Original Article
Medical Journal of Islamic Republic of Iran, Vol. 26, No. 4, Nov. 2012, pp. 172-178

Comparison of hematological parameters in untreated and treated subclinical hypothyroidism and primary hypothyroidism patients

Haamid Bashir[1], Mohmmad Hayat Bhat[2], Rabia Farooq[3], Sabhiya Majid[4], Sheikh Shoib[5], Rabia Hamid[6], Arshed Ahmad Mattoo[7], Tabassum Rashid[8], Arif Akbar Bhat[9], Hilal Ahmad Wani[10], Akbar Masood[11]

Department of Biochemistry Govt. Medical College Srinagar, Kashmir, India.

Received: 28 April 2012 Revised: 1 September 2012 Accepted: 8 September 2012

Abstract

Backgrounds: Thyroid hormones play an important physiological role in human metabolism. Erythrocyte abnormalities are frequently associated with thyroid disorder. However, they are rarely investigated and related to the subclinical and primary hypothyroidism in Kashmiri Patients. In this study an attempt was made to study hematological parameters in untreated and treated subclinical hypothyroidism and primary hypothyroidism patients.

Methods: This retrospective study included 600 subjects**,** among which were untreated subclinical hypothyroid (n=110), treated subclinical hypothyroid (n=110), untreated primary hypothyroid (n=100), treated primary hypothyroid (n=100) and euthyroid (n=180). This study was carried out at Department of Biochemistry, Government Medical College Srinagar. The hematological parameters and thyroid profile of the subjects were assessed by the Sysmex (Italy) and ECLIA (Germany) 2010 automatic analyzer. Mean, standard deviation (SD), analysis of variance (Two-way ANOVA), and multiple comparisons were used to report our results, with $p<0.05$ or $p<0.01$ considered as statistically significant.

Results: In this study group we compared the hematological parameters in these groups, untreated subclinical hypothyroid, treated subclinical hypothyroid, untreated primary hypothyroid**,** treated primary hypothyroid and euthyroid. We found that hematological parameters like Hb, RBC, MCV, HCT, RDW,RBC% were significantly increased in untreated subclinical hypothyroidism and untreated primary hypothyroidsm, with the p value being less than 0.05 whereas, in treated SCH & Pr. Hypothyroid, results were insignificant. The results reported in these groups as mean±SD, were statistically tested by ANOVA and multiple comparison tests. In untreated subclinical hypothyroid the values were: Hb (10.83±1.33 g/dl), RBC (4.21±0.66 10^6/µl), MCV (84.56±6.84 fL), HCT (38.5±2.2 %), RDW (17.91±2.37 fL), RBC% (84.36±13.2 %) and in untreated primary hypothyroid, Hb (10.73±0.86 g/dl), RBC (4.63±0.51 10^6/µl), MCV (83.34±6.92 fL), HCT (38.6±2.6%), RDW (14.93±5.47 fL), RBC% (92.63±10.30%) suggesting that these patients were at risk of anemia and other erythrocyte abnormalities. MCV is an inexpensive approach to study the types of anemia and explore related information like production, destruction, loss and morphological changes of RBC'S.

Conclusion: The thyroid dysfunction is frequently associated with anemia in subclinical hypothyroidism and primary hypothyroidism. Subclinical hypothyroidism (SCH) is associated with serious complications. Substantial numbers of patients with the risk of SCH could be getting converted into primary hypothyroidism. Such conditions should be identified and corrected. On the other hand, their presence could move to a thyroid dysfunction, allowing its early management.

Keywords: Subclinical hypothyroidism, Primary hypothyroidism, Blood count, Hemoglobin, Red cell distribution, Mean corpuscular volume.

Introduction

Thyroid hormones are essential for the normal development, differentiation, metabolic balance, and physiological function of virtually all tissues and thyroid function disorders are among the most common endocrine diseases (1). Hypothyroidism is the most common functional disorder of the

1. MSc, MPhil, Department of biochemistry, GMC, Srinagar, Kashmir, India. haamidb7@gmail.com
2. MD, DM, Consultant endocrinologist, Department of Medicine, SMHS Hospital, GMC Srinagar. hayatmb@rediffmail.com
3. MSc, MPHILL, Department of biochemistry, GMC, Srinagar, Kashmir, India. rabiajan4uuu@gmail.com
4. (**Corresponding author**), PhD, Prof, & Head, Department of Biochemistry, GMC, Srinagar, Kashmir, India. sabumajid@yahoo.com
5. MD, Department of Psychiatry, GMC, Srinagar, Kashmir, India. sheikhshoib22@yahoo.com
6. PhD, Sr Asst Prof, Dept of Biochemistry, University of Kashmir. rabeyams@yahoo.co.in
7. MSc, MPhil, Department of biochemistry, GMC, Srinagar, Kashmir, India. almhdars12345@gmail.com
8. PhD, Department of biochemistry, GMC, Srinagar, Kashmir, India. tabassum.123@gmail.com
9. MSc, MPHIL, Department of biochemistry, GMC, Srinagar, Kashmir, India. ariefbhat19@gmail.com
10. MSc, MPhil, Department of biochemistry, GMC, Srinagar, Kashmir, India. hilalbiochm2007@gmail.com
11. PhD, Prof, Dept of Biochemistry, University of Kashmir, Srinagar India. akbarmasood@hotmail.com

thyroid gland. Pathology of the thyroid gland (primary hypothyroidism) accounts for over 99.5% of cases of thyroid gland failure and < 0.5% result from disorders of the pituitary gland or hypothalamus (central hypothyroidism). Overt primary hypothyroidism refers to cases in which the serum thyrotropin (TSH) concentration is elevated and the serum free thyroxine (T4) level is below the reference range, while subclinical hypothyroidism is defined as an elevated serum TSH value associated with a serum free T4 that is still within the reference range. The incidence of overt hypothyroidism has been estimated to be 4.1 cases per 1000 women per year and 0.6 cases per 1000 men per year (2). The prevalence has been reported to be approximately 1-2% in women and 0.1% in men in large population studies (3-5). The presence of subclinical hypothyroidism is far higher, and reported to be about 4-10% in multiple populations and as high as 18% in the elderly (6-9). In iodine deficient areas such as India the incidence can reach as high as 10-20 times more than non-iodine areas like U.S.A (3, 10-11). Subclinical hypothyroidism may progress to overt hypothyroidism in approximately 2-5% cases annually. All patients with overt hypothyroidism and subclinical hypothyroidism with TSH >10 mIU/L should be treated (12). Anemia is a decrease in number of red blood cells (RBC's) or less than the normal quantity of hemoglobin in the blood .Anemia can have several reasons, such as, abnormality of the formation (13) and reduction on the half life time of the red cells (14). The size is reflected in mean corpuscular volume (MCV). The prevalence of anemia in patients with hypothyroidism has been shown to be 20-60% (15). Thyroid hormone is involved in hemoglobin synthesis in adults and maturation of hemoglobin in fetus (16, 17) and by affecting hematopoietic process, hypothyroidism results in anemia through slowing the oxygen process (18).

The present study was therefore undertaken to find out the association between hematological parameters in untreated and treated subclinical hypothyroidism and primary hypothyroidism patients of Kashmir valley. Srinagar (Kashmir valley) reported that substantial increase of thyroid dysfunction patients have increased in past few years. Hence further research is needed to address the metabolic diseases and to understand the etiology and to create awareness among people.

Methods

Subjects and recruitment process:

This retrospective-hospital based study was conducted at the department of Biochemistry Government Medical College Srinagar from April 2011 to February 2012. All patients were referred from out-patient department (OPD) and Inpatient Department (IPD) of Government Medical College Srinagar and its associated Shri-Mahraja Hari Singh Hospital (SMHS) hospital, a major referral hospital of Kashmir valley (North-India), to the diagnostic Biochemistry and Haematology laboratory of Government Medical College Srinagar for the evaluation of thyroid function and performing complete blood count (CBC). All the patients were examined by an endocrinologist. The study was approved by Departmental ethical committee of Biochemistry, Government Medical College (GMC) Srinagar. Individuals who fulfilled exclusion criteria for both diseases and gave consent to participate in the study were recruited as normal. All the Subjects' information was kept confidential. Patients and normal subjects recruited for study were selected for age matched and gender matched. A total of 600 subjects were selected for the study. These included the subclinical hypothyroid untreated (n=110), subclinical hypothyroid treated (110), primary untreated hypothyroid (n=100), primary hypothyroid treated (n=100) and normal-controls (n=180). Subclinical hypothyroid patients were treated as SCH, after 3 months of follow up.

Table 1. General characteristics of study population
[All reported values are numbers and frequency as percentages (%)]

Variables			Cases (both SCH and Primary Hypothyroid un-treated and treated) N=420	Controls N=180	p-Value
Age	25-45		250(59.5%)	100(55.55%)	0.36
	45-60		170(40.4%)	80(44.44%)	
Gender	Male		150(35.7%)	70(38.88%)	0.51
	Female		270(64.2%)	110(61.11%)	
Life style	Smoker		140(33.3%)	60(33.33%)	1.0
	Non-smoker		280(66.6%)	120(66.66%)	
Diet	Vegetarian		100(23.8%)	40(22.22%)	0.67
	Non-Vegetarian		320(76.19%)	140(77.77%)	
	Goitrogen intake (Cauliflower turnip etc)	Yes	300(71.4%)	50(27.77%)	
		No	120(28.57%)	130(72.22%)	<0.001
	Iodised food (Fish, meat, egg, milk, salt etc		300(71.4%)	140(77.77%)	0.10
	Non –Iodised food		120(28.57%)	40(22.22%)	
Drinking water facility	Boiled		200(47.61%)	120(66.66%)	<0.001
	Un boiled		220(52.38%)	60(33.33%)	
	Tap water		200(47.61%)	120(66.66%)	<0.001
	Well water/ River water		220(52.38%)	60(33.33%)	
Previous Goitre History	Yes		20(4.76%)	2(1.1%)	0.02
	No		400(95.23%)	178(98.88%)	
Residence	Urban		210(50%)	80(44.44%)	
	Rural		210(50%)	100(55.55%)	0.21

*Exclusion criteria***:**

Patients with ischemic heart disease, cerebrovascular and neurological diseases, diabetes mellitus, chronic renal impairment, known psychological illnesses, previous history of thyroid disease or previous thyroxine therapy, asthma and pregnancy.

Inclusion criteria:

Hypothyroid patients, Kashmiri ethnicity and normal patient.

Blood Sample collection:

About 5-6 ml of venous blood was collected, in which 3 ml blood was taken in EDTA vials and remaining 3 ml centrifuged to separate serum from the cells as soon as the clot formed.

Measurement of Hematological parameter:

The 3ml peripheral venous blood was taken in sterilized EDTA vials. The CBC and haemogram comprised of (Hb, TLC, DLC, RBC, PLT, MHC, MCV, MCHC, PDW, RDCV, LYM%, GRA%, HB%, RBC%, Color Index, ESR). Blood samples were processed manually for various hematological indices mainly hemoglobin (Hb), total erythrocyte counts (TEC), total leukocyte count (TLC), mean corpuscular value (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Red cell width distribution(RDW). The CBC and hemogram were assayed in Sysmex (Italy) hemocytometer analyzer. The Erythrocyte sedimentation rate (ESR) was determined by Wintrobe's method. The Hb%, RBC% and Color Index determined by the formulae (Godkar et al., 2006).

Hb%= 100*Hb value/14.5
RBC%= 100* RBC Count/5.0
Color Index= Hb%/RBC%

Measurement of thyroid hormone profile:

Serum aliquots were stored at 4^{o}C to be run in batches. The samples were allowed to thaw prior to assay, mixed thoroughly. Hemolysed and lipemic samples were rejected. Bi level i.e. high and low control was run with each batch .Thyroid function test (TFT) comprising of T3, T4 and TSH levels was carried out by electrochemi-

Table 2. Comparison of hematological parameters and thyroid hormone levels in untreated and treated subclinical hypothyroid and primary hypothyroid patients.

Parameters	Euthyroid N=180	Subclinical hypothyroid		Primary hypothyroid		p-value	
		Untreated SCH n=110 Mean±SD	Treated SCH n=110 Mean±SD	Untreated Pr. Hypothyroid n= 100 Mean±SD	Treated Pr. Hypothyroid n=100 Mean±SD	Untreated primary hypo-thyroid vs. treated pr. hypothyroid	Untreated SCH vs. treated SCH
T3(ng/dl)	1.052±0.17	1.062±0.28 (0.0)	1.060±0.28 (0.01)	0.82±0.41 (-0.01)	0.82±0.41 (-0.00)	0.92	0.99
T4(µg/dl)	7.42±1.63 (0.0)	7.52±1.53(0.0)	7.52±1.53 (0.0)	5.54±1.53 (+2.06)	9.54±2.53 (-1.84)	<0.0001	<0.0001
TSH(µIU/ml)	2.23±0. 93	19.37±10.54 (-12.73)	14.22±8.20 (-3.67)	18.67±11.34 (-10.82)	15.28±7.3 0(-5.46)	<0.001	<0.001
Hb(g/dl)	14.72±1.77	10.83±1.33	12.01±1.20	10.73±0.86	12.64±1.33	<0.001	<0.001
RBC(10^6/µl)	5.15±1.59	4.21±0.66	5.14±0.62	4.63±0.51	5.14±0.62	0.04	0.01
WBC(10^3/µl)	7.4±1.06	6.71±0.91	6.81±1.01	7.25±0.86	6.14±0.96	0.006	0.002
HCT(%)	41.5±2	38.5±2.2	39.4±2.8	38.6±2.6	39.5±2.5	<0.001	<0.001
MCV(fL)	86.34±5.71	84.56±6.84	86.19±6.43	83.34±6.92	85.81±6.22	<0.05	<0.05
LYM (%)	34.63±7.85	31.44±12.55	19.82±11.4	17.85±9.19	28.17±13.6	0.008	0.006
RBC (%)	82.71±12.3	84.36±13.2	82.85±12.4	92.63±10.30	82.71±12.30	0.05	0.04
RDW (fL)	-	15.5±1.85	17.91±2.37	14.93±5.47	14.61±3.61	0.089	0.057

luminescence Immunoassay method using fully automatic analyzer ECLIA 2010 (Roche Diagnostic Germany). Patients with thyroid hormone evaluation picture of elevated serum TSH levels (>4.3 to ≥10 mIU/ml) with normal levels of serum thyroxine (T_4) and triiodothyronine (T_3) were categorized as subclinical hypothyroidism (SCH) if similar levels observed in repeated thyroid profile after a lapse of three months.

Statistical Analysis

Data were extracted and analysed by GraphPad Prism 5.0. The results were expressed as mean ± standard deviation (SD). Differences in variables were analyzed by an analysis of variance (ANOVA), Dunnet's Multiple comparisons test, Bonferroni multiple comparisons, two-way ANOVA and Chi square test. The differences were considered to be significant at $p<0.05$ or $p<0.01$.

Results

In this study, the total of 600 subjects participated in the research among which 64% were females and 36% males, in the age group between 25-60. There were 180 euthyroid (normal), 110 Subclinical hypothyroid (untreated), 110 Subclinical hypothyroid (treated), 100 Primary hypothyroid (untreated) and 100 primary hypothyroid (treated). Median + Standard deviation values of Hb, RBC,WBC, MCV, RDW, Hct, Lym%, Hb% and RBC% with respect to T4 and TSH were assessed and data are presented as F-value and P-value. The value of $P<0.05$, denotes in results were statistically significant and had association in the thyroid disorder. Results are shown in Table 1-3.

In untreated subclinical hypothyroid the values obtained were: Hb (10.83±1.33 g/dl), RBC (4.21±0.66 10^6/µl), MCV (84.56±6.84 fL), HCT (38.5±2.2 %), RDW (17.91±2.37 fL), RBC% (84.36±13.2 %) and in untreated primary hypothyroid, Hb (10.73±0.86 g/dl), RBC (4.63±0.51 10^6/µl), MCV (83.34±6.92 fL), HCT (38.6±2.6 %), RDW (14.93±5.47fL), RBC% (92.63± 10.30%) which supports the fact that these patients are at risk of anemia (Normocytic). And also, patients treated with Thyroxine-therapy show correction in these erythrocyte abnormalities. As compared with patients with euthyroid status for TSH values, the RDW values showed statistically highly significant difference. It was found to be significantly increased in both subclinical hypothyroid and primary hypothyroid untreated patients. MCV values showed statis-

Table 3. Euthyroid vs cases (using two-way ANOVA and Bonferroni multiple comparisons)

Parameters	Euthyroid vs Untreated SCH (p value)	Euthyroid vs treated SCH (p value)	Euthyroid vs Untreated Pr. Hypothyroid (p value)	Euthyroid vs treated Pr. Hypothyroid (p value)
T3 (ng/dl)	p<0.05	p<0.05	p<0.05	p<0.05
T4 (µg/dl)	p<0.05	p<0.05	p<0.001	p<0.05
TSH (µIU/ml)	p<0.001	p<0.05	p<0.001	p<0.05
Hb (g/dl)	p<0.001	p<0.05	p<0.001	p<0.05
RBC (10^6/µl)	p<0.001	p<0.05	p<0.001	p<0.05
WBC (10^3/µl)	p<0.05	p<0.05	p<0.05	p<0.05
HCT (%)	p<0.001	p<0.05	p<0.001	p<0.05
MCV (fL)	p<0.001	p<0.05	p<0.001	p<0.05
LYM (%)	p<0.05	p<0.05	p<0.001	p<0.05
RBC (%)	p<0.001	p<0.05	p<0.001	p<0.05
RDW (fL)	p<0.001	p<0.05	p<0.001	p<0.05

* p<0.05 or 0.01 is significant.

tically significant difference among patients with abnormal thyroid function. MCV values were significantly increased in both overt and SCH. Other parameters like Hb, RBC, WBC, Hct, Lym%, Hb% and RBC% were also significantly increased in the hypothyroid patients. Anemia was classified into three types: Macrocytic anemia (MCV>100), Normocytic anemia (MCV 80-100) and Macrocytic anemia (MCV <80). Also, all patients and controls were interviewed by questionnaires and the information extracted from them. It was found that patients using goitrogen foods in their diet with a poor drinking water facility had significance increased in illness (p<0.001) which might be etiologically important in subclinical and primary hypothyroidism susceptibility.

Discussion

This retrospective hospital based study conducted at SMHS hospital Srinagar, main referral hospital of Kashmir valley, where witnessing heavy patients rush at routine basis, helped us to understand the problem, simultaneously address the management of this metabolic diseases among the patients. Kashmir valley is a mountainous region demographically, here six month of winter season receives heavy snow fall and rains. The soil contains less amount of iodine mineral, since it is leached out by the snow and rain (24). The agriculture grown here has less amount of iodine, main mineral necessary for proper thyroid hormone synthesis. That is why substantial increase of patients are at the risk of thyroid dysfunction. Subclinical hypothyroidism (SCH) is associated with serious complications. Substantial number of patients have risk of SCH getting converted into primary hypothyroidism (23). The prevalence of subclinical hypothyroidism and primary hypothyroidsm is constantly increasing, especially in women. It is now widely recognized that TSH measurement is a sensitive test for detecting both subclinical hypothyroidism and primary hypothyroidism. This measurement is recommended as the first test for diagnosing thyroid disorder in patients (18). In the present study predominant population with thyroid dysfunction was observed in females. Thyroid diseases are frequently associated with erythrocyte abnormalities (19). Although it has been reported that thyroid dysfunction might be associated with some forms of anemia, especially in childhood, the prevalence of this association in adults varies widely

(18). Kinetic approach and morphological approach were better studied by low cost assement of MCV in whole blood along with these informations. Hypothyroidism can cause certain forms of anemia on the one hand or hyperproliferation of immature progenitors on the other hand. The anemia is usually macrocytic hypochromic and/ or normocytic anemia with an increased MCV, and hypothyroidism with moderate severity (18,25). The anemia of hypothyroidism has been ascribed to a physiological compensation for the diminished need of tissues for oxygen. The low plasma erythropoietin levels found in hypothyroid anemia is in accord with this hypothesis. An overall increase in the size of the red cells has been observed after thyroidectomy in patients with uncomplicated primary hypothyroidism. Hypothyroidism should always therefore be considered as a possible cause of unexpected and unexplained anemia. An increase in MCV may develop rapidly in association with the evolving hypothyroidism. On replacement therapy with thyroxine the MCV was found to fall progressively, even if the initial value was within the normal range. The cause of the increase in size of the red cells and of the minor degree of anisocytosis in uncomplicated hypothyroidism is unknown (20, 21). The present study showed increased MCV values in untreated and treated subclinical hypothyroidism and primary hypothyroidism subjects. Although no definitive mechanism(s) can be suggested to explain the larger prevalence of increased RDW in patients with thyroid dysfunction, results of this retrospective cross-sectional analysis suggest that abnormal levels of thyroid hormones might substantially influence the size variability of circulating RBCs (22). The present study also showed increased RDW, HB, HCT and RBC in untreated SCH and primary hypothyroid as compared to treated SCH and primary hypothyroid patients. On the basis of assessment of MCV, we found patients were at the risk of normocytic anemia.

Conclusion

Thyroid hormones (T3 and T4) have a significant influence on erythropoiesis. In view of this present study among 600 subjects, we found increased levels of haematological parameters like Hb, RBC, MCV, HCT, RBC% and RDW in thyroid dysfunction patients of kashmir valley, which suggests that abnormal levels of thyroid hormones might substantially influence the size variability of circulating RBC's, predisposing patient to normocytic anemia. There might be some limitation with this study like, insufficient data, and small sample size. Since this was retrospective-hospital based study, further investigation is needed in studying the role of all types of anemias, erythrocyte abnormalities with increased sample size in thyroid dysfunction patients at district levels of state. Mass screening of thyroid hormone profile and TSH value greater than 10 mIU/ml required intervention and proper follow-up. Substantial numbers of patients have risk of SCH which could be converted into primary hypothyroidism and psychiatric problems. These abnormalities should be investigated and corrected and their presence could steer towards thyroid dysfunction allowing its early management. We suggest those people with thyroid disorder should have routine screening of haematological, biochemical and hormonal profile assay and simultenously proper management of this metabolic disease should be provided base on American endocrinologists guidline etc. There is no need to fear from this disease, only locally or externally available foods high in iodine mineral are good source and supplement.

Acknowledgements

We thank lab staff of department of biochemistry and pathology at GMC, especially Mr Zahoor Ahmad, Mr Javaid, Ms Fizalah, Ms Ishrat and Ms Sumaira for the technical assistance. We specially are thankful to reviewers who helped us in the necessary correction of this manuscript.

References

1. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev. 2001; 81(3): 1097-142.
2. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995; 43:55-68.
3. Helfand M, Redfern CC. Clinical Guideline Part 2: Screening for thyroid disease: An update. Ann Intern Med 1998; 129:144-58.
4. Vanderpump MP, Tunbridge WM. The epidemiology of thy roid disease. In: Braverman LE, Utiger RD, eds. The Thyroid, 9th edn, Philadelphia: Lippencott-Raven 1996; p. 474-82.
5. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrinol (Oxf) 1977;7:481-93.
6. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160:526-34.
7. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANESIII). J Clin Endocrinol Metab 2002; 87:489-99.
8. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years. A study in an urban U.S. community. Arch Intern Med 1990; 150:785-7.
9. Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P. The aging thyroid. Increased prevalence of elevated serum thyrotropinlevels in the elderly. JAMA 1979; 242:247-50.
10. Kochupillai N, Mehta M. Iodine deficiency disorders and their prevention in India. Rev Endocr Metab Disord 2008;9:237-244.
11. UshaMenon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, NairV, Kumar H. High prevelance of undetected thyroid disorders in an iodine sufficient Adult South Indian population. J Indian Med Assoc 2009; 107:72-77.
12. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012; Jan 1;72(1):17-33.
13. Thorley-Lawson DA. Basic virological aspects of Epstein-Barr virus infection. Semin Hematol. 1988; 25(3):247-60.
14. Lande WM, Mentzer WC. Hemolytic anaemia associated with increased action permeability. Clin Haematol. 1985; 14(1):89-103.
15. Kosenli A, Erdogan M, Ganidagli S, Kulaksizoglu M, Solmaz S, Kosenli O,Unsal C, Canataroglu A. Anemia frequency and etiology in primary hypothyroidism. Endocr Abstr 2009; 20: 140.
16. Chu JY, Monteleone JA, Peden VH, Graviss ER, Vernava AM. Anemia in children and adolescents with hypothyroidism. Clin Pediatr (Phila). 1981Nov; 20(11): 696-9.
17. Franzese A, Salemo M, Argenziano A, Buongiovanni C, Limauro R, Tenore A. Anemia in infants with congenital hypothyroidism diagnosed by neonatal screening. J Endocrinol Invest 1996; 19:613-19.
18. Lippi G, Montagnana M, Salvagno GL and Guidi GC. Should women with abnormal serum thyroid stimulating hormone undergo screening for Anaemia? Arch Pathol Lab Med 2008; 132(3):321-2.
19. Omar S, Hadj-Taeib S, Kanoun F, Hammami MB, Kamoun S, Ben Romdhane N et al. Erythrocyte abnormalities in thyroid dysfunction. Tunis Med 2010; 88(11):783-8.
20. Sahin M, Toprak SK and Altintas ND. Should Women with Abnormal Serum Thyroid Stimulating Hormone Undergo Screening for Anemia? Arch Pathol Lab Med 2009; 133(8): 1188-9.
21. Horton L, Coburn RJ, England JM, Himsworth RJ. The Thehematology of hypothyroidism. Q J Med 1976; 45(177):10123.
22. Montagnana M, Lippi G, Targher G, Salvagno GL and Guidi GC. The red blood cell distribution width is associated with serum levels of thyroid stimulating hormone in the general population. Int J Lab Hematol 2009; 31:581-2.
23. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004; 291(2): 228-3.
24. Sethi V, Kapil U. Iodine Deficiency and Development of Brain. Indian J Pediatr 2004; 71:325-9.
25. Ibrahim A, Nurcan B, Nihat S and Halil LK. Evaluation of biochemical, hematological and thyroid function parameters in nondipper and dipper hypertensive patients. Cent Eur J Med 2012; 124(13-14: 439-443.