Original article:

Pattern of hypothyroid cases in Bangladeshi People: A pilot study

Islam S[1], Hassan Z[2], Pathan F[3]

Abstract

***Aims**:* The present study was undertaken to explore the pathological basis of hypothyroidism and it relationship to clino-biochemical features of Bangladeshi patients. ***Material and Methods**:* A total number of 47 hypothyroid patients with duration less than two years and had no other comorbid disease were consecutively recruited from BIRDEM Out-patient department. Patients having serum FT_4 level <9.14 pmol/L and serum TSH >5.01 IU/ml were identified as hypothyroidism. Presence of either anti TG antibody >40 IU/ml or anti TPO antibody > 35 IU/ml or both were defined as autoimmune hypothyroidism. Thyroid gland was examined and classified according to joint criteria of WHO, UNICEF and ICCIDD criteria. ***Results**:* Female preponderance was observed in this series though small total number of samples. Familial hypothyroidism was reported in 19% of cases and 8% of patients came from iodine deficient area. Out of 47 cases autoimmune markers were done in 40 and of them 32 (68%) were positive for autoantibodies. Of the positive case 22% were positive for anti TPO antibody and 6% for anti TG antibody; 72% cases both. Drug and radiation were excluded as the cause of hypothyroidism in this series. Family history of hypothyroidism was positive in 22% and 25% autoimmune and non-autoimmune study cases. Of the autoimmune case 44% had age between 30-44 years and among non-autoimmune case 37% were 15-30 years. Eleven of 32 (34%) autoimmune hypothyroid cases presented with irregular menstrual cycle. Out of 47 hypothyroid patients in this study, 36 (77%) had palpable or enlarged thyroid gland. Of the 40 cases autoimmune status evaluated palpable among 25 (78%) autoimmune and 6 (75%) non-autoimmune hypothyroid patients. ***Conclusions**:* It is concluded that higher proportion of hypothyroid cases are of antoantibody positive. These subjects have heterogeneous phenotypic presentation. This necessitates that all newly detected hypothyroidism should be screened for autoimmune status with the same importance as given for thyroid hormone level and managed accordingly.

Introduction:

Hypothyroidism is the second most common endocrine disorder in the world after diabetes mellitus[1]. It may affect individual at all age and shown to have heterogeneity in symptoms and wide arrange of morbidity[2,3]. Maternal hypothyroidism found to be associated with preterm delivery, low birth weight baby and their delayed neurological development[4]. Poor school achievements and cognitive functions observed in rural Bangladeshi children and found to be related to biochemical hypothyroidism[5] which has highlighted the need for increased awareness and early diagnosis of those at risk.

Understanding the cause of hypothyroidism and it distributions play important role in the management. It is understood that primary hypothyroidism results from abnormality in the thyroid gland itself and secondary hypothyroidism linked to pituitary cause(s). About 55% percent of the primary hypothyroidism found to be of autoimmune origin, characterised by presence of anti thyroglobulin and anti thyro-peroxidase antibodies in the blood[6]. However, there are other preventable causes of primary hypothyroidism such as iodine deficiency, drug, radiotherapy or chemotherapy[7]. Thus, it is important to explore the distribution of the causes of non-autoimmune and

1. Dr Sunjidatul Islam, Sr Sallimullah Medical College, Dhaka-1100

2. Dr Md Zahid Hassan, Dept of Physiology and Molecular Biology,

3. Prof Dr Md Faruque Pathan, Dept of Endocrinology and Diabetology,
BIRDEM General Hospital & Ibrahim Medical College, 122 Kazi Nazrul Islam Avenue, Dhaka-1000

Corresponds to;

Prof Dr Md. Faruque Pathan, Unit 2, Dept of Endocrinology and Diabetology, BIRDEM General Hospital & Ibrahim Medical College, 122 Kazi Nazrul Islam Avenue, Dhaka-1000, E-mail: pathan279@yahoo.com

autoimmune hypothyroidism in terms of clinical and population health perspectives.

Clinico-biochemical data regarding thyroid disorders among the Bangladeshi population are lacking. Almost two decades ago nationwide survey revealed higher prevalence of goiter and biochemical iodine deficiency disorders[8]. Later on studies involving newborn and school children demonstrated incidence of congenital hypothyroidism to be 1.5 per 1000 live births and 4.97% among the school children respectively[9,10]. Of the patients attending the thyroid clinic at Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders (BIRDEM) and Bangabandhu Sheikh Mujib Medical University (BSMMU) 48.36% had presence of auto-immunity and 55% of them were suffering from autoimmunity hypothyroidism[11]. In the management of hypothyroid cases knowledge about their autoimmune status impart important role. The present study was aimed to explore the involvement of autoimmunity in hypothyroid cases, their sociodemographic status and its association with clinocobiochemical features.

Materials and Methods:

The cross sectional study was conducted at Endocrine Outpatient Department, BIRDEM, the central institute of Diabetic Association of Bangladesh (DAB) which is a tertiary care centre during the period of November 2010 to May 2011. Patients with hypothyroidism, confirmed by clinical findings and laboratory tests, consecutively attending the OPD were enrolled in the study. Those diagnosed with hypothyroidism two years earlier and any other comorbid disease were excluded from the study. Informed consent was obtained from participants. The protocol was approved by the ethical review board of the institute.

Patients having serum FT_4 level <9.14 pmol/L and serum TSH >5.01 IU/ml were identified as hypothyroidism. Presence of either anti TG antibody >40 IU/ml or anti TPO antibody > 35 IU/ml or both were defined as autoimmune hypothyroidism.

Clinoco-biochemical, sociodemographic and family history data were recorded in a predesigned case record form. Drug history particularly of radioactive iodine, amiodarone, lithium, interferon-alfa was explored and recorded. Patient's neck was examined for enlarged thyroid gland and we classified the enlargement of thyroid gland (goiter) according to joint criteria of WHO, UNICEF and ICCIDD criteria: Grade 0 (no palpable or visible goiter); Grade 1 (palpable but not visible goiter when the neck is in the normal position). Thyroid nodules, which is otherwise, not enlarged fall into this category; Grade 2 (a clearly visible swelling in the neck when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated)[12].

Statistical methods

Data were presented as mean±SD and number (percent) as appropriate. Unpaired student's 't' test and Chi-squared test were performed as applicable. Analyses were performed statistical tool STATA version 10. A p value <0.05 was taken as level of significance.

Results:

A total number of 47 hypothyroid patients were enrolled in the study. Male female distribution was 5:42. Mean (±SD) age (yrs) was 35.4±13.8 years and BMI of 26.8±3.96 kg/m^2. Socio-demographic and biochemical features of the study participants were presented in Table 1.

Table 1: Socio-demographic and biochemical data of the study subjects

Variables	Number (Percent)
N	47
Female (%)	42 (89)
Age (years) [mean±SD, range]	35.4 ±13.8
BMI	26.8 ± 3.96
Blood pressure (mmHg)	
Systolic	120 ± 19
Diastolic	76 ± 9
Residence	
Iodine deficient area	3 (7.5)
Iodine plenty area	37 (92.5)
F glucose	5.5 ± 1.4
Lipids	
TG	176 ± 92
T chol	224 ± 81
HDL-c	49.8 ± 54.8
LDL-c	127.5 ± 79.5

Results were expressed as mean±SD and number (percent) as appropriate.

Out of 47 hypothyroid patients, autoimmune status was known for 40 patients and of them 32 (68%) patients were autoimmune positive. Among autoimmune hypothyroid patients, 22% were positive for anti TPO antibody and 6% for anti TG antibody; 72% cases had both antibodies (Figure 1).

Twenty-four patients (60%) had anti-TPO antibody of >100 U/ml (131 to >1000) and 19 patients (48%) had anti TG antibody of >100 U/ml (223 to >3000) (Figure 2).

Familial hypothyroidism was reported in 19% of cases and 8% of patients came from iodine deficient area. Both thyroid surgery and drug history were responsible for two percent of hypothyroid cases. None of the subjects presented with history of radiation and chemotherapy exposure (Figure 3). Among autoimmune hypothyroid patients, 7 (22%) had family history of thyroid disorder while 2 (25%) of non-autoimmune hypothyroid patients had family history (Table 2).

Among autoimmune hypothyroid patients, 44% were in 30-44 years age group while 28% had age 45 years or more and 37% of non-autoimmune hypothyroid cases were of 15-29 years of age. Among patients with regular menstrual cycle, 21 (78%) and 6 (22%) cases were diagnosed with autoimmune and non-autoimmune hypothyroid respectively; eleven of 32 (34%) autoimmune hypothyroid patients presented with irregular cycle. Eight autoimmune (89%) and 1 (11%) non-autoimmune cases were found to be oligomenorrheic (Table 3).

Out of all hypothyroid patients in this study, 36 (77%) participants had palpable or enlarged thyroid gland. Thyroid gland was palpable among 25 (78%) autoimmune and 6 (75%) non-autoimmune hypothyroid patients. Forty nine percent (49%) of hypothyroid patients presented with grade 2 goiter according to the WHO grading of goiter. Among patients with grade 2 goiter, 18 patients (86%) were identified as autoimmune cases and 3 (14%) as non-autoimmune (Table 3). Mean cholesterol and LDL level among autoimmune patients were of 239 (mg/dl) and 152 (mg/dl) whereas non-autoimmune hypothyroid patients presented with 153 (mg/dl) and 65 (mg/dl) (p=0.041 (Table 3).

Discussion:

We estimated 80% autoimmunity and 20% non-autoimmunity among the hypothyroid patients in our study. Previously it was shown that among all autoimmune thyroid disorder cases in two referral centers (BIRDEM and BSMMU) 55% were hypothyroid[11]. However, we investigated for proportion of autoimmune cases among the hypothyroid patients. A study among the Danish hypothyroid population showed 95% autoimmunity among patients with overt hypothyroidism. This study also identified that more patients were positive with anti TPO antibody than anti TG antibody[13], this was consistent with our findings of more hypothyroid positive patients with anti TPO antibody (22%) than anti TG antibody (6%). Among all autoimmune hypothyroid patients 60% presented with anti TPO antibody of more than 100 U/ml with a range of 131 to >1000 U/ml. However, in a study anti-TPO antibody (>100 U/ml) was found in 22 children and adolescents with a median of 765 U/ml (ranged 110 to >3000 U/ml)[14].

Beside the autoimmune status, we have observed factors that might have prevailed as leading causes of hypothyroidism among these subjetcs. Among all hypothyroid patients, we detected 19% familial hypothyroidism and other 8% percent were from iodine deficient area. It has been reported in a multicenter cohort study in UK that almost half of the patients with Grave's disease and Hashimoto's thyroiditis had family history of thyroid disorder[15]. In this study, very few patients were from iodine deficient area. This may be due to improvement of iodine status of people from iodine deficient area following implementation of law to make all edible salt to be iodized and social awareness program[16]. National surveys observed an improvement of iodine status of Bangladeshi populations, the prevalence of goiter and biochemical iodine deficiency were 47.1% and 68.9% in 1993, 17.8% and 43.1% in 1999 [17,18]. Another study done in 2004-05 showed that total goiter rate were 6.2% among children and 11.7% among women in Bangladesh. This study also reported 33.8% and 38.6% prevalence of biochemical iodine deficiency among children and women respectively[19-20].

Among other prevalent causes of hypothyroidism, hemithyroidectomy[21], pesticide[22], amiodarone[23], radiotherapy and chemotherapy[24] had been noted. In this study we found only two percent of hypothyroid cases had history of thyroid surgery or drug exposure. History of radiation or chemotherapy was not found in any hypothyroid case of our study.

Majority of our autoimmune hypothyroid subjects (44%) came from middle age (30 to 44 years of age) group. This was consistent with a study among patients with Grave's disease and Hashimoto's thyroiditis in which peak age for diagnosis was from

fourth to sixth decades[15]. Seventy eight percent autoimmune and 75% non-autoimmune hypothyroid patients had palpable thyroid gland. We found grade 2 goiter among 49% hypothyroid patients; 86% were from autoimmune group compared to 14% from non-autoimmune hypothyroid cases. The population based Danish study reported thyroid enlargement among patients with higher thyroid autoantibody level[13].

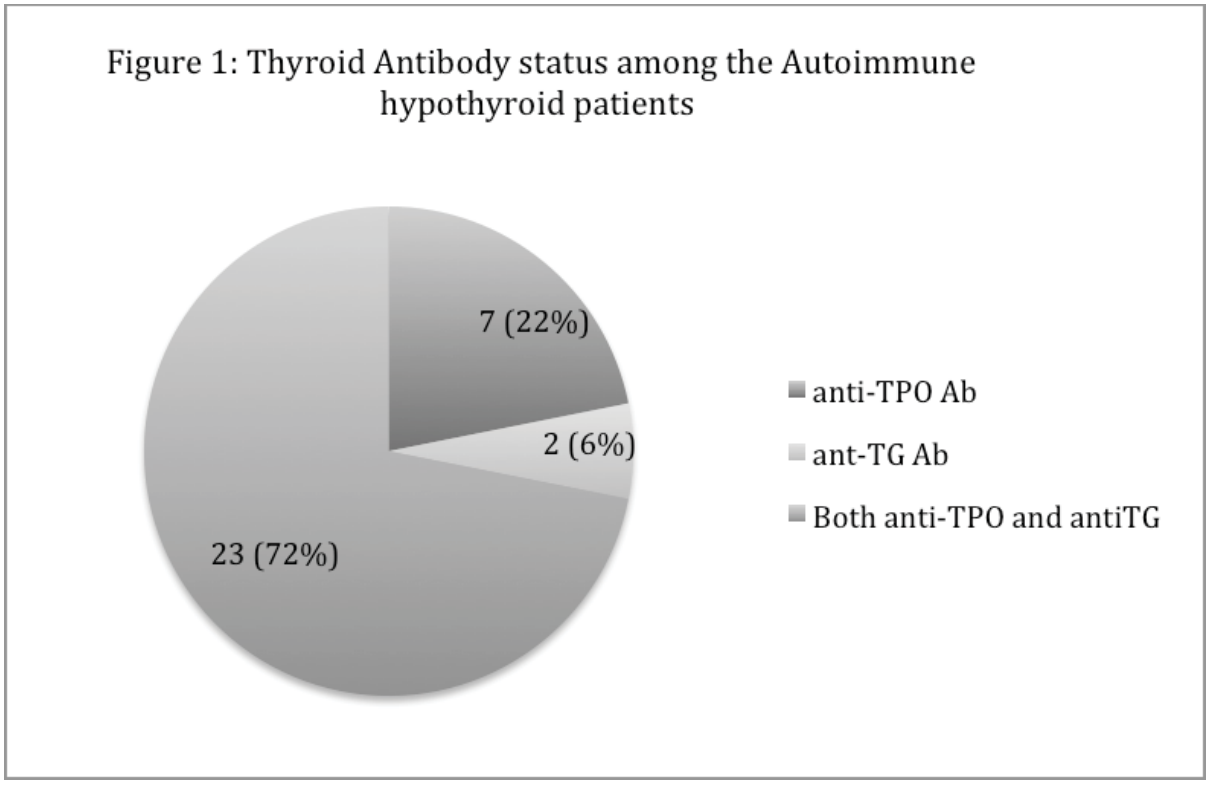
There are certain limitations in our study. We conducted this study for seven months, very short period to get enough samples. For this limited period of time and small sample size, our findings might not be generalized and we did not stratify our estimates for different age categories and gender. We need a population-based study to broaden our understanding about the disease burden in the community. However, our study will help to generate hypothesis for the future studies.

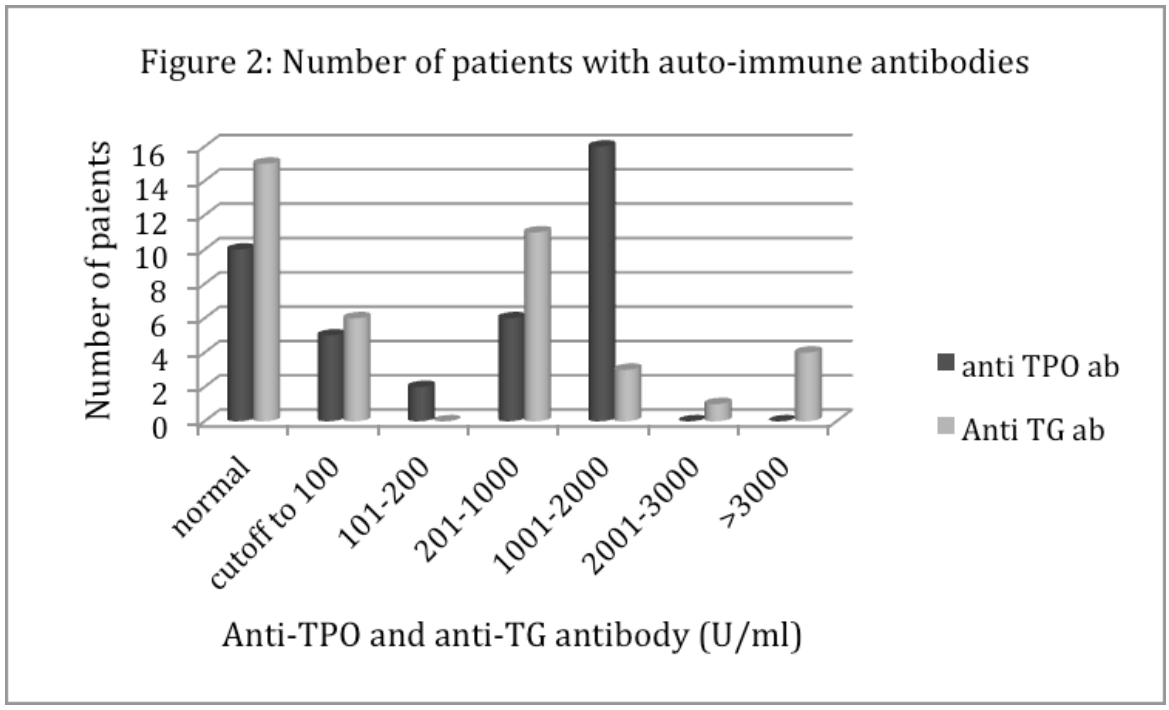
Secondly, this was a single centre study. Therefore, we might have an underestimated prevalence and region wise variation might not be well captured. A Nationwide study should be conducted to capture the variations especially in the iodine deficient regions. Still this study had been conducted in BIRDEM, only specialized hospital for endocrine disorders in the country, and might have addressed this issue to some extent. Besides, an underestimated prevalence will at least gain some attentions to the policy makers in a resource poor settings rather than having no estimates.

In our study we presented a small proportion of non-autoimmune cases based on different aetiologies. However, a further large-scale population based study could better identify the distribution of these risk factors such as diet, drug and agro-chemicals in different regions of Bangladesh and help us to adopt preventive interventions and conclusive recommendations.

Conclusions

This is the first study to report the autoimmune status of the hypothyroid patients in Bangladesh. It is concluded that higher proportion of hypothyroid cases are of antoantibody positive. These subjects have heterogeneous phenotypic presentation. This necessitates that all newly detected hypothyroidism should be screened for autoimmune status with the same importance as given for thyroid hormone level and managed accordingly.





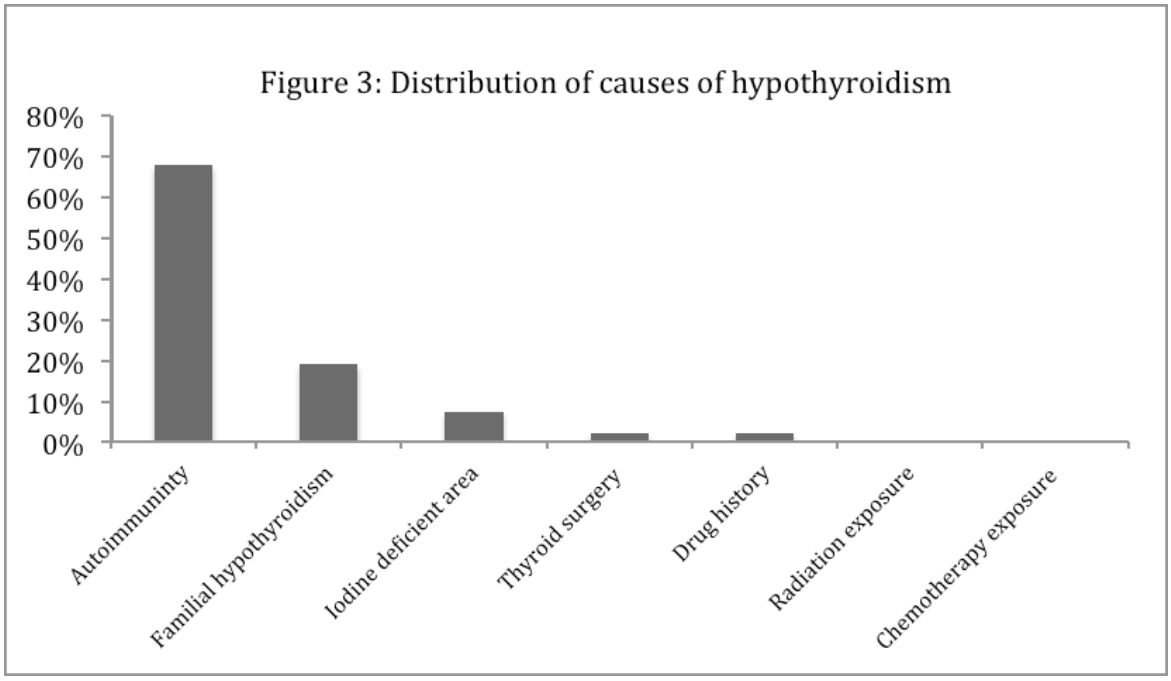


Table 2: Thyroid related antibody status in respect to family history of hypothyroidism of the study subjects

Family history	Autoimmune	Non-autoimmune
Positive (n=9)	7 (21.9%)	2 (25.0%)
Negative (n=30)	24 (75.0%)	6 (75.0%)

Table 3: Clinical characteristics and laboratory parameters of autoimmune and non-autoimmune hypothyroid patients

Variable (N)	Autoimmune (mean±SD)	Non-autoimmune (mean±SD)
BMI (38)	26.6 ± 3.9	28.5 ± 4.5
Waist circumference (25)	92.6 ± 9.1	93.3 ± 11.0
Menstrual cycle (40)	32 (80.0%)	8 (20.0%)
Regular (27)	21 (77.8%)	6 (22.2%)
Irregular (13)	11 (84.6%)	2 (15.4%)
Menstrual amount and duration (40)		
Normal (27)	21 (77.8%)	6 (22.2%)
Oligomenorrhoea (9)	8 (88.9%)	1 (11.1%)
Menorrhagia (2)	1 (50.0%)	1 (50.0%)
Polymenorrhea & menorrhagia (2)	2 (100.0%)	0 (0%)
WHO size (40)		
G0 (9)	7 (77.8%)	2 (22.2%)
G1 (10)	7 (70.0%)	3 (30.0%)
G2 (21)	18 (85.7%)	3 (14.3%)
Texture of gland (31)		
Diffuse (30)	24 (80.0%)	6 (20.0%)
Nodular (1)	1 (100.0%)	0
Tenderness (40)		
Non tender (40)	32 (80.0%)	8 (20.0%)
Tender	-	-
Consistency (24)		
Firm (23)	18 (78.3%)	5 (21.7%)
Hard	1 (100.0%)	0
Lipids		
Cholesterol (22)	239 ± 84	153 ± 50
Triglyceride (23)	187 ± 89	153 ± 50
LDL (22)	152 ± 77	65 ± 48
HDL (23)	57.6± 62.2	33.5 ± 10.2

Results were expressed as mean±SD and number (percent) as appropriate.

References:

1. Flinders DC, MD. Clinical feature. When thyroid hormone levels are insufficient. December 28, 2006. http://www.clinicaladvisor.com/clinical-feature/printsection/236/0

2. Iglesias P and D?'ez JJ. Thyroid dysfunction and kidney disease. *Euro J Endocrinol* 2009; **160:** 503–515 http://dx.doi.org/10.1530/EJE-08-0837 PMid:19095779

3. Squizzato A, Gerdes VEA, Brandjes DPM, Buller HR, Stam J. Thyroid Diseases and Cerebrovascular Disease. *Stroke* 2005; **36;** 2302-2310 http://dx.doi.org/10.1161/01.STR.0000181772.78492.07 PMid:16179578

4. Stagnaro-Green A. Maternal Thyroid Disease and Preterm Delivery. *J Clin Endocrinol Metab* 2009; **94**: 21–25. http://dx.doi.org/10.1210/jc.2008-1288 PMid:18984665

5. Huda SN, Grantham-McGregor SM, Rahman KM, Tomkins A. Biochemical hypothyroidism secondary to iodine deficiency is associated with poor school achievement and cognition in Bangladeshi Children. *JNutr* 1999;**129**: 980–987. PMid:10222389

6. Kostoglou-Athanassiou I and Ntalles K. Hypothyroidism - new aspects of an old disease. *Hippokratia* 2010, **14**: 2: 82-87. PMid:20596261 PMCid:PMC2895281

7. Almandoz JP, Gharib H. Hypothyroidism: Etiology, Diagnosis, and Management. *Med Clin North Am* 2012; **96:** 203–221. http://dx.doi.org/10.1016/j.mcna.2012.01.005 PMid:22443971

8. Yusuf HKM, Quazi S, Kahn MR, Mohiduzzaman M, Nahar B, Rahman MM et al. Iodine Deficiency Disorders in Bangladesh. *Indian Pediatr* 1996; **63**: 105-110. http://dx.doi.org/10.1007/BF02823878

9. Rasul CH, Lucky SN, Miah SR, Moslem F. Congenital Hypothyroidism in the Southern Bangladesh. *Bangladesh J Child Health* 2005; **29**: 88-92.

10. Paul AK, Miah SR, Mamun AA, Islam S. Thyroid disorders in Khulna district: a community based study. *BMRC Bull* 2006; **32:** 66-71

11. Hasanat MA, Rumi MAK, Alam MN, Hasan KN, Salimullah M, Salam MA et al. Status of antithyroid antibodies in Bangladesh. *Postgrad Med J* 2000; **76**:345–349 http://dx.doi.org/10.1136/pmj.76.896.345 PMid:10824048 PMCid:PMC1741600

12. Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. A guide for programme managers. Geneva: 2001. WHO document WHO/NHD/01.1.

13. Carle A, Laurberg P, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Pedersen I. Thyroid peroxidase and thyroglobulin auto-antibodies in patients with newly diagnosed overt hypothyroidism. *Autoimmunity* 2006; **39:** 497–503. http://dx.doi.org/10.1080/08916930600907913 PMid:17060029

14. Kabelitz FM, Liesenkotter KP, Stach B, Willgerodt H, Stablein W, Singendonk W et al. The prevalence of anti-thyroid peroxidase antibodies and autoimmune thyroiditis in children and adolescents in an iodine depleted area. *Euro J Endocrinol* 2003; **148:** 301–307. http://dx.doi.org/10.1530/eje.0.1480301 PMid:12611610

15. Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK et al. Influences of Age, Gender, Smoking, and Family History on Autoimmune Thyroid Disease Phenotype. *J Clin Endocrinol Metab* 2006; **91**: 4873–4880. http://dx.doi.org/10.1210/jc.2006-1402 PMid:16968788

16. Country Profiles: Bangladesh; http://www.iodinenetwork.net/countries/Bangladesh.htm#1

17. Yusuf HK, Quazi S, Kahn MR, Mohiduzzaman M, Nahar B, Rahman MM et al. Iodine deficiency disorders in Bangladesh. *Indian J Pediatr* 1996; **63:** 105-110. http://dx.doi.org/10.1007/BF02823878 PMid:10829973

18. Dhaka University/IPHN/BSCIC/UNICEF/ ICCIDD. Report of the National Iodine Deficiency Disorders Survey of Bangladesh 1999. Dhaka University/IPHN/BSCIC/ UNICEF/ICCIDD, Dhaka, 2001.

19. HKM Yusuf, AKMM Rahman, FP Chowdhury, M Mohiduzzaman, CP Banu, MA Sattar and MN Islam. Iodine deficiency disorders in Bangladesh, 2004-05: ten years of iodized salt intervention brings remarkable achievement in lowering goitre and iodine deficiency among children and women. *Asia Pac J Clin Nutr* 2008; **17:** 620-628 PMid:19114400

20. A Gulshan, B Tahmina, M Fouzia, R Mizanur. Neurodevelopmental outcome of congenital hypothyroidism in children between 1-5 years of age. *Bangladesh Journal of Medical Science.* 2011; **10 (**4): 245-251. DOI:

http://dx.doi.org/10.3329/bjms.v10i4.9495 http://dx.doi.org/10.3329/bjms.v10i4.9495

21. Miller FR, Paulson D, Prihoda TJ, Otto RA. Risk Factors for the Development of Hypothyroidism after Hemithyroidectomy. *Arch Otolaryngol Head Neck Surg* 2006; **132:** 36-38 http://dx.doi.org/10.1001/archotol.132.1.36 PMid:16415427

22. Goldner WS, Sandler DP, Yu F, Hoppin JA, Kamel F, LeVan TD. Pesticide Use and Thyroid Disease among Women in the Agricultural Health Study. *Am J Epidemiol* 2010; **171:** 455–464. http://dx.doi.org/10.1093/aje/kwp404 PMid:20061368 PMCid:PMC2842196

23. Triggiani V, Iacoviello M, Monzani F, Puzzovivo A, Guida P, Forleo C et al. Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. *Endocr Metab Immune Disor d Drug T argets.* 2012; 12: 86-94. http://dx.doi.org/10.2174/187153012799278947 PMid:22214334

24. Srikantia N, Rishi KS, Janaki MG, Bilimagga RS, Ponni A, Rajeev AG et al. How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients? *Indian J Med Paediatric Oncology* 2011; **32 (**3)