

Original Research Articles

**SERUM OSTEOCALCIN LEVELS IN
HYPERTHYROIDISM: A CASE CONTROL
STUDY**

ABSTRACT

Aims: The aim of this study was to estimate the serum osteocalcin levels before and during treatment in hyperthyroidism and to compare with healthy controls.

Study design: Case control study.

Place and Duration of Study: Department of Biochemistry, Department of Endocrinology. M.S. Ramaiah medical college, Bangalore. December 2014 to May 2015.

Methodology: 25 newly diagnosed hyperthyroid patients ,25 patients who are euthyroid during treatment and 25 healthy controls in the age group of 20-50yrs were enrolled in this study. Serum T3,T4,TSH were assayed by electrochemiluminescence assay and serum Osteocalcin was estimated by ELISA. Calcium values were taken from my previous study which was estimated spectrophotometrically.

Results: Kruskal wallis test was used to compare T3,T4,TSH and calcium levels between three groups. There was a statistically significant difference for T3, T4, TSH and osteocalcin values among the different groups ($p < 0.001$). Post Hoc test for multiple comparisons between two groups revealed that osteocalcin levels were significantly high in newly diagnosed hyperthyroid patients compared to controls ($p = 0.02$) indicating high bone turnover. There was also a significant difference in osteocalcin levels between newly diagnosed hyperthyroid patients and patients who are euthyroid on treatment ($p = 0.04$) indicating values decreased on treatment. ROC analysis showed serum osteocalcin is a good marker for assessing bone remodeling status in hyperthyroid stage.

(Area under curve= 86.6 and p value = 0.001)

Conclusion: Osteocalcin levels in newly diagnosed hyperthyroid patients is significantly high compared to patients who are euthyroid during treatment and controls. On treatment osteocalcin levels decreases but still there is some residual bone resorption taking place. Serum osteocalcin levels can be used as a screening marker and prognostic marker for assessing hyperthyroidism induced bone remodeling. Normalizing thyroid function with anti

thyroid drugs and supplementation of calcium, vitamin D and bisphosphonates improves bone mineralization and prevent osteoporosis.

Keywords: Hyperthyroidism, osteocalcin, resorption, euthyroid, remodeling.

1. INTRODUCTION

Hyperthyroidism is an endocrinological disorder that exhibits low serum TSH levels and elevated levels of the thyroid hormones. Hyperthyroidism includes diseases that are a subset of thyrotoxicosis, caused by excess synthesis and secretion of thyroid hormone. Graves disease is an autoimmune thyroid disease in which anti TSH receptor autoantibodies cause hyperthyroidism.[1]

Hyperthyroidism is accompanied by osteoporosis with increased rate of bone formation and bone resorption caused from direct stimulation of bone cells by increased level of thyroid hormones. The severity of hyperthyroidism is directly related to the alteration in the levels of biochemical markers of bone turnover and bone loss.[2] Studies have shown that euthyroid state will only partially reduce hyperthyroid osteopenia with a bone mass recovery during 6-9 months of effective treatment. [3]

Osteocalcin is a non collagenous protein found in bone and dentin. It is secreted solely by osteoblasts and is pro-osteoblastic or bone building by nature. It is implicated in bone mineralization and calcium ion homeostasis. [4]

Calcium is one of the abundant extracellular cations in the body and it plays an important role in bone formation. Thyroid hormones stimulate bone resorption directly there by increasing the serum calcium levels and suppressing parathyroid hormone. [5]

Osteocalcin being a bone formation marker is supposed to increase in hyperthyroidism. [2]

Therefore, the present study has been taken up to show the correlation between serum osteocalcin levels and hyperthyroidism which may suggest the requirement of calcium supplementation to prevent osteoporosis in patients with hyperthyroidism.

2. MATERIAL AND METHODS

This study was conducted in department of Biochemistry, M.S.Ramaiah medical college, bangalore from December 2014 to May 2015. Patients attending outpatient department of

39 Endocrinology M.S.Ramaiah hospitals for evaluation of their thyroid status were enrolled in
40 the study.

41 A case control study which included

42 Group 1:-25 Newly diagnosed hyperthyroid patients (graves disease, multinodular goitre).

43 Group 2:- 25 Age and sex matched healthy controls

44 Group 3:- 25 Patients who are euthyroid during treatment for atleast 3 months.

45 All subjects were in the age group of 20-50 years. Written informed consent was taken from
46 both cases and controls. Study protocol was approved by Ethical committee.

47 Patients of age group>50yrs, postmenopausal women , history of osteoporosis, fractures,
48 hepatic dysfunction, parathyroid dysfunction, renal disease, malignancies and patients who
49 were on calcium supplements, vitamin D supplements, steroids and thiazides were excluded
50 from the study.

51 After taking informed consent, about 2ml of venous blood was drawn. Serum was separated
52 by centrifugation and stored at -20°C until the estimation of biochemical parameters.

53 Serum T3,T4 and TSH were assayed by electrochemiluminescence assay on Roche cobas
54 analyzer.[6,7,8]

55 Serum osteocalcin levels were estimated by ELISA.[9]

56 Serum calcium levels were taken from my previous study which was estimated by o-
57 Cresolphthalein method spectrophotometrically. [10,11]

58

59 **3. RESULTS**

60

61 The results of all variables are expressed as median values as our data did not follow normal
62 distribution. Kruskal wallis test was used to compare T3,T4,TSH, osteocalcin and calcium
63 levels among three groups. Post Hoc test is used for multiple comparisons between two
64 groups. Results were computed using SPSS (Statistical Package for the Social Sciences)
65 software version 2. The correlation between serum osteocalcin and hyperthyroidism is
66 estimated by spearman's correlation coefficient.

67

68 **Table 1: Comparison of the median values of different variables**
 69 **among newly diagnosed hyperthyroid patients, patients who are**
 70 **euthyroid during treatment for atleast 3 months and controls using**
 71 **kruskal wallis test.**

72

	Group1(Newly diagnosed hyperthyroid patients)	Group2(Controls)	Group3(Patients euthyroid on treatment)	p value
T3(nmol/l)	4.56(3.03-5.60)	1.81(1.64-1.98)	2.07(1.42-2.65)	<0.001
T4(nmol/l)	230.8(171.35-292.10)	109.4(97.44-128.5)	190(161-250.54)	<0.001
TSH(μIU/ml)	0.005(0.005-0.010)	2.56(1.61-3.23)	1.5(0.5-1.9)	<0.001
Calcium(mg/dl)	11.33(10.76-12.21)	10.3(9.2-11.19)	11.07(10-11.96)	<0.008
Osteocalcin (ng/ml)	9.9(0.35-35.55)	0.001(0.001-0.15)	0.1(0.001-2.20)	<0.001

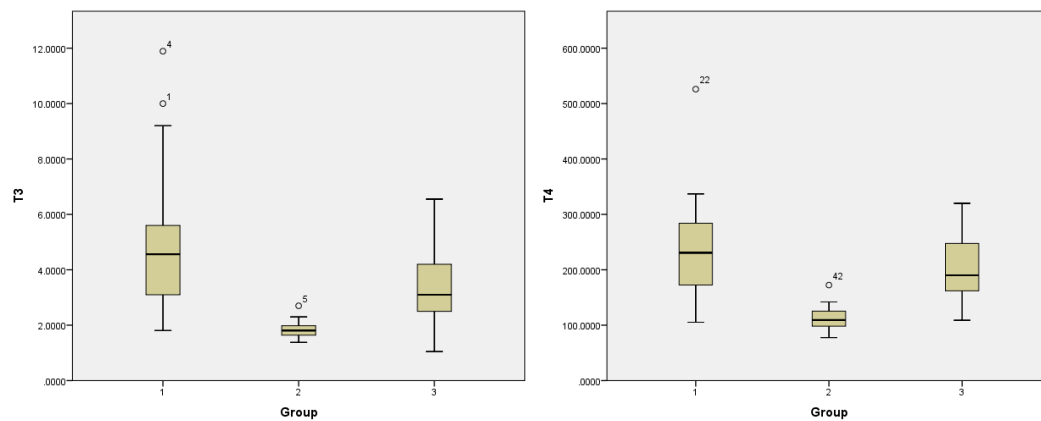
73

74 There is a statistically significant difference for T3, T4, TSH and osteocalcin values among
 75 the different groups with p value <0.001 and for calcium among different groups with p value
 76 < 0.008.

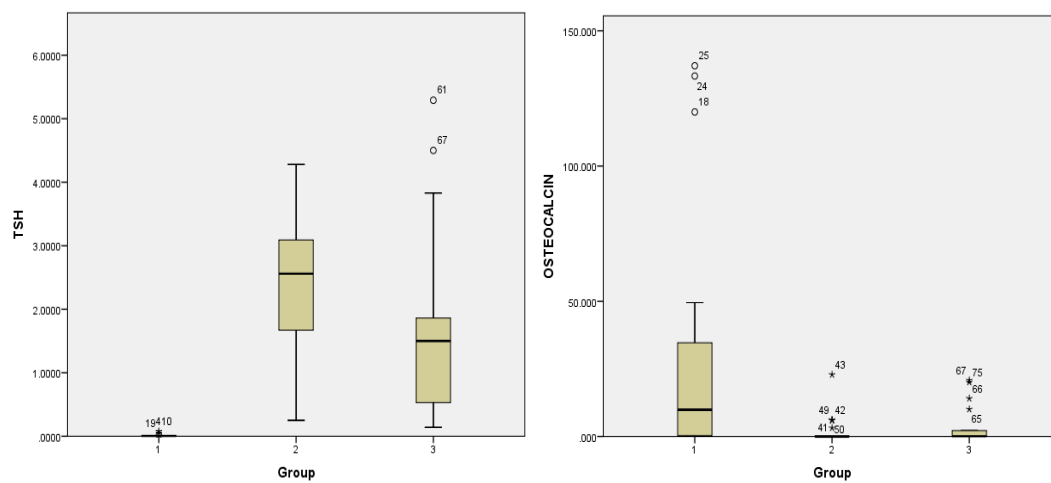
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78 **Figure 1: Comparison of median values of T3,T4,TSH, Osteocalcin and**
 79 **Calcium levels in newly diagnosed hyperthyroid patients, controls and**
 80 **patients who are euthyroid during treatment for hyperthyroidism.**

81

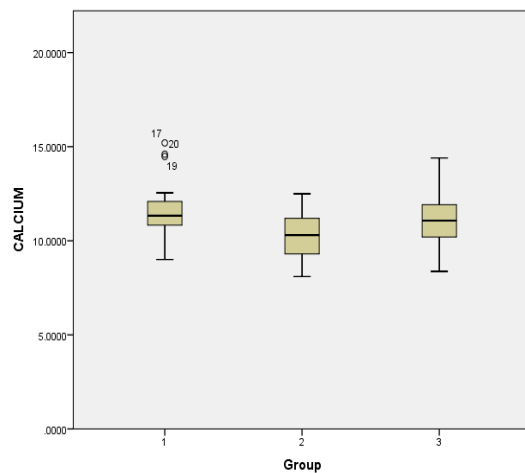


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86

87 Median values for T3 and T4 in newly diagnosed hyperthyroid patients were found to be
88 increased when compared to controls and patients on treatment in the euthyroid state.
89 Patients on treatment have achieved T3 and T4 values which is almost normal.

90 Median values for TSH in newly diagnosed hyperthyroid patients were low compared to
91 controls and patients on treatment with a statistically significant difference of $p=0.001$.

92 Osteocalcin levels were elevated in hyperthyroid state compared to controls. In euthyroid
93 stage, serum osteocalcin levels decreased considerably but were found to be marginally
94 high as compared to the control group.

95 Median values obtained for calcium in group 1 is 11.33(10.6- 12.21), group 3 is 11.07(10-
96 11.96) and in controls 10.3(9.2-11.19). This indicates that compared to the controls the
97 calcium concentration is highest in the serum in newly diagnosed hyperthyroid patients and
98 tending towards normal but higher than that of controls.

99 **Table 2:- Post Hoc test for multiple comparisons between two groups**
100 **for T3, T4 and TSH:**

Dependent Variable			Mean Difference	Std. Error	Significance
T3 (nmol/l)	1	2	3.13280 [*]	0.43254	0.001
		3	2.91440 [*]	0.43254	0.001
	2	1	-3.13280 [*]	0.43254	0.001
		3	-.21840	0.43254	1.000
	3	1	-2.91440 [*]	0.43254	0.001
		2	.21840	0.43254	1.000
T4 (nmol/l)	1	2	122.28520 [*]	16.62	0.001
		3	115.01440 [*]	16.62892	0.001
	2	1	-122.28520 [*]	16.62892	0.001
		3	-7.27080	16.62892	1.000
	3	1	-115.01440 [*]	16.62892	0.001

		2	7.27080	16.62892	1.000
TSH (μIU/ml)	1	2	-2.4300800 *	.2833591	0.001
		3	-1.5890000 *	.2833591	0.001
	2	1	2.4300800 *	.2833591	0.001
		3	.8410800 *	.2833591	0.012
	3	1	1.5890000 *	.2833591	0.001
		2	-.8410800 *	.2833591	0.012

101

102 T3 and T4-

103 There is a significant difference in T3 and T4 values between newly diagnosed hyperthyroid
 104 cases and controls as also between newly diagnosed hyperthyroid and patients who are
 105 euthyroid during treatment. There is no significant difference in T3 and T4 values between
 106 controls and patients who are euthyroid during treatment as the patients have attained T3
 107 and T4 values which is almost normal.

108

109 TSH-

110 There is a significant difference in TSH values between newly diagnosed hyperthyroid
 111 patients and controls as also between newly diagnosed hyperthyroid patients and patients
 112 who are euthyroid during treatment.

113 There is moderate significant difference between controls and patients who are euthyroid
 114 during treatment which indicates TSH values are increasingly tending towards normal.

115

116 **Table 3: Post Hoc test for multiple comparisons between two groups for Osteocalcin**
 117 **and calcium**

Variable			Mean difference	Std error	Significance
OSTEOCALCIN(ng/ml)	1	2	24.215360 *	6.932379	.002
		3	22.955680 *	6.932379	.004
	2	1	-24.215360 *	6.932379	.002

	3	3	-1.259680	6.932379	1.000
		1	-22.955680*	6.932379	.004
		2	1.259680	6.932379	1.000
CALCIUM(mg/dl)	1	2	1.3880000*	.4172263	.004
		3	.4152000	.4172263	.969
	2	1	-1.3880000*	.4172263	.004
		3	-.9728000	.4172263	.068
	3	1	-.4152000	.4172263	.969
		2	.9728000	.4172263	.068

118

119 There is a significant difference in osteocalcin levels between newly diagnosed hyperthyroid
120 patients and controls indicating hyperthyroid patients have a high bone turnover.

121 There is a significant difference in osteocalcin levels between newly diagnosed hyperthyroid
122 patients and patients who are euthyroid on treatment indicating values decreased on
123 treatment. There is no significant difference between patients who are euthyroid on
124 treatment and controls.

125 There is a significant difference in calcium levels between newly diagnosed hyperthyroid
126 patients and controls. There is no significant difference in calcium levels between newly
127 diagnosed hyperthyroid patients and patients who are euthyroid on treatment and also
128 between patients who are euthyroid on treatment and controls.

129

130 **Table 4: Spearman's correlation between osteocalcin and T3.**

131

Group		Osteocalcin	Calcium	age	T3	T4	TSH
1(Newly diagnosed)							

hyperthyroid)							
Osteocalcin	Correlation coeffecient	1.000	.012	.306	.537**	.342	-.330
	Significance	-	.954	.137	.006	.094	.107

There is a positive correlation between T3 and osteocalcin in newly diagnosed hyperthyroid patients with a correlation coefficient of 0.537.

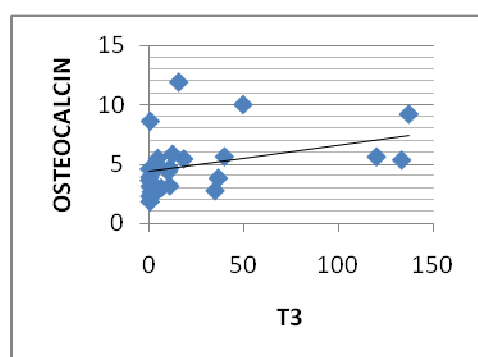
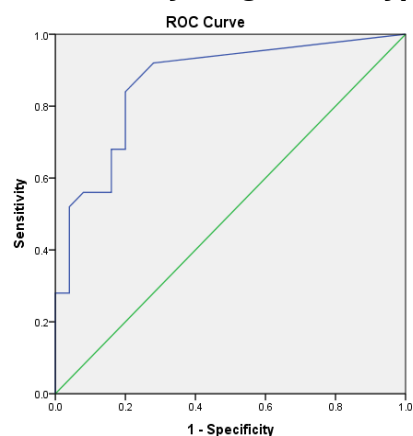


Figure 2: ROC analysis for Osteocalcin

a) Between newly diagnosed hyperthyroid patients and controls.



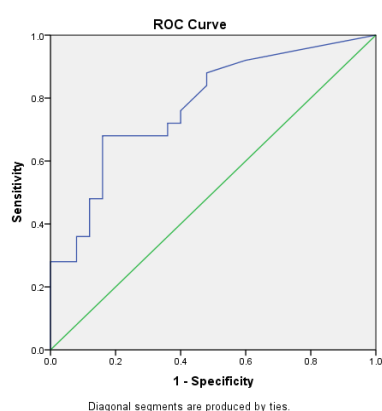
Diagonal segments are produced by ties.

145 ROC analysis between Newly diagnosed Hyperthyroid patients and Controls reveal that the
146 sensitivity of Osteocalcin was found to be 84% and specificity was 80% at a cut off value of
147 0.25.

148 Area under curve was 86% and p value was 0.001 which is statistically significant.

149

150 **b)Between newly diagnosed hyperthyroid patients and patients who are**
151 **euthyroid during treatment:-**



152

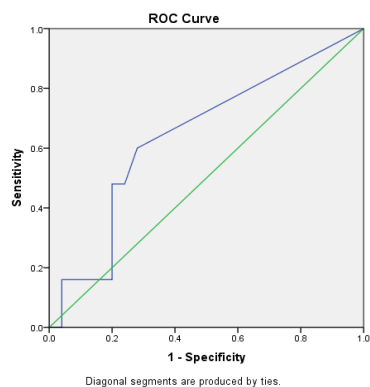
153

154 ROC analysis between Newly diagnosed Hyperthyroid patients and patients who are
155 euthyroid during treatment reveal that the sensitivity of Osteocalcin was found to be 68%
156 and specificity was 68% at a cut off value of 1.55.

157 Area under curve was 77.7% and p value was 0.001 which is statistically significant.

158

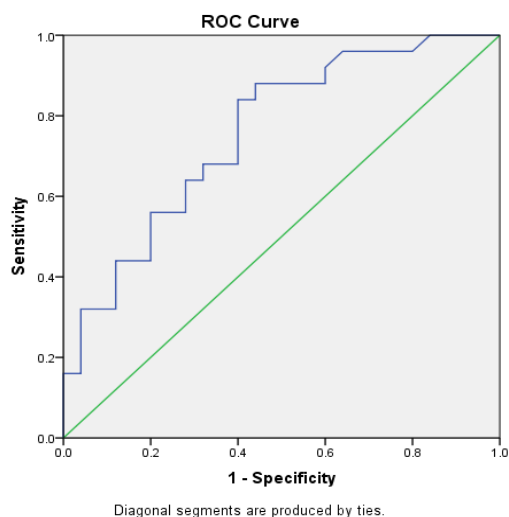
159 **c) Between patients who are euthyroid during treatment and controls:**



160
161
162 ROC analysis between patients who are euthyroid during treatment and controls reveal that
163 the sensitivity of Osteocalcin was found to be 60% and specificity was 72% at a cut off value
164 of 0.05.
165 Area under curve was 64.2 and p value was 0.08 which is statistically not significant.

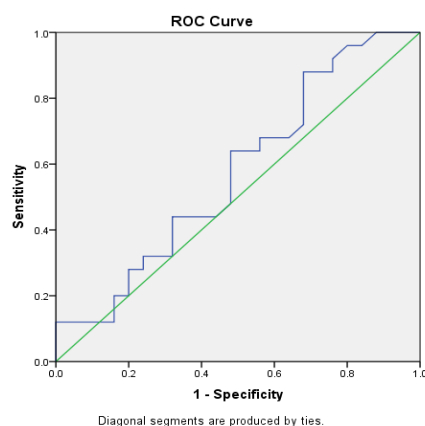
166
167
168 **Figure 3:- ROC analysis for calcium**

169
170 **a)Between newly diagnosed hyperthyroid patients and controls.**



171
172 ROC analysis between Newly diagnosed Hyperthyroid patients and Controls reveal that the
173 sensitivity of calcium was found to be 68% and specificity was 68% at a cut off value of
174 10.98.
175 Area under curve was 75.7 and p value was 0.002 which is statistically significant.

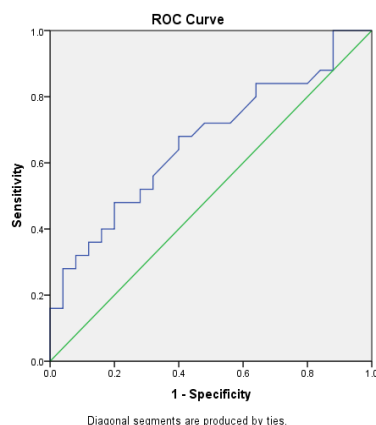
176 **b)Between newly diagnosed hyperthyroid patients and patients who are**
 177 **euthyroid during treatment.**



178
 179 ROC analysis between Newly diagnosed Hyperthyroid patients and patients who are
 180 euthyroid during treatment reveal that the sensitivity of calcium was found to be 68% and
 181 specificity was 64% at a cut off value of 10.95.
 182 Area under curve was 57.4 and p value was 0.36 which is statistically not significant.

183

184 **c) Between patients who are euthyroid during treatment and controls:**



185

186 ROC analysis between patients who are euthyroid during treatment and controls reveal that
187 the sensitivity of calcium was found to be 68% and specificity was 60% at a cut off value of
188 10.75.

189 Area under curve was 66.6 and p value was 0.45 which is statistically not significant

190

191

192 **DISCUSSION**

193

194 Hyperthyroidism is characterized by accelerated bone turnover, caused from direct
195 stimulation of bone cells by increased thyroid hormones. The cycle of bone remodeling is
196 shortened to almost 50% (from 200 to 113 days), and the proportions between bone
197 formation and bone resorption are disturbed. Those with a history of untreated
198 thyrotoxicosis extending more than a year may have severe and premature
199 osteoporosis.[11]

200 Triiodothyronine (T3), is responsible for major actions of thyroid hormones. T3 binds to
201 nuclear receptors that regulate gene transcription via interaction with thyroid hormone
202 response elements of specific genes.[12]

203 T3 regulates the chondrogenesis bone mineralization, angiogenesis and bone matrix
204 formation. T3 stimulates the IL-6 and IL-8, intensifies the effects of IL-1 and IL-6, augments
205 the synthesis of osteocalcin, collagen type 1, increases proliferation, differentiation and
206 apoptosis of osteoblasts.[13] Also, TSH deficiency could be partly responsible for the
207 skeletal loss seen in thyrotoxicosis, because it has been proposed that TSH may be a direct
208 negative regulator of bone turnover acting via the TSH receptor on both osteoblasts and
209 osteoclasts, as TSH inhibits osteoclast formation and survival. It also inhibits differentiation
210 of osteoblasts.[14]

211 Similar study conducted by Barsal et al showed that there is increase in bone formation
212 marker Osteocalcin and ALP as well as bone resorption marker, urinary calcium/ creatinine
213 levels in Hyperthyroidism. These markers failed to normalize even after attaining
214 euthyroidism. Hence he concluded that hyperthyroid patients have a high bone turnover of
215 formation and resorption even after attainment of euthyroidism and osteocalcin is a sensitive
216 marker in documenting bone remodeling during treatment of Hyperthyroidism. [15]

217 Study conducted by siddiqi et al observed a fall of the bone resorption markers urinary
218 collagen pyridinoline and deoxypyridinoline and bone formation markers osteocalcin and
219 bone ALP after 4-8 weeks of antithyroid treatment.[16]

220 The accelerated bone remodeling cycle in hyperthyroid state results in increased bone
221 resorption and a subsequent increased release of calcium into systemic circulation.[17]

222 High levels of serum calcium inhibit parathyroid hormone (PTH) secretion and create a
223 negative calcium balance through prolonged urinary and fecal losses. Decreased PTH
224 secretion causes hypercalciuria as a protective mechanism against hypercalcemia .[17]

225 With low PTH, Vitamin D is not converted into its active form, leading to low gastrointestinal
226 calcium and phosphorous absorption and resultant fecal calcium losses.[17]

227 Calcium balance which was negative during the hyperthyroid status was converted to
228 positive soon after attainment of euthyroidism which is due to healing of the metabolic bone
229 disease and increased calcium deposition in to the bone. [18]

230 ROC analysis showed that serum osteocalcin is a good marker in assessing bone
231 remodeling in hyperthyroid patients and also during treatment and serum calcium levels are
232 not sensitive markers of bone remodeling.

233 Calcium levels in newly diagnosed hyperthyroid patients is in upper normal range when
234 compared to lower normal range of controls. There is no significant difference in calcium
235 levels in newly diagnosed hyperthyroid and patients who are euthyroid during treatment and
236 also between patients who are euthyroid during treatment and controls. Hence calcium
237 levels cannot be used as marker to identify patients in whom bone resorption is taking place.

238 Where as Osteocalcin levels in newly diagnosed hyperthyroid patients is significantly high
239 compared to patients who are euthyroid during treatment and controls. On treatment
240 osteocalcin levels decreases but still there is some residual bone resorption taking place.
241 Therefore osteocalcin can identify those patients in whom bone resorption is really taking
242 place.

243 **4. CONCLUSION**

244
245 Serum osteocalcin levels can be used as a screening marker and prognostic marker for
246 assessing hyperthyroidism induced bone remodeling. Normalizing thyroid function with anti

thyroid drugs alone is able to effect some reversal of bone loss. Patients should be monitored with serum osteocalcin levels to assess the bone remodeling so that patients can be supplemented with calcium, vitamin D and bisphosphonates to improve bone mineralization and prevent osteoporosis.

251 252 **CONSENT (WHERE EVER APPLICABLE)**

253
254 No manuscripts will be peer-reviewed if a statement of patient consent is not presented
255 during submission (wherever applicable).

256 This section is compulsory for medical journals. Other journals may require this section if
257 found suitable. It should provide a statement to confirm that the patient has given their
258 informed consent for the case report to be published. Journal editorial office may ask the
259 copies of the consent documentation at any time.

260
261 Authors may use a form from their own institution or SDI Patient Consent Form 1.0. It is
262 preferable that authors should send this form along with the submission. But if already not
263 sent during submission, we may request to see a copy at any stages of pre and post
264 publication.

265
266 If the person described in the case report has died, then consent for publication must be
267 collected from their next of kin. If the individual described in the case report is a minor, or
268 unable to provide consent, then consent must be sought from their parents or legal
269 guardians.

270
271 Authors may use the following wordings for this section: "All authors declare that 'written
272 informed consent was obtained from the patient (or other approved parties) for publication of
273 this case report and accompanying images. A copy of the written consent is available for
274 review by the Editorial office/Chief Editor/Editorial Board members of this journal."

275 276 277 **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**

278
279 This section is compulsory for medical journals. Other journals may require this section if
280 found suitable. If human subjects are involved, informed consent, protection of privacy, and
281 other human rights are further criteria against which the manuscript will be judged. It should
282 provide a statement to confirm that the authors have obtained all necessary ethical approval
283 from suitable Institutional or State or National or International Committee. This confirms
284 either that this study is not against the public interest, or that the release of information is
285 allowed by legislation.

286
287 All manuscripts which deal with animal subjects must be approved by an Institutional Review
288 Board (IRB), Ethical Committee, or an Animal Utilization Study Committee. , and this
289 statement, and approval number, must accompany the submission. If required, author
290 should be ready to submit a scanned copy of the IRB or Ethical Committee Approval at any
291 stage of publication (Pre of post publication stage). The manuscript should contain
292 information about any post-operative care and pain management for the animals.

293
294 For manuscripts involving animal experiments, Authors may use the following wordings for
295 this section "All authors hereby declare that "Principles of laboratory animal care" (NIH

296 publication No. 85-23, revised 1985) were followed, as well as specific national laws where
 297 applicable. All experiments have been examined and approved by the appropriate ethics
 298 committee”
 299

300 All manuscripts which deal with the study of human subjects must be accompanied by
 301 Institutional Review Board (IRB) or Ethical Committee Approval, or the national or regional
 302 equivalent. The name of the Board or Committee giving approval and the study number
 303 assigned must accompany the submission. If required, author should be ready to submit a
 304 scanned copy of the IRB or Ethical Committee Approval at any stage of publication (Pre of
 305 post publication stage).
 306

307 For manuscripts involving human experiments, Authors may use the following wordings for
 308 this section: “All authors hereby declare that all experiments have been examined and
 309 approved by the appropriate ethics committee and have therefore been performed in
 310 accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.”
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352

353 Definitions, Acronyms, Abbreviations

354 Here is the Definitions section. This is an optional section.

355 **Term:** Definition for the term

356

357 **APPENDIX**