the participants. Those aged 40 years and above accounted for 87.9% (n = 123) of the total sample size. In addition, more females participated in the study, and there was no significant difference between cases and control regarding religion, ethnicity, and occupation.

Table 2 correlates the TV with the biochemical parameters. Among the diabetics, the mean TV was slightly higher in those with normal TSH than those with abnormal (high) TSH (6.9 ± 3.6 vs. 6.1 ± 0.1). This difference was not statistically significant (P = 0.309). Mean TV was also higher among people with diabetes who had poor control than those who had borderline levels of HbA1c and good control. The difference was statistically significant (P = 0.020). At *post hoc* test, the difference in TV between those with borderline control and good control was not statistically significant (P = 1.000).

In the apparently healthy adults, mean TV was higher in the subgroup with high TSH than those with normal TSH. The difference was statistically significant. Based on the HbA1c

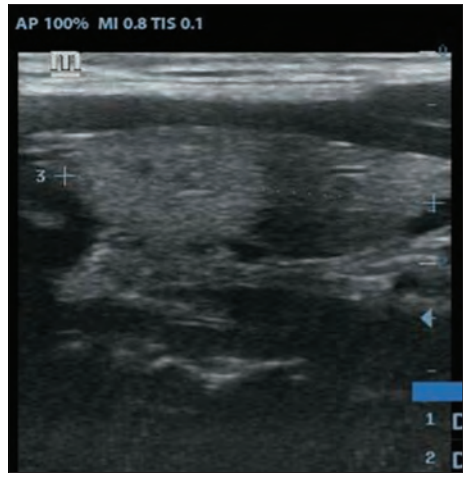

Figure 1: Longitudinal B-mode sonogram showing measurement of the right thyroid lobe's craniocaudal diameter (length)

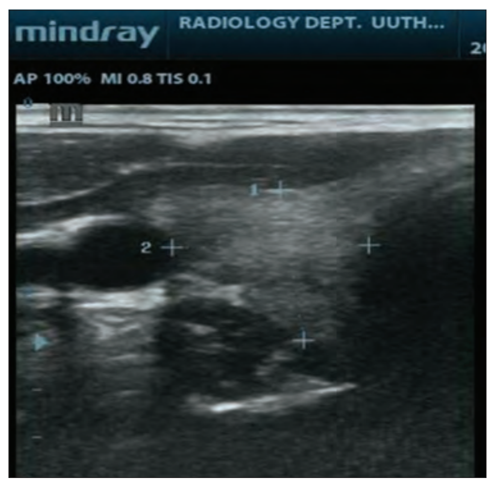

Figure 2: Transverse B-mode sonogram showing measurement of the right thyroid lobe's anteroposterior (thickness) and transverse (width) diameters

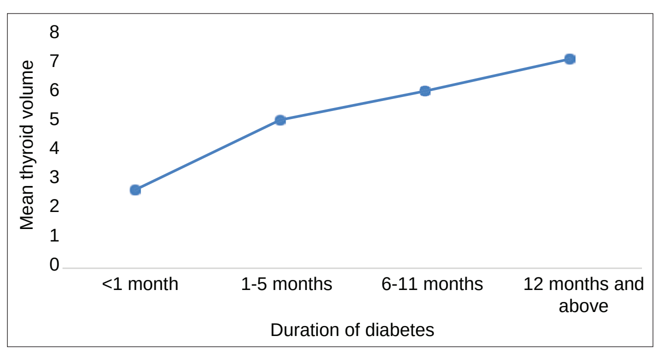

Figure 3: A line graph showing the relationship between mean thyroid volume and duration of diabetes among adult diabetics (P = 0.205)

Table 1: Sociodemographic characteristics of adult diabetics and apparently healthy adults (n=140)

	Diabetics, *n* (%)	Healthy, *n* (%)	Total (*n*=140), *n* (%)	FET	*P*
Age group/years					
18-29	0 (0.0)	1 (1.4)	1 (0.7)	FET, 1.354	1.000
30-39	8 (11.4)	8 (11.4)	16 (11.4)		
40-49	18 (25.7)	19 (27.1)	37 (26.4)		
50-59	22 (31.4)	21 (30.0)	43 (30.7)		
60-69	19 (27.1)	17 (24.3)	36 (25.7)		
70-79	3 (4.3)	4 (5.7)	7 (5.0)		
Sex					
Male	20 (28.6)	20 (28.6)	40 (28.6)	0.036	0.850
Female	50 (71.4)	50 (71.4)	100 (71.4)		
Religion					
Christianity	69 (98.6)	70 (100.0)	139 (99.3)	FET, 1.393	1.000
Traditional religion	1 (1.4)	0	1 (0.7)		
Ethnicity					
Igbo	4 (5.7)	4 (5.7)	8 (5.7)	FET, 5.372	0.421
Yoruba	1 (1.4)	4 (5.7)	5 (3.6)		
Efik	5 (7.1)	1 (1.4)	6 (4.3)		
Ibibio	43 (61.4)	47 (67.1)	90 (64.3)		
Annang	14 (20.0)	13 (10.0)	27 (19.3)		
Others	3 (4.3)	1 (1.4)	4 (2.9)		
Occupation					
Civil servant	28 (40.0)	32 (45.7)	60 (42.9)	FET, 2.855	0.457
Self-employed	28 (40.0)	20 (28.6)	48 (34.3)		
Unemployed	14 (20.0)	18 (25.7)	32 (22.8)		

FET: Fisher's exact test

Table 2: Relationship between thyroid volume and biochemical parameters (thyroid-stimulating hormone and hemoglobin A1c) in adult diabetics and apparently healthy adults

Biochemical parameters	Adult diabetics (*n*=70)			Apparently healthy adults (*n*=70)		
	Mean thyroid volume	Test statistics	*P*	Mean thyroid volume	Test statistics	*P*
TSH						
Normal	6.9±3.6	*t*-test, 0.309	0.758	6.2±2.8	*t*-test, 2.288	0.025*
Abnormal	6.1±0.1			12.9±0.0		
HbA1c						
Good control	5.7±3.2	ANOVA, 4.147	0.020*	5.4±3.1	*t*-test, 0.820	0.445
Borderline	5.6±1.8			6.5±2.3		
Poor control	8.1±3.7					

*Statistically significant. TSH: Thyroid-stimulating hormone, HbA1c: Hemoglobin A1c or Glycosylated hemoglobin, ANOVA: Analysis of variance

levels, the mean TV was higher among healthy adults within the prediabetic range, though the difference was not statistically significant.

Table 3 shows that the mean TV was higher among diabetic adults compared to their apparently healthy counterparts. Across age groups, the mean TV is not significantly different in both the diabetic and apparently healthy groups. Similarly, the mean TV did not differ significantly across the BMI categories and different waist circumferences. Although the mean TV is higher in males than females in both groups, it was not significantly different statistically among people with diabetes ($P = 0.616$), while it was in the apparently healthy group ($P = 0.023$).

Figure 3 shows that the TV increased steadily with the increasing duration of diabetes. However, this did not show a significant difference statistically ($P = 0.205$).

The bar chart in Figure 4 shows that the proportion of respondents with heterogeneous echo pattern was higher among the diabetic adults compared with the nondiabetic adults, 59.6% ($n = 28$) versus 40.4% ($n = 19$).

Table 4 illustrates that among people with diabetes, the proportion of those with heterogeneous echo pattern was higher among those with poor control than those with good control, while the proportion of those with homogeneous echo pattern was higher among those with

Table 3: Relationship between mean thyroid volume and age, gender, height, body mass index, and waist circumference among diabetic and apparently healthy adults

Variable	Adult diabetics (n=70)			Apparently healthy adults (n=70)		
	Mean thyroid volume	Test statistics	P	Mean thyroid volume	Test statistics	P
Age group (years)						
18-29	-	ANOVA, 0.792	0.534	3.9±0.0	ANOVA, 0.727	0.606
30-39	7.0±3.0			8.0±2.7		
40-49	5.8±2.0			5.9±3.7		
50-59	7.2±3.4			6.2±2.5		
60-69	7.0±4.2			6.3±3.0		
70-79	9.3±8.5			5.9±0.6		
Total mean thyroid volume±SD	6.8±3.5			6.3±2.9	0.943	0.347
Sex						
Male	7.2±3.5	*t*-test, 0.504	0.616	7.6±3.5	*t*-test, 2.319	0.023*
Female	6.7±3.6			5.8±2.5		
BMI (kg/m²)						
Underweight	7.8±0.0	ANOVA, 0.062	0.980	-	ANOVA, 0.178	0.837
Normal	6.6±3.8			6.1±2.5		
Overweight	6.8±4.4			6.3±3.7		
Obese	6.9±3.0			6.6±2.7		
Height (m)						
1.40-1.49	6.2±4.1	ANOVA, 1.191	0.323	4.2±0.6	ANOVA, 2.007	0.105
1.50-159	6.8±3.6			6.6±3.9		
1.60-1.69	6.9±0.5			6.9±2.2		
1.70-1.79	7.1±1.9			7.1±2.3		
1.80-1.89	-			9.9±3.7		
Waist circumference (cm)						
Good	7.4±3.9	*t*-test, 0.884	0.380	6.4±3.4	*t*-test, 0.265	0.791
Increased	6.6±3.4			6.2±2.7		

*Statistically significant. SD: Standard deviation, BMI: Body mass index, ANOVA: Analysis of variance

Table 4: Relationship between echo pattern and hemoglobin A1c among diabetic adults (n=70)

	HbA1c category				Fisher's exact	P
	Good control (n=36)	Borderline (n=2)	Poor control (n=32)	Total (n=70)		
Echo pattern						
Homogeneous	25 (59.5)	0	17 (40.5)	42 (100.0)	4.505	0.100
Heterogeneous	11 (39.3)	2 (7.1)	15 (53.6)	28 (100.0)		

HbA1C=Hemoglobin A1c

good control. However, the difference was not statistically significant (P = 0.100).

Discussion

In this study, the mean TV of subjects with diabetes was higher than that of the controls (6.8 ± 3.5 cm³ vs. 6.3 ± 2.9 cm³). Similar observations were made by Bianchi *et al.* with the TV in the diabetic group exceeding the 95% confidence limit of the matched control, Heba-Allah *et al.* (3.4 ± 1.5 ml vs. 2.9 ± 0.9 ml) and Nduka and Adeyekun (11.5 ± 5.2 cm³ vs. 7.4 ± 1.9 cm³ for males and 9.9 ± 6.2 cm³ vs. 7.1 ± 3.4 cm³ for females).[15,17,22]

Similar mean TV to the control (healthy) group of the index study was obtained by Kamran *et al.* (6.26 ± 2.89 ml) among 421 euthyroid participants in Karachi, Pakistan, and Yousef *et al.* (6.44 ± 2.44 ml) in 103 healthy Sudanese adults.[23,24] Slightly higher values were obtained by Nduka and Adeyekun (7.18 ± 2.9 cm³), Alazigha *et al.* (6.81 ± 2.18 cm³), and Msuega *et al.* (6.91 ± 2.41 cm³) in other regions of Nigeria,[22,25,26] Kayastha *et al.* (6.63 ± 2.50 ml) in Nepal, and Turcios *et al.* (6.6 ± 0.26 ml) in Cuba.[27,28] However, Ahidjo *et al.* in northern Nigeria got a moderately higher value of 8.55 ± 1.82 cm³ in a study of 143 healthy subjects.[29] This higher value is probably due to the tall stature of the two major ethnic groups (Hausa and Fulani) in this region.

This study also revealed a higher mean TV in males than females, which is similar to the findings of most studies.[22-24,26,28-31] This difference was statistically significant in the nondiabetic group but not in the diabetic group. The proliferative effect of diabetes on the thyroid gland may account for this difference not being

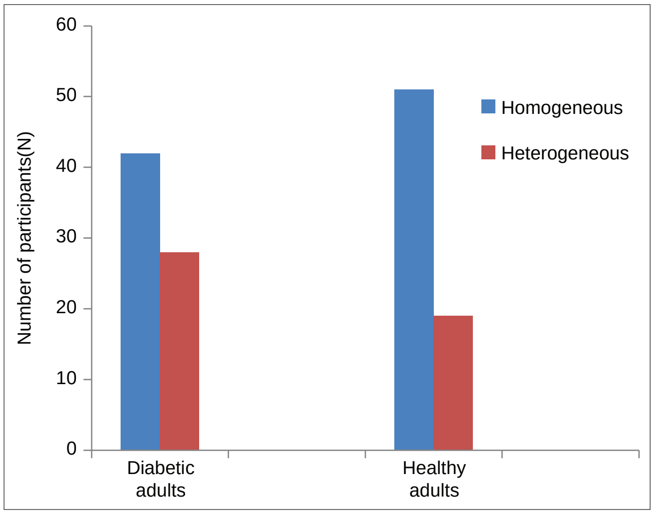

Figure 4: A bar chart showing the thyroid echo-pattern distribution among the diabetic and healthy adults

significant in the diabetic group. Many explanations have been given for the difference in TVs between the two genders. Kamran *et al*. suggested that the larger size of anatomical structures in males could account for increased thyroid gland volume in the male gender.[23] While Nafisi *et al*. suggested that the difference in body weight was responsible for this.[31] Nduka and Adeyekun and Kayastha *et al*., on the other hand, did not observe any difference in TV between the genders.[22,27] The mean TV obtained amongst the healthy adults in this and most of the other studies in Nigeria, Africa, South/West Asia and Cuba were lower than the values observed in western population studies. Junik *et al* observed a mean TV of 14.4 cm^3 in Poland, Ivanac *et al* (10.68 ± 2.83ml) in Croatia, Barrere *et al* (females > 8.6ml and males >12.1ml) in France, and Maravall *et al* (8.22ml) in spain.[16, 32-34] However, much lower mean TV (3.4 ± 1.5 ml vs. 2.9 ± 0.9 ml) was obtained in the diabetic and healthy groups, respectively, in a study by Heba-Allah *et al*. in Cairo, Egypt.[17] Variations in TVs could be due to differences in diet, ethnicity,[35] and genetic makeup.[36] The larger TVs in the western population may also be due to lower iodized salt coverage reported in industrialized countries, especially Europe, and the decline in salt consumption partly through concern and awareness about hypertension.[37]

The positive linear correlation between TV and height in this study has also been reported in several other studies.[29,32,38] However, Junik *et al*. did not observe any effect of height on the TV.[16] This study did not observe any relationship between TV, weight, and BMI. This is in agreement with the findings by Nduka and Adeyekun and Ivanac *et al*.[22,32] On the other hand, Alazigha *et al*. and Kayastha *et al*. reported a positive correlation between TV and weight in normal subjects.[25,27] This variation could be due to the larger sample sizes of 400 and 485 used, respectively, by Alazigha *et al*. and Kayastha *et al*. Alsaqer *et al*. in their study of the effects of body weight, height, and BMI on TV among healthy male undergraduates, aged 8–22 years, in Saudi Arabia reported a significant decrease in TV, as weight and BMI increased.[38]

No correlation between TV and age was observed in this study. Similar studies in various regions of Nigeria by Alazigha *et al*., Nduka and Adeyekun, and Ahidjo *et al*. also did not report any correlation between TV and age.[22,25,29] The studies by Kayastha *et al*. and Moifo *et al*., on the other hand, showed that TV increased with advancing age.[27,30] In Pakistan, Kamran *et al*. also reported an increase in TV with age only up to the 60th year, and after that, the TV began to decrease.[23] It was suggested to be due to Pakistan's severe and prolonged iodine-deficient status until the recent past. Age-related atrophy was also suggested as a reason for reduced thyroid gland volume in the elderly group.

There appears to be no correlation between TV and waist circumference in this study [Table 3]. In contrast, Zakaria *et al*., in their study comprising 80 females aged 25–45 years, reported an association between greater waist circumference and TV.[13] However, they were able to establish that it was not much of the greater waist circumference but the insulin resistance in these subjects that caused their higher TV.

There were no differences in blood TSH levels between the diabetic group and the control as three individuals in each group had abnormal (high) TSH levels (TSH >7.0 μIU/ml). In the nondiabetic group, the mean TV was higher in the subgroup with abnormal TSH. In the diabetic group, on the other hand, a negative linear correlation was noted between abnormal TSH levels and mean TV. This observation in the study is similar to that of Junik *et al*., who also reported a negative linear correlation between TSH levels and TV in type 2 diabetics used in their study.[16] The possible explanation was that hyperinsulinemia, which is frequent in diabetes, is a known growth factor that stimulates cell-cycle progression and proliferation in various cells including thyrocytes. In addition, several studies have shown that metformin, an oral medication used to treat type 2 diabetes, lowers TSH levels and also reduces thyroid size.[39-43]

In terms of HbA1c levels, among subjects with diabetes, mean TV was higher among those who had poor glycemic control, compared with those with borderline and those with good control. This is in agreement with the study by Blanc *et al*.[44] This relationship suggests that worse metabolic control as reflected by higher HbA1c levels could be a possible risk factor for the growth of thyroid tissues. However, there was a paucity of literature on studies carried out on this subject for further consideration.

There appeared to be a direct relationship between TV and duration of diabetes, as TV increased steadily with the duration of diabetes in this study. However, the difference in TVs across the categories did not show a statistically significant difference. Unfortunately, we could not find any literature on studies evaluating TV and duration of diabetes for comparison.

The proportion of respondents with heterogeneous echo pattern was higher among the diabetic group. The increased incidence of nodules in those with diabetes agrees with the study done by Adeyekun *et al*. (33.3% vs. 12.5%) in Benin, Nigeria,[45] and several other studies.[11,13,17,18,46] In the present study, the proportion of those with heterogeneous echo pattern was higher among those with poor glycemic control than those with good glycemic control. This is in line with the findings of Blanc *et al*.[44] It was suggested that higher HbA1c levels are associated with an alteration of the morphology of the thyroid gland.

Limitations of the study include the relatively small sample size, and unequal sample size of the age groups, which might be the reason for no observable trend in the TV, and there were more female participants.

Conclusion

The mean TVs of adults with diabetes in UUTH, Uyo, were generally higher than their nondiabetic counterparts. This study accepts that TV is significantly affected by gender in both diabetics and nondiabetics. The overall mean TV obtained in this study was lower than the values reported among Caucasians. Poor glycemic control was associated with larger TVs and more heterogeneous thyroid echo patterns.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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