

**EFFECT OF SUPPLEMENTATION OF VITMAIN C ON THYROID STATUS IN
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ABSTRACT

Context: In hypothyroidism because of unknown reasons, large doses of levothyroxine are required to achieve a therapeutic endpoint, preliminary observations indicated that hypoacidic gastric environment is associated with reduction in levothyroxine bioavailability and co-administration of vitamin C might enhance absorption. **Aims:** We assessed whether this effect would be obtained taking levothyroxine with vitamin C. **Settings and design:** A hospital based Prospective interventional comparative Study was carried out on 80 patients. **Materials and methods:** The study population consisted of 80 subjects divided into 4 groups. 20 into Normal untreated Healthy Subjects, 20 into Thyroid Patients treated only with levothyroxine, 20 into 25µg of Levothyroxine+VitaminC [10patients with 500mg and 10 patients with 1000mg], 20 into 50µg Levothyroxine+Vitamin C [10patients with 500mg and 10 patients with 1000mg of vitamin C]. This study examined the levels of triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone, (TSH). The mean TSH level was significantly higher whereas T3 and T4 were lower in hypothyroid patients than in normal untreated Healthy Subjects. **Results:** After 12weeks of taking levothyroxine with vitamin C, serum TSH decreased in all patients. mean±SEM for [25µg of levothyroxine TSH was 9.19±1.17µIU/L vs TSH on 500mg vitamin C treatment of 5.65±0.041µIU/L (p<0.0001). 50µg of levothyroxine TSH was 9.70±0.0330µIU/L vs TSH on 500mg vitamin C treatment of 6.45±0.0417µIU/L (p<0.0001). 25µg of levothyroxine TSH was 9.64±0.141µIU/L vs TSH on 1000mg vitamin C treatment of 5.12±0.04435µIU/L (p<0.0001), 50µg of levothyroxine TSH was 9.86667±0.0924µIU/L vs TSH on 1000mg vitamin C treatment of 4.173±0.0566µIU/L (p<0.0001). **Conclusions:** Vitamin C enhances oral absorption of levothyroxine. Co-administration of Vitamin C with levothyroxine should be considered in patients with difficulties in the absorption of levothyroxine.

KEYWORDS: Hypothyroidism, levothyroxine, triiodothyronine (T3), thyroxine (T4).**INTRODUCTION**

Levothyroxine sodium is commonly prescribed for the treatment of hypothyroidism and thyroid neoplasia. As a result of hypofunction or absence of the thyroid gland, the level of serum thyroid stimulating hormone (TSH) is elevated because of the absence of the regulatory negative feedback mechanism. Patients with hypothyroidism are supplemented with synthetic thyroxine (i.e. levothyroxine, LT4) in oral doses to achieve physiological T4 and TSH serum levels. The mean treatment dosage of LT4 is 1.6ug/kg body weight/day.^[1]

The absorption of levothyroxine is approximately 50-100 % after oral administration,^[2-6] but there is considerable inter-individual and intra-individual variability,^[7] On occasions, when extraordinarily large doses of LT4 are

required to achieve a therapeutic endpoint, clinicians should suspect either some interference with absorption or non-compliance. Of note in this regard are the several factors relating to LT4 absorption in the stomach, including the role of gastric acid secretion, timing of food ingestion, gastric pH impairment, and the effect of the latter on facilitating LT4 absorption in the gut.^[8]

Dissolution of LT4 is a crucial step in its oral absorption and bioavailability,^[9] and tablets of LT4 need intragastric acid pH in order to achieve an adequate dissolution. Decreased dissolution of LT4 with higher gastric pH as described by Pabla et al confirmed the relationship of LT4 absorption to alterations in gastric pH and the importance of variable dissolution of LT4 on the bioavailability of LT4.^[9] Conceivably, even physiological variations in intragastric pH might

determine differences in LT4 tablets dissolution, and therefore LT4 absorption. Preliminary observations indicated that coadministration of acidic compounds –as officinal HCl- might enhance absorption of LT4.

Similarly, a favourable effect of taking certain drugs with orange juice has been described; thus, in *H pylori* and HIV-positive hypochlorhydric subjects, delavirdine absorption increased by 57% with orange juice administration.^[10] Although controversial, in certain cases it has been found that vitamin C improves iron absorption.^[11]

In this study we evaluated whether a beneficial effect on LT4 absorption of co-administration of Vitamin C, an acidic compound, might be observed in patients with hypothyroidism refractory to oral LT4 alone.

METHODOLOGY

Study population

The study population consisted of 80 subjects (age and sex-matched) divided into 4 groups. 20 patients into Normal untreated Healthy Subjects, 20 patients into Thyroid Patients treated only with levothyroxine, 20 patients into 25µg of Levothyroxine+ Vitamin C [10patients with 500mg and 10 patients with 1000mg] and 20 patients with 50µg Levothyroxine + Vitamin C [10patients with 500mg and 10 patients with 1000mg of vitamin C]. All the patients and controls were recruited from Malla Reddy teaching hospital during January to June of 2016. The study was conducted in Malla Reddy Hospital. It is a Prospective, Interventional and Comparative study

STUDY CRITERIA

Inclusion Criteria: Patients who have been diagnosed with Hypothyroidism, Patients of either sex, Patients of age greater than 18years.

Exclusion Criteria: Patients with co-morbid conditions, Patients who have undergone thyroidectomy, Pregnancy and lactating women, Patients who are not willing to cooperate.

STUDY PROCEDURE

Ethical committee approval

Permission to carry this study was obtained from the authorities of ethical committee after submission of the study protocol. The IEC approval code of the study is IEC/MRGI/PROT/2015-16/0007.

Proforma (Data Entry Form): A separate data entry form was designed for incorporating the patient details. The format contains the details such as patient demographic details (Name, Age, Weight, OP number, DOA, Complaints, Patient past medical and medication history), Thyroid levels, Oxidative stress levels, Blood pressure, Family history, Marital status, therapy given,

Follow up's. Patients were counseled regarding the Hypothyroidism and provided with information leaflets.

Blood Collection and hemolysate preparation

Blood samples were collected by venous puncture in plain tubes and the plasma was separated by centrifugation at 1000g for 15 minutes after centrifugation, the Buffy coat was removed and the packed cells were washed three times with physiological saline. A known volume of the erythrocytes was lysed with hypotonic phosphate buffer (pH 7.5). The hemolysate was separated by centrifugation at 2500g for 15 minutes.

Hormonal analyses

The levels of serum thyroid stimulating hormone (TSH), total triiodothyronine (T3), and total thyroxine (T4) were measured by using enzyme immuno assay (EIA) methods (according by kits from Biocheck, Inc.).

Statistical analysis

Data are expressed as mean ± SD, and TSH pre and post vitamin C are expressed as median as well. Student's *t*-test (paired) is used to detect significant differences between TSH levels before and after co-administration with vitamin C. For all the tests, *P* < 0.05 was considered to be a significant difference. In all cases, statistical analyses were performed on absolute values.

RESULTS

Tables show the mean values of serum TSH before and after ingestion of levothyroxine along with vitamin C.

Serum TSH levels decreased remarkably and significantly after changing LT4 ingestion from tap water to tap water + vitamin C. After 12 weeks of taking LT4 along with vitamin C, serum TSH decreased in all patients. The difference between TSH levels before and after co-administration of LT4 along with vitamin C was significant. mean±SEM for [25µg of levothyroxine TSH was 9.19±1.17µIU/L vs TSH on 500mg vitamin C treatment of 5.65±0.041µIU/L (*p*<0.0001). 50µg of levothyroxine TSH was 9.70±0.0330µIU/L vs TSH on 500mg vitamin C treatment of 6.45±0.0417µIU/L (*p*<0.0001). 25µg of levothyroxine TSH was 9.64±0.141µIU/L vs TSH on 1000mg vitamin C treatment of 5.12±0.04435µIU/L (*p*<0.0001), 50µg of levothyroxine TSH was 9.86667±0.0924µIU/L vs TSH on 1000mg vitamin C treatment of 4.173±0.0566µIU/L (*p*<0.0001). No patient experienced any adverse effect related to the ingestion of vitamin C.

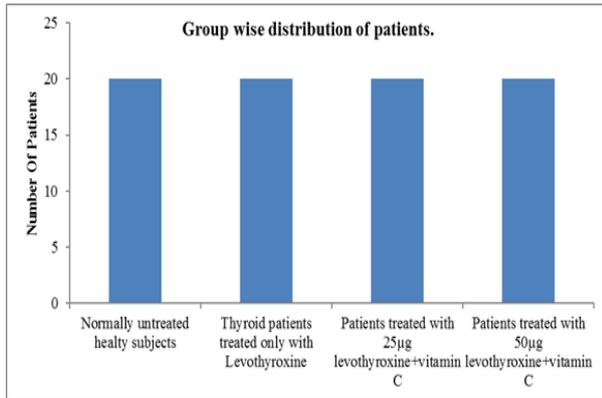


Figure 1: Illustrates out of 80 patients 20 are Normal untreated healthy subjects ,20 are Thyroid patients treated only with Levothyroxine,20 are Patients treated with 25µg of Levothyroxine+ vitamin C and 20 Patients are treated with 50µg of Levothyroxine + Vitamin C.

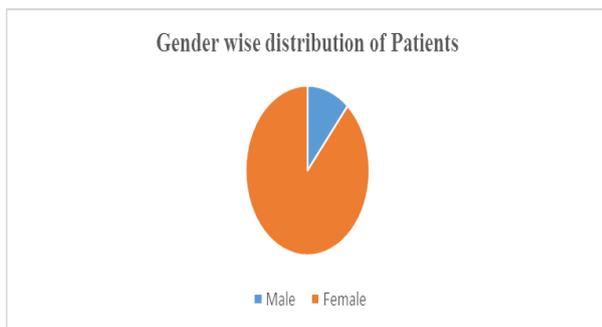


Figure 2: Illustrates out of 80 patients 71 are female and 9 are male.

INFERENCE: From this figure we can observe that female patients are more affected with hypothyroidism than male patients.

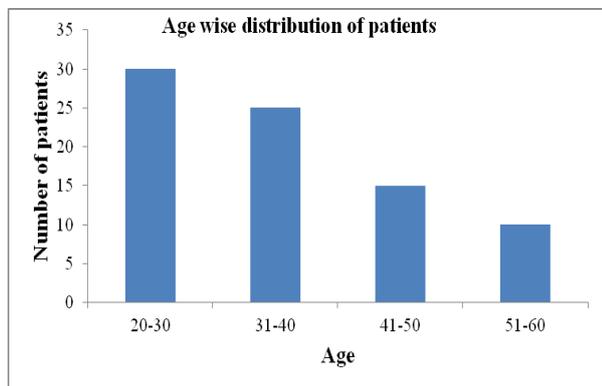


Figure 3: Illustrates out of 80 patients 30 are between 20-30 years,25 are between 31-40 years,15 are between 41-50 years,10 are between 51-60 years.

INFERENCE: From the figure we can observe that hypothyroidism is more prevalent in age group between 20-40 years.

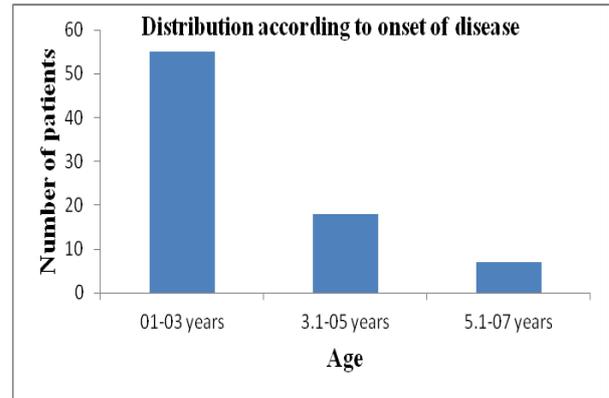


Figure 4: Illustrates out of 80 patients 55 are between 1-3 years,18 are between 3.1-5 and 7 are between 5.1-7years.

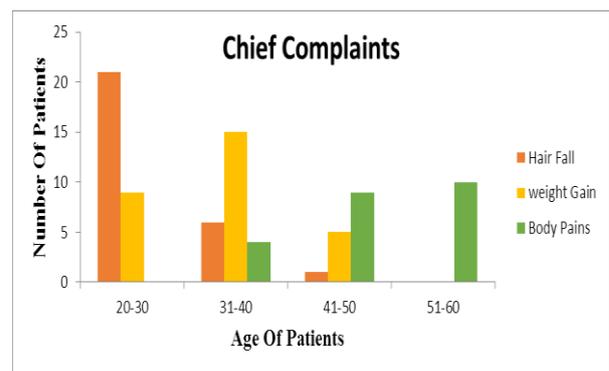


Figure 5: Illustrates about chief complaints of patients.

INFERENCE: It was observed that Hair fall was the major symptom between the age group 20-30years. Weight gain was the major symptom between the age group 31-40 years. Body pains was the major symptom between the age group 41-60 years.

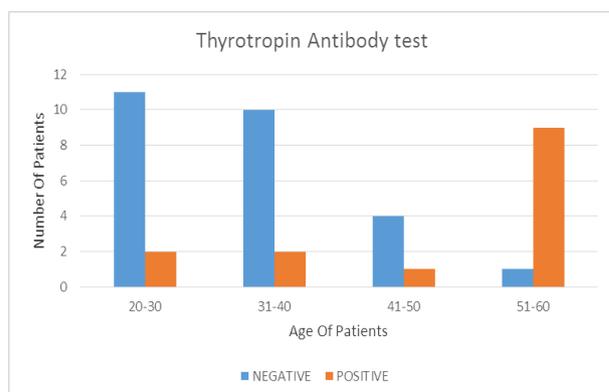


Figure 6: Illustrates out of 40 patients 26 are negative and 14 are positive for Thyrotropin antibody test.

INFERENCE: Thyrotropin antibody test indicates whether the thyroid disease is caused due to hormonal changes or due to an abnormality in the thyroid gland. It was observed that most of the female patients are suffering from hormonal changes and it can be subsided over time.

Table 1: This table indicates mean \pm standard error of mean values of T3, T4, TSH levels before and after administration of 500mg of Ascorbic acid.

Groups	Pre treatment only with levothyroxine			Post treatment with 500mg vitamin c		
	T3 [ng/ml] mean \pm SEM	T4[ng/ml] mean \pm SEM	TSH[μ IU/L] mean \pm SEM	T3 [ng/ml] mean \pm SEM	T4[μ g/dl] mean \pm SEM	TSH[μ IU/L] mean \pm SEM
Normal untreated healthy subjects	2.3007 \pm 0.0173	12.5000 \pm 0.0038	3.0200 \pm 0.0932	2.520 \pm 0.0745	12.6020 \pm 0.0105	3.0560 \pm 0.0325
Thyroid subjects treated only with levothyroxine	0.9020 \pm 0.0096	5.9527 \pm 0.0056	9.2193 \pm 0.4712	0.603 \pm 0.0072#	5.6380 \pm 0.0123#	8.6680 \pm 0.5905#
Patients treated with 25mcg levothyroxine+ vitamin C	1.2933 \pm 0.0076	7.5493 \pm 0.0069	9.1973 \pm 1.1781	1.55 \pm 0.1075*	9.88 \pm 0.0023*	5.65 \pm 0.0417*
Patients treated with 50mcg levothyroxine+ vitamin C	1.31 \pm 0.0336	6.91 \pm 0.0961	9.70 \pm 0.0330	1.62 \pm 0.0385**	9.95 \pm 0.0102**	6.45 \pm 0.0417**

Data is expressed as mean \pm SEM, n=10. The intergroup variation between various groups was conducted by Graph pad prim 7.0 software using paired t-test.

P<0.0132 compared with thyroid subjects treated only with levothyroxine before treatment.

*P<0.0001 compared with 25 μ g levothyroxine +500mg ascorbic acid before treatment

**P<0.0001 compared with 50 μ g levothyroxine +500mg ascorbic acid before treatment

Table 2: This table indicates mean \pm standard error of mean values of T3, T4, TSH levels before and after administration of 1000mg of Ascorbic acid. Data is expressed as mean \pm SEM, n=10. The intergroup variation between various groups was conducted by Graph pad prim 7.0 software using paired t-test.

Groups	Pre treatment only with levothyroxine			Post treatment with 1000mg vitamin c		
	T3 [ng/ml] mean \pm SEM	T4[ng/ml] mean \pm SEM	TSH[μ IU/L] mean \pm SEM	T3[ng/ml] mean \pm SEM	T4[ng/ml] mean \pm SEM	TSH[μ IU/L] mean \pm SEM
Normal untreated healthy subjects	2.3007 \pm 0.0173	12.5000 \pm 0.0038	3.0400 \pm 0.0180	2.5200 \pm 0.0745	12.6020 \pm 0.0105	3.0407 \pm 0.0188
Thyroid subjects treated only with levothyroxine	0.9020 \pm 0.0096	5.9527 \pm 0.0056	13.2367 \pm 0.5905	0.6033 \pm 0.0072#	5.6380 \pm 0.0123#	11.8800 \pm 0.7537#
Patients treated with 25mcg levothyroxine+ vitamin C	1.31 \pm 0.1133	7.41 \pm 0.1290	9.64 \pm 0.141	1.75 \pm 0.1202*	10.82 \pm 0.1668*	5.12 \pm 0.04435*
Patients treated with 50mcg levothyroxine+ vitamin C	1.43 \pm 0.1072	6.75 \pm 0.1398	9.86667 \pm 0.0924	2.06 \pm 0.1211**	11.26 \pm 0.1203**	4.173 \pm 0.0566**

Data is expressed as mean \pm SEM, n=10. The intergroup variation between various groups was conducted by Graph pad prim 7.0 software using paired t-test.

P<0.0132 compared with thyroid subjects treated only with levothyroxine before treatment.

*P<0.0001 compared with 25 μ g levothyroxine +1000mg ascorbic acid before treatment.

**P<0.0001 compared with 50 μ g levothyroxine +1000mg ascorbic acid before treatment.

DISCUSSION

In some patients with hypothyroidism, because of unknown reasons, large doses of levothyroxine are required to achieve a therapeutic endpoint, and preliminary observations have indicated that an hypoacidic gastric environment is associated with a reduction in levothyroxine bioavailability, and that co-administration of vitamin C might enhance absorption of certain drugs, we assessed whether this effect would be obtained taking levothyroxine with vitamin C.

We have demonstrated an improvement in circulating concentrations of TSH, by vitamin C in patients with hypothyroidism receiving L-T4 replacement therapy. It is possible that some of the patients were on suboptimal L-T4 doses before receiving vitamin C. However, because the dose was not changed throughout the study, the change induced by vitamin C is valid.

Patients require large doses of LT4 to achieve euthyroidism. Often, however, no explanation for reduced bioavailability can be found, and this situation may be addressed with an empirical solution. Preliminary observations indicated that co-administration of acidic compounds –as officinal HCl- might enhance absorption of LT4, and vitamin C as acidic compound has better tolerability.

CONCLUSION

Our study demonstrated that changing the vehicle for ingestion of LT4 from plain water to the same volume of plain water with 1 g vitamin C improves the apparent absorption of LT4 –as it was evaluated indirectly by reduction in TSH level- in a subset of patients receiving this hormone for primary hypothyroidism who do not reach the target TSH level with the usual dose/weight of LT4. The important practical consequence of our finding is that a trial of coadministration of LT4 with vitamin C

to enhance LT4 absorption should be considered in patients requiring high doses of LT4 with no obvious cause of LT4 malabsorption.

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CONFLICTING INTEREST

(If present, give more details): No conflicts of interest have been declared.

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