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REVIEW ARTICLE

Impact of Thyroidectomy in BMI and Some Biochemical Markers related with Bone Turnover in Hypothyroidism Women

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ABSTRACT:
In common, thyroid hormones (TH) have intense effect on bone strength and mineral metabolism. The aims of this study was To investigate the impact of body mass index (BMI) in some physio-biochemical tests related with bone metabolism. This study included 51 hypothyroidism women and 43 healthy women divided according to BMI (normal, overweight and obese) groups and hypothyroidism patients were subdivided into: first diagnosed, prethyroidectomy and postthyroidectomy, the physio-biochemical assay included (BMI, CYP1A1, calcium and phosphorus) and hormonal assay (osteopontin (OPN), TSH, fT3, fT4 and calcitonin (CT)). The results showed that there was a significantly increased (P≤ 0.05) in TSH level and significantly decreased (P≤ 0.05) in fT4 and OPN levels in post thyroidectomy groups when compared to pre thyroidectomy groups for different BMI categories. As well as there was a significantly increase (P≤0.05) in BMI and significantly decrease(P≤0.05) in TSH and fT4 levels at duration after thyroidectomy > 1 year when compared to duration after thyroidectomy ≤ 1 year. There was higher levels of TSH and lower levels of fT3, fT4, OPN, CYP1A1 and calcium in hypothyroidism women when compared to control group. First diagnosed hypothyroidism women showed a significantly decrease(P≤ 0.05) in OPN level when compared to pre thyroidectomy and post thyroidectomy groups. **Conclusion:** Total thyroidectomy can cause a significant increase in BMI and significant decrease in thyroid hormones, OPN and calcium levels in hypothyroid women.

KEYWORDS: Thyroidectomy, Thyroid hormones, OPN, Cyp4501A1, Calcitonin, Calcium, phosphorus.

INTRODUCTION:
Hypothyroidism is referred to a deficiency of thyroid hormones production (2). Obesity is progressively more being recognized as a major epidemic disease. Previous studies suggested that BMI profile can be affected by even small changes in TSH level (1).

Thyroid hormones impact growth, development, metabolism (3), bone and heart physiology (4), so hypothyroidism effect on numerous metabolic processes and in all tissues of the body and so every tissue in the body is affected to a greater or lesser extent in thyroid hormone deficiency and the cardiovascular system is the most sensitive one (5,6) and hypothyroidism revealed to be significantly associated with female gender and old age (7). Thyroid hormones play an important role in the regulation of metabolic state (8) and it can alter the number and activity of the components of mitochondrial respiratory chain. This may lead to increasing in the generation of reactive oxygen species (ROS) (9). Oxidative stress is referred to the damage of tissue which caused by ROS (10) and interferes with several cellular functions, in particular transcriptional regulation. In addition, TSH is associated with OPN that

is phosphoglycoprotein that produced by several cell types, including fibroblasts, osteocytes, immune cells like activated macrophages and T cells, cells of brain and kidney, vascular smooth muscle cells, hepatocytes, neural cells (11,12) endothelial and epithelial cells (13) .So it is produced by the cells of local tissue and enters in the blood via its attachment with CD44 and integrin receptors (14), OPN play a role in thyroid dysfunction diseases (15,16).

Human cytochrome P450 1A1 (CYP1A1) is down regulated by oxidative stress (17) which is one isoform of cytochromes P450 (CYP) superfamily and responsible for oxidation of xenobiotic and play a crucial role in the safety of drug (18). Previous study indicated that hypothyroid condition can reduce the activity of CYP in humans (19) and the mRNA expression of CYP have been decreased in hypothyroid rats (20).

Thyroid hormones regulate bone remodeling cycle. In hypothyroidism, bone turnovers reduced and the phases of bone re sorption and formation are impaired that result in increasing the duration of the bone remodeling cycle which in turn can lead to prolonged period of secondary mineralization (21).

The current study aimed to investigate the impact of body mass index (BMI) in some physio- biochemical tests that related with bone turnover as an early indicator which may can prognostic use to hypothyroidism occurrence.

MATERIALS AND METHODS:

Samples were collected from Mrjan teaching hospital/in Babylon province/Iraq and included 51 hypothyroidism women and43 healthy women. Both groups were divided according to BMI for three sub groups: 33 healthy women and 9 hypothyroidism women with normal (BMI 18.5-24.9) kg/m^2.5 healthy women and 9 hypothyroidism women with over weight (BMI 25-29.9) kg/m^2 and finally 5 healthy women and 27 hypothyroidism women with obesity (BMI≥30)kg/m^2. BMI was calculated by using the formula BMI=weight (kg)/height^2 (m)^2(22). In addition, hypothyroidism patients were subdivided into: first diagnosed (6patients), pre-thyroidectomy (21patients) and post thyroidectomy (24 patients) and all study samples were undergo to biochemical assay (CYP1A1, calcium and phosphorus) and hormonal assay (osteopontin, TSH, fT3, fT4 and calcitonin). A questionnaire was designed to obtain information from patients and controls groups according to ethical approval of Iraqi ministry of health and permission of patients to enrolled to this study.

Exclusion Criteria:
Included several pathological, normal physiological conditions and daily habitat can interfere with hypothyroidism case such as: heart disease, hypertension, diabetes mellitus, pregnancy and smokers, all of these were excluded in this study.

Blood Sampling:
3ml of blood was centrifuged at 3000 rpm for 5 minutes. Levels of TSH (BiomerieuxSA/France), fT3, fT4, osteopontin, CYP1A1and calcitonin (Elabscience) were evaluated by Enzyme-Linked-Immuno-Sorbant Assay (ELISA).The concentrations of calcium (Randox/United Kingdom) and phosphorus (Spinreact, S.A.U./SPAIN) levels were done by colorimetric method and absorbance of color was read by spectrophotometerat 570 nm for calcium and 710 nm for phosphorus.

Statistical Analysis:
Statistical analysis were done using SPSS version (19) and differences in means analyzed by t-student test and completely randomized design test (CRD). The results were present as sample size (n), mean±standard error (SE). P-value ≤0.05 was statistically significant.

RESULTS:

In this study, the frequency percentage of the participant with normal body mass index were 33(76.74%) and 10(19.60%) while the frequency percentage of the participant with overweight were 5 (11.62%) and 11(21.56%) and finally the frequency percentage of the participant with obesity were 5(11.62%) and 30(58.82%) for control and hypothyroidism women respectively as shown in figure (1).

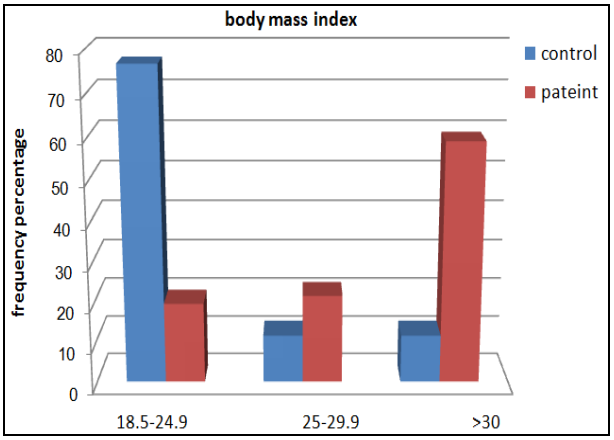

Figure (1):The frequency percentage for patients (hypothyroidism women) and control according to body mass index.

In this study, the comparison between patients and healthy subjects referred to significant increase (P≤ 0.05) in body mass index and TSH levels while fT3, fT4, OPN, Cyp450 1A1and calcium concentrations had significantly decreased (P≤0.05) in hypothyroidism

women when compared to healthy subjects. Also, there was no significant mean differences of calcitonin and phosphorus concentrations between patients and healthy subjects as shown in table (1).

Table (1):Mean levels of study parameters in hypothyroidism women patients and healthy women.

Study parameters	Control (N=43)	Hypothyroidism patients (N=51)	Sig. level
	Mean±S.E	Mean±S.E	
BMI (Kg/m^2)	23.74±0.37	30.54±0.74	0.0013 *
TSH (μIu/ml)	1.86±0.14	14.20±3.42	0.001 *
fT_3 (Pg/ml)	2.56±0.25	1.57±0.12	0.0041 *
fT_4 (ng/dL)	1.80±0.02	0.59±0.04	0.0069 *
OPN (ng/ml)	5.85±0.13	3.71±0.23	0.0024 *
CT (Pg/ml)	50.50±1.72	54.21±1.32	0.086
CYP (ng/ml)	8.22±0.10	7.52±0.14	0.0015 *
Ca (mg/dL)	10.22±0.44	8.18±0.16	0.0011 *
P (mg/dL)	3.87±0.13	4.26±0.27	0.229

t-student test

***Significant differences at p≤0.05**

Table (2) shows a significant increase (P<0.05) in OPN hormone levels in pre and post hypothyroidism women in compare with first diagnosed group, while there were no significant differences (P>0.05) in BMI, TSH, fT3, fT4, CT, CYP 450 1A1, Ca and phosphorus levels among different groups of hypothyroidism women (Table 2)

Table (2): Mean levels of study parameters in different groups of hypothyroidism patients .

Groups Parameters	First diagnosed	Prethyroidect-omy	Postthyroidect-omy	$LSD_{(0.05)}$
	Mean±S.E (N=6)	Mean±S.E (N=21)	Mean±S.E (N=24)	
BMI(Kg/m^2)	31.10±2.29	29.72±1.21	31.12±1.05	2.792
TSH (μIu/ml)	24.08±8.47	7.35±2.20	17.73±6.56	17.537
fT_3 (Pg/ml)	1.17±0.04	1.86±0.23	1.42±0.15	0.641
fT_4 (ng/dL)	0.48±0.01	0.67±0.09	0.55±0.02	0.139
OPN (ng/ml)	1.57±0.08	5.54±0.09	2.64±0.13	0.244 *
CT (Pg/ml)	51.58±2.47	56.91±2.96	52.49±0.73	4.840
CYP (ng/ml)	7.07±0.33	7.82±0.26	7.38±0.15	0.499
Ca (mg/dL)	8.91±0.68	8.27±0.23	7.93±0.22	0.599
P (mg/dL)	4.34±0.59	4.10±0.26	4.37±0.53	1.041

Completely randomized design (CRD)

***Significant differences at p≤0.05**

According to the BMI, the results showed that the hypothyroidism women patients with normal BMI were revealed a significant increase (p≤0.05) in TSH level while fT4,OPN,CYP4501A1and Ca levels had significantly lower (p≤0.05) level in hypothyroidism women when compared to control. In overweight and obese hypothyroidism patients, there was a significant increase (P≤ 0.05) in TSH levels in comparing with control group. While fT3, fT4and OPN had significantly lower (p≤0.05)than control group, whereas the obese hypothyroidism patients had significantly lower(p≤0.05)levels of Ca concentration than control group as show in table (3).

Table (3):Mean levels of physio biological parameters in hypothyroidism women patients and control group according to BMI.

BMI	Normal (18.5-24.9)		Sig. level	overweight (25-29.9)		Sig. level	Obese (≥30)		Sig. level
Groups parameters	control Mean±S.E (N=33)	Hypothyroidism patients Mean±S.E (N=10)		control Mean±S.E (N=5)	Hypothyroidism patients Mean±S.E (N=11)		control Mean±S.E (N=5)	Hypothyroidism patients Mean±S.E (N=30)	
TSH(μIu/ml)	1.87±3.15	16.12±5.72	0.009*	1.79±0.71	15.00±5.45	0.007*	2.14±0.53	13.27±3.30	0.005*
fT_3 (Pg/ml)	2.41±0.22	1.89±0.41	0.334	3.03±0.41	1.58±0.39	0.039*	4.01±0.89	1.46±0.23	0.0006 *
fT_4 (ng/dL)	1.81±0.04	0.73±0.07	0.0007 *	1.78±0.07	0.60±0.06	0.0003 *	1.69±0.04	0.54±0.04	0.0002 *
OPN(ng/ml)	5.87±0.23	4.35±0.42	0.0004 *	5.76±0.42	3.42±0.40	0.001*	6.24±0.42	3.60±0.24	0.002*
CT (Pg/ml)	51.08±1.78	50.99±3.24	0.983	48.61±3.24	53.36±3.09	0.152	61.09±8.54	55.59±1.87	0.376
CYP(ng/ml)	8.28±0.15	7.41±0.27	0.003*	8.04±0.26	7.86±0.25	0.443	7.82±0.17	7.44±0.15	0.463
Ca (mg/dL)	9.89±0.36	7.92±0.66	0.004*	11.29±0.65	8.56±0.63	0.089	10.05±1.04	8.13±0.38	0.005*
P (mg/dL)	3.92±0.27	4.76±0.49	0.236	3.72±0.49	4.27±0.47	0.307	4.25±0.49	4.09±0.28	0.754

t-student test

***Significant differences at p≤0.05**

Table (4) shows that there was a significantly increase (P≤ 0.05) in TSH level and significantly decrease(P≤ 0.05) in fT4 and OPN levels in post thyroidectomy groups when compared to pre thyroidectomy groups for different BMI categories. Both of pre thyroidectomy and post thyroidectomy groups with normal BMI had significantly(P≤0.05)higher mean levels of TSH and significantly(P≤0.05)lower mean levels of fT4,

OPN, CYP4501A1, CT and Ca than control group with normal BMI, while phosphorus (p) was no significant decrease. In overweight groups, TSH had significantly higher(P≤0.05)level and OPN had significantly lower (p≤0.05) level in post thyroidectomy group than both control and pre thyroidectomy groups; as well as, there were a significant decrease (p≤0.05)of fT3 and fT4 levels in both pre thyroidectomy and post thyroidectomy groups in compered to healthy subjects. In obese groups, **t**here was a significant increase (P≤0.05) in TSH level and significant decrease(P≤0.05) in the levels of fT3, fT4, OPN and Ca in pre and post thyroidectomy groups in compered to healthy subjects. In addition, CT and CYP had revealed a significant increase(P≤ 0.05) in their mean levels in compered to both post thyroidectomy and control groups.

Table (4): Mean levels of phyio-biocbemical parameters in prethyroidetomy postthyroidecomy patients and control groups according to BMI

	Normal (18.5-24.9)			**LSD**	**Overweight (25-29.9)**		
Groups parameters	**Control Mean±S.E (N=33)**	**Prethyroid-ectomy Mean±S.E (N=7)**	**Postthyroid-ectomy Mean±S.E (N=5)**		**Control Mean±S.E (N=5)**	**Prethyroid-ectomy Mean±S.E (N=3)**	**Postthyroid-ectomy Mean±S.E (N=6)**
TSH(µIu/ml)	1.87±2.93	7.54±6.37	50.02±11.92	0.034*	1.79±5.33	0.99±0.07	21.51±6.88
fT_3 (Pg/ml)	2.41±0.23	1.81±0.50	2.47±0.94	1.271	3.03±0.42	2.69±0.77	1.16±0.54
fT_4 (ng/dL)	1.81±0.04	0.83±0.082	0.52±0.15	0.052*	1.78±0.07	0.79±0.12	0.54±0.09
OPN(ng/ml)	5.87±0.13	5.18±0.27	2.78±0.51	0.509*	5.76±0.23	5.92±0.42	2.79±029
CT (Pg/ml)	51.08±1.78	51.16±3.86	48.89±7.22	0.038	48.61±3.23	51.77±5.89	55.06±45.17
CYP(ng/ml)	8.28±0.13	7.44±0.29	7.49±0.54	0.543*	8.04±0.24	8.39±0.44	7.72±0.31
Ca (mg/dL)	9.89±0.37	7.88±0.81	8.61±1.52	0.230*	11.29±0.68	9.21±1.24	7.96±0.88
P (mg/dL)	3.92±0.24	3.72±0.52	4.01±0.97	0.261	3.72±0.43	4.43±0.79	4.06±0.56

Continue-Table no (4)

	LSD	**Obese (≥30)**			**LSD**
Groups parameters		**Control Mean±S.E (N=5)**	**Prethyroid-ectomy Mean±S.E (N=11)**	**Postthyroid-ectomy Mean±S.E (N=13)**	
TSH(µIu/ml)	0.036*	2.14±0.53	9.31±5.33	12.27±4.21	0.041*
fT_3 (Pg/ml)	0.509*	4.02±0.89	1.73±0.42	1.38±0.33	0.723*
fT_4 (ng/dL)	0.492*	1.69±0.04	0.54±0.07	0. 55±0.05	0.392
OPN(ng/ml)	1.209*	6.28±0.43	5.66±0.23	2.56±0.18	1.098*
CT (Pg/ml)	7.106	61.09±8.54	63.18±3.23	51.98±2.55	0.061*
CYP(ng/ml)	1.531	7.82±0.18	8.19±0.24	7.214±0.19	0.720*
Ca (mg/dL)	0.208	10.05±1.04	8.28±0.68	7.83±0.54	0.600*
P (mg/dL)	1.632	4.26±0.49	4.19±0.43	3.86±0.34	1.687

CRD

***Significant differences at P≤ 0.05**

According to the duration after thyroidectomy, there was a significant increase (*P*≤0.05) in BMI and TSH levels and significant decrease (P≤0.05) in fT3, fT4, OPN, CYP4501A1 and Ca levels in both durations thyroidectomy≤ 1 year and thyroidectomy >1 year when compared to control group. There was a significantly increase(P≤0.05) in BMI and significantly decrease(P≤0.05) in TSH and fT4 levels at duration after thyroidectomy>1 year when compared to duration after thyroidectomy ≤ 1 year but other parameters(CT phosphor) did not reveal any significant difference between these two groups as shown in table (5).

Table (5): Mean levels of physio-biochemical parameters in groups according to the duration after thyroidectomy.

Groups Parameters	control (N=43)	≤ 1 year (N=5)	> 1 year (N=19)	LSD
BMI (Kg/m^2)	23.74±0.37	29.77±1.73	31.48±1.26	0.149*
TSH (µIu/ml)	1.86±0.14	26.99±18.38	15.29±6.93	0.02 *
fT_3 (Pg/ml)	2.56±0.25	1.69±0.49	1.34±0.14	0.382 *
fT_4 (ng/dL)	1.80±0.02	0.57±0.05	0.54±0.02	0.026 *
OPN(ng/ml)	5.85±0.13	2.78±0.18	2.59±0.16	0.681 *
CT (Pg/ml)	50.50±1.72	51.00±1.74	52.89±0.80	0.058
CYP (ng/ml)	8.22±0.10	7.36±0.52	7.39±0.14	0.774 *
Ca (mg/dL)	10.22±0.44	7.91±0.34	7.93±0.27	0.225 *
P (mg/dL)	3.87±0.13	3.13±0.28	4.70±0.64	0.329

CRD

***Significant differences at p≤0.05**

DISCUSSION:

The results of this study referred to significantly increase in BMI in hypothyroidism women when compared to control group, this may be due to leptin level which may play a role in the hyper thyrotropinemia of obesity and also rise susceptibility to thyroid autoimmunity and consequent hypothyroidism. The chief action of leptin is related with increasing in appetite and food intake. Leptin has also been shown to excite the transcription of pro thyrotropinreleasing hormone (TRH) and subsequently TSH (23). Another explanation is that adipose tissue secrete inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)‑1 and IL‑6 which had inhibiting both mRNA expression of sodium/iodide symporter and the activity of iodide uptake (24). In this study the

significant increase ($p \leq 0.05$) in BMI of post thyroidectomy group at period>1year after total thyroidectomy may be due to absence of native thyroid hormones in the body of this patients group. Deficiency of thyroid hormone is associated with decreased thermogenesis, decreased metabolic rate, and correlate with a higher body mass index (BMI) and a higher prevalence of obesity (1).

The result of this study revealed that TSH level was significantly increased ($p \leq 0.05$) and thyroid hormones were significantly decreased ($p \leq 0.05$) in hypothyroidism women when compared with control, this result due to the activity of the thyroid gland is mainly regulated by the concentration of the pituitary thyroid stimulating hormone (TSH). The deficiency in the function of pituitary or thyrotropin would result in hypothyroidism (25). In this study, the significantly decreased($p \leq 0.05$) inTSH and fT4 levels of post thyroidectomy group at period after thyroidectomy >1 year when compared to Thyroidectomy≤ 1 year group may be due to the effect of thyroxin treatment for long time period in the patients of this group.

Osteopontin was not only establish to be involved in the bone formation and calcification, but also in processes such as inflammation, cell adhesion and migration and inhibition of apoptosis therefore it had expressed by various body tissues (26). In this study serum OPN levels were decreased in hypothyroidism women, may be due to these some cell processes going on in the thyroid gland which probably decrease OPN receptor co expression. There was no exact function of OPN in thyroid dysfunction has been reported (16). In this study, the levels of OPN hormone found to be decreased significantly ($P<0.05$) in first diagnosed and post thyroidectomy groups when compared to pre thyroidectomy group of patients, which may be due to more deficiency of thyroid hormone in first diagnosed hypothyroidism women who they were did not consume any thyroxin treatment and in post thyroidectomy group who they were totally thyroidectomized which lead to acute deficiency in serum thyroxin hormone when compared to prethyroidectomy group who had thyroid gland and consumed thyroxin treatment or may be due to thyroxin level in each patients groups. Reza *et al*. (16) found a positive correlation between osteopontin and thyroxin hormone. The results of osteopontin in this study are accordance with Reza *et al*, (16) and Alwakeel*et al*,(27), who they were revealed that OPN was elevated in hyperthyroidism and decreased in hypothyroidism.

Besides OPN physiological functions it is associated with bone metabolism and remodeling. OPN is required for osteoclastic resorption of bones (28).In this study, the results shows the low level of calcium in hypothyroidism patients when compared to control, this is may be due to that thyroxin normally regulates calcium levels in the blood through releasing calcium from the osteoclast cells of bone tissue (29). Normally, thyroxin regulates blood calcium levels by releasing calcium from the cells so less calcium was released in hypothyroidism patients (30) and hypocalcaemia in hypothyroidism may also be due to the deficiency of thyroid hormones or undetectable levels of thyroid hormones in the serum would suppress the activation of osteoclasts. This results in deceleration of bone resorption and decreased bone turnover(31). Moreover, hypocalcaemia in hypothyroidism patients may be due to the deficiency of thyroid hormones that in turn lead to increase the urinary excretion of calcium and decrease in the absorption of calcium at tubular levels (23).

Our result accordance with previous study indicated that the activity of CYP450 was decreased in hypothyroidism women patients (19), this may be due to the low level of thyroid hormone in hypothyroidism patients which is responsible for regulation of the expression of CYP through its control on cellular levels of CYP reductase, which had ability to inactivate CYPs (33).

In this study the level of CT was decreased for most hypothyroidism women patients after total thyroidectomy, this decreasing may be referred to that the abundant source of Ct level in the serum of these participants was thyroid gland.

CONCLUSION:

Thyroidectomy can cause a significant increase in BMI and there was a significant decrease in thyroid hormones and OPN levels in hypothyroid women which may be associated with suppress the bone remodelling causing a significant decrease in calcium level in this study.

REFERENCES:

1. Knudsen N, Laurberg P, Rasmussen L B, Bülow I, Perrild H, Oves-en L. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J ClinEndocrinol Metab*, 90;2005:4019‑24.
2. Dunn D. Hypothyroidism in Women. *Nursing for Women's Health*; 20 (1); 2016:150-155.
3. Damiano F, Rochira A, Gnoni A, and Siculella L. Action of Thyroid Hormones, T3 and T2, on Hepatic Fatty Acids: Differencesin Metabolic Effects and Molecular Mechanisms. *Int. J. Mol. Sci.* 18;2017: 744.
4. Pedro J, TárragaLópez P J, López C F, Naharrode Mora F, Montes J A R, Albero J S, Mañez A N, Casas A G. Osteoporosis in patients with subclinical hypothyroidism treated with thyroid hormon. *Clinical Cases in Mineral and Bone Metabolism,* 8(3); 2011: 44-48.
5. Kumar R, Sitaram C M, and Anusha K. Clinical profile of patients with hypothyroidism. *MRIMS J of Health Sciences*, 4 (2);2016:7476.
6. Vairamanikandan S, Sathyamurthy P, Rajkumar M, and Vaasanthi A. Clinico laboratory Profile of Hypothyroidism with Emphasis

on Cardiovascular Manifestations. *Panacea Journal of Medical Scie-nces*, 6 (2);2016: 59-65.
7. Gopalakrishnan A. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian J Endocrinol Metab*; 17(4); 2013:647-52.
8. Klein I, and Danzi S. Thyroid disease and the heart. *Circulation*, 116;2007: 1725-1735.
9. Petrulea M, Muresan A, and Duncea I. Oxidative Stress and Antioxidant Status in Hypo and Hyperthyroidism. Creative Comm-ons Attribution License;2012.
10. Jenkins R. Exercise and oxidative stress methodology: a critique. *Am J ClinNutr*, 72(2);2000: 670-674.
11. Wen Y, Jeong S, Xia Q, and Kong X. Role of osteopontin in liver diseases. *International Journal of Biological Sciences*, 12 (9);2016: 1121–1128.
12. Kothari A N, Arffa M L, and Chang V. Osteopontin a master regulator of epithelial-mesenchymal transition, *Journal of Clinical Medicine*, 5(4); 2016: 39.
13. Gursoy G, Acar Y, and Alagoz S. Osteopontin: A multifunctional molecule. *J Med Sci*; 1;2010: 55–60.
14. Nau G J . Osteopontin receptor. In: Oppenhium JJ, Feldmann M, Duru, S.K. Cytokine reference: A compendium of cytokines and other mediators of host defense. 1st ed. San Diego: Academic press.2000:1859–1870.
15. Ambrosi G J, Catalan V, Ramirez B, Rodriguez A, and Colina I. Plasma osteopontin levels and expression in adipose tissue are increased in obesity. *J ClinEndocrinolMetab*; 92;2007: 3719-3727.
16. Reza S, Shaukat A, Arain T M, Riaz Q S, and Mahmud M. Expression of Osteopontin in Patients with Thyroid Dysfunction. *PLoS ONE*, 8(2):2013: e56533.
17. Morel Y, and Barouki R . Down-regulation of Cytochrome P450 1A1 Gene Promoter by Oxidative Stress. *Journal of Biological Chemistry*, 273 (41);1998: 26969–26976.
18. Nembri S, Grisoni F, Consonni V, and Todeschini R . In Silico Prediction of Cytochrome P450-Drug Interaction: QSARs for CYP3 -A4 and CYP2C9. *Int. J. Mol. Sci.*, 17;2016: 914.
19. Haas M, Kletzmayer J, Staudinger T, Bohmig G, Mayer G, LekoMohr Z. andDruml, W. Hypothyroidism as a cause of tacrolimus intoxication and acute renal failure: a case report. *Wien KlinWochenschr*.,112;2000:939–941.
20. Ram P A, and Waxman D J. Hepatic P450 expression in hypothyroid rats: differential responsiveness of male-specific P450 forms 2a (IIIA2), 2c (IIC11), and RLM2 (IIA2) to thyroid hormone. *Mol Endocrinol*., 5;1991:13–20.
21. Williams G R . Thyroid Hormone Actions in Cartilage and Bone. *Eur Thyroid J*, 2 ;2013:3–13.
22. WHO. Expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet*, 2;2006: 157-163.
23. Nannipieri M, Cecchetti F, Anselmino M, Camastra S, Niccolini P, and Lamacchia M.Expression of thyrotropin and thyroid hormonereceptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: Effects of weight loss. *Int J Obes*, 33;2009:1001‑6.
24. Sanyal D and Raychaudhuri M. Hypothyroidism and obesity: An intriguing link. *Indian J EndocrMetab*, 20;2016:554-7.
25. Agrawal P, Philip R, Saran S, Gutch M, MohdSayedRazi M, and Agroiya, P. Congenital hypothyroidism. *Indian J of Endocrinol and Metab*, 19 (2);2015:221-227.
26. Liou YM, Chang LY, Liaw JM, Jiang MJ. Osteopontin gene expression in the aorta and in the heart of propylthiouracil induced hypothyroid mice. *JBiomed Sci*, 12;2005: 869–880.
27. Alwakeel M A. Hend M. and Abd El Hamid S M. Osteopontin as a new biomarker for diagnosis patients with thyroid dysfunction. *AAMJ, (10);2012: 3.*
28. Asou Y, Rittling S R, Yoshitake H, and Tsuji K. Osteopontin Facilitate Angiogenesis, Accumulation of Osteoclasts, and Resorption in Ectopic Bone. *Endocrinology*, 142;2001:1325–1332.
29. Murgod R, and Soans G. Changes in electrolyte and lipid profile in hypothyroidism. *Life Science Bio Chemistry*, 2(3); 2012:150-155.
30. Roopa M, and Gladys S. Changes in electrolyte and lipid profile in hypothyroidism. *International Journal of Life Science and Pharma Research*, 2 (3);2012:154-162.
31. Mane A Y and Bhagwat V R Assessment of some biochemical markers of bone turnover in thyroid dysfunction state. *Int J Pharm Bio Sci*, 3(3);2012: 126–133.
32. Malik I, Sachdeva A, Ghalaut V S, Badra J and Sangwan L. Effect of hypothyroid state on bone metabolism and renal handling of biochemical parameters. *Sch. Acad. J. Biosci*. 3(2);2015:120-123.
33. O'Leary K A, Li H C, Ram P A, Mc Quiddy P, Waxman D J.and Kasper CB.Thyroid regulation of NADPH: cytochrome P450 oxidoreductase: identification of a thyroid-responsive element in the 5'-flank of the oxidoreductase gene. *Mol. Pha-rmacol*. 52 (1);1997:46-53.