

## Relation between Hypercholesterolemia and Insulin like growth factor-1 in Elderly Women suffer from Hypothyroidism

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### Abstract

The present study included 40 female subjects. They were classified into two groups: group I included 20 females diagnosed as primary hypothyroidism with age ranged between 45 – 65 years and group II included 20 ages matched normal female volunteers and served as control group. Insulin like growth factor -1, (IGF-1) cholesterol, triglycerides, Thyroid stimulating hormone, thyroxine-3 (T<sub>3</sub>) and thyroxine-4 (T<sub>4</sub>) hormones were measured in both groups. The obtained results revealed that, there was a significant decrease in IGF-1 level in group I, when compared to control group ( $P \leq 0.01$ ). Correlation studies showed that IGF-1 is strongly positively correlated with T<sub>3</sub> ( $R=0.81$ ,  $P \leq 0.01$ ) and moderately positively correlated with T<sub>4</sub> ( $R= 0.58$ ,  $P \leq 0.05$ ). Meanwhile, it was moderately negatively correlated with cholesterol ( $R= 0.6$ ,  $P \leq 0.05$ ). The results indicate that IGF-1 deficiency in elder women suffering from hypothyroidism may have a direct relation in the pathogenesis of hypercholesterolemia.

**Keywords:** Hypercholesterolemia: Insulin like growth factor -1: Elderly: Hypothyroidism: growth hormone: thyroid hormone: cholesterol.

### 1. Introduction

Insulin like growth factor-1 is the precise test for human growth human activity (HGH). It is a polypeptide hormone synthesized in the liver after stimulation of the pituitary gland. It is also called Somatomedine C. Clinical studies have shown that pituitary human growth hormone administration to the elderly has significantly increased IGF-1, which improves cognizance, muscle and bone strength, libido enhancement, and athletic performance.

Low levels of IGF-1 are described in hypopituitarism, diabetes mellitus, dwarfism, malnutrition, hypothyroidism, maternal deprivation syndrome, pubertal delay, cirrhosis, hepatoma and some cases of short stature and normal growth hormone response. High levels of IGF-1 are described in adolescence, true precocious puberty, pregnancy, obesity, pituitary gigantism, acromegaly and diabetic retinopathy (**Werstemark et al., 2006**).

Hypothyroidism cases pronounced hypercholesterolemia. This may be due to an increase in both low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) (**Gross et al., 2008**). The mechanisms responsible for these hypothyroidism related changes are completely understood. During hypothyroidism and spite of the hypercholesterolemia; cholesterol synthesis estimated by hydroxyl methyl glutaryl-CoA reductase activity in the liver is often decreased (**Field et al., 2008**). However, degradation of lipoproteins is decreased secondary to a reduction in the number of LDL receptors (**Chait et al., 2009**). It has been suggested that the decrease in lipoprotein lipase activity and/or salt resistant liver lipase activity are major contributors to the abnormalities in lipid profile in hypothyroidism (**Valdemarsson, 2006**). On the other hand, several data pointed to a relationship between hypothyroidism, growth hormone activity and hypercholesterolemia. It has been suggested that, in thyroidectomized rats, the main cause of hypercholesterolemia might be the effect of hypothyroidism on the secretion of growth hormone. The administration of growth hormone to these thyroidectomized rats was essentially as effective in preventing the occurrence of hypercholesterolemia as the thyroid extract (**Bayers et al., 1970**). It is not known in what way these effects are mediated through growth hormone, whether directly or by its chief mediator insulin like growth factor-1 (Somatomedine C).

The aim of this work is to study the relation between somatomedine C and pathogenesis of hypercholesterolemia in elder women suffering from hypothyroidism.

## 2. Subjects and methods

### 2.1. Subjects

The study included 40 female subjects. They were classified into two groups: group I included 20 females suffering from primary hypothyroidism, aged between 45- 65 years and group II of 20 females, age matched normal female volunteers.

Through history and clinical examination with special emphasis on excluding history of drug intake that might alter serum lipids such as diuretics and beta-blockers. None of the patients had clinical or biochemical evidences of diabetes, liver or kidney diseases nor had any of the primary hyperlipoproteinaemia. Nutritional history was obtained and a good nutritional status was ensured.

### 2.2. Chemical investigation

Cholesterol and triglycerides “mg / dl” were determined according to the methods of Fossati and Prencipe (1982).

Insulin like growth factor-1 (Somatomedine C), TSH,  $T_3$  and  $T_4$  were carried out by radio-immunoassay technique using DPD kits “Diagnostic Products, Los Angeles, USA” (Westgard and klee, 1987).

### 2.3. Statistical analysis:

The results were computed and statistical analysis was done. Student’s T-test and correlation study between various parameters were done.

## 3. Results and discussion

The results of this study revealed a low IGF-1 in hypothyroid patients when compared with the normal subjects (table 1). In hypothyroid patients both reduced and unchanged IGF-1 levels have been reported (Westermarck et al., 2006). Several reports have documented growth hormone dysfunction in hypothyroid patients. However, the degree of growth hormone secretory dysfunction in humans with hypothyroidism has not been established. Indeed, approximately 50 % of patients with hypothyroidism have putatively normal growth hormone secretion in response to pharmacologic stimuli (Chernauek and Turner, 1989). In the present study, we measured IGF-1 as it was concluded that IGF-1 is a good reflection of growth hormone secretion; so the reduced IGF-1 levels observed is a reflection of decreased growth hormone secretion in hypothyroidism. The reasons for growth hormone decreased secretion may be due to several causes, among them, altered synthesis and release of GH-RH (Katakami et al., 1988), changes of sensitivity of the pituitary gland to GH-RH (Chernauek and Turner, 1989), and reduced growth hormone synthesis due to reduced transcription of the growth hormone gene (Marital et al., 1977). On the other hand reduced IGF-1 observed in the present study may not be solely due to decreased growth hormone release. It is a well known fact that serum IGF-1 level responds to both protein and energy (Isley et al., 1983), and suboptimal nutrition is perhaps the most common cause of low IGF-1 level (Bellet et al., 1984). Hypothyroidism is usually accompanied by loss of appetite and impaired gastrointestinal tract motility which result in a state of malnutrition (Larson and Ingbar, 1992). However, some authors reported that IGF-1 concentration was higher in thyrotoxic patients despite nutritional deficiency and decreased when they become euthyroid, supporting the role of thyroid hormone in IGF-1 production (Westermarck et al., 2006). Moreover, exogenous growth hormone failed to raise IGF-1 levels in hypothyroid rats denoting a direct role for thyroid hormone in the production of IGF-1 (Colonna et al., 1991). Also, in keeping with this view, is the finding that  $T_3$ , in addition to growth hormone and cortisol, are needed to restore plasma IGF-1 to normal level in hypothyrectomized rats (Schalch et al., 2007). Now we can say that the low IGF-1 level observed in the present study is due to decreased growth hormone secretion and due to decreased thyroid hormones stimulatory effect on IGF-1 production.

Correlation studies (Figure 1-3) showed that IGF-1 is strongly positively correlated with  $T_3$  ( $R=0.81$ ,  $P<0.01$ ), and moderately positively correlated with  $T_4$  ( $R=0.85$ ,  $P<0.05$ ). Meanwhile, it is moderately negatively correlated to cholesterol ( $R=0.6$ ,  $P<0.05$ ). In agreement with our results a positive linear correlation was found between IGF-1 and  $T_4$  and a negative correlation between IGF-1 and plasma cholesterol (Hoogerbrugge et al., 1989). Moreover, physiological doses of growth hormone could reduce hypercholesterolemia in hypothyroid rats (Hoogerbrugge et al., 1989). On the other hand, it was suggested that hypercholesterolemia observed in hypothyroidism is due to lack of a stimulatory effect of thyroid hormones on lipoprotein lipases claiming direct effect for thyroid hormones in hypercholesterolemia (Valdemarsson, 2006). The fact that we found a positive correlation between IGF-1 and  $T_3$ ,  $T_4$  and a negative correlation between IGF-1 and cholesterol suggest a direct role of IGF-1 in the process of hypercholesterolemia.

The question is how IGF-1 deficiency can induce hypercholesterolemia. It has recently been showed that IGF-

1 augments the binding capacity and uptake of LDL (Veldhuis et al., 1987). Meanwhile, it was also demonstrated that a defect of receptor mediated LDL catabolism in hypothyroidism is present (Thompson et al., 1981). It was also reported that studies of the different lipoprotein classes revealed an increase predominantly of LDL cholesterol and only a minor changes in the concentrations of high density lipoprotein (HDL) cholesterol (Abrams and Grundy, 1981), i.e. the main cholesterol fraction that is increased in hypothyroidism is the LDL cholesterol.

From the above data, we may conclude that hypercholesterolemia present in hypothyroidism is mainly due to the increased LDL cholesterol which is due to lack of IGF-1 stimulatory effect on LDL-receptor mediated uptake. The proof that IGF-1 deficiency has a role in the pathogenesis of hypercholesterolemia in primary hypothyroidism may raise a question about its role in mediated several clinical aspects of hypothyroidism. For example, IGF-1 has a stimulatory effect on myelination by stimulating the activity of the myelin marker enzyme 2, 3 cyclic nucleotide 3-phosphohydrolase (McMorris et al., 1986) that may suggest a role for IGF-1 deficiency in neurological manifestations of hypothyroidism. Indeed primary hypothyroidism may clinically reflect a multiple hormonal deficiency disorder including T<sub>3</sub>, T<sub>4</sub>, growth hormone and IGF-1 deficiencies.

#### 4. Conclusion

IGF-1 is decreased in primary hypothyroidism which may be due to decreased hormone secretion and/or lack of direct thyroid hormone stimulation on IGF-1 production. IGF-1 deficiency has a role in the pathogenesis of hypercholesterolemia through lack of this stimulatory effect on LDL uptake and degradation.

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**Table (1):** Serum T<sub>3</sub>, T<sub>4</sub>, TSH, Cholesterol, triglycerides and IGF-1 levels of tested subjects (Means ± S. E., n = 20)

Groups	T <sub>3</sub> (ng/dl)	T <sub>4</sub> (ug/dl)	TSH (uU/ml)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	IGF-1 (ng/dl)
(I)	0.27±0.16	0.62±0.80	33.20±17.43*	274.4±95.4*	152.5±37.43	4.29±2.52
(II)	1.80±0.23**	7.40±0.81**	5.600±0.380	193.2±26.3	130.3±14.85	12.95±3.57**

\*Significant at < 0.05

\*\*Highly Significant at < 0.01

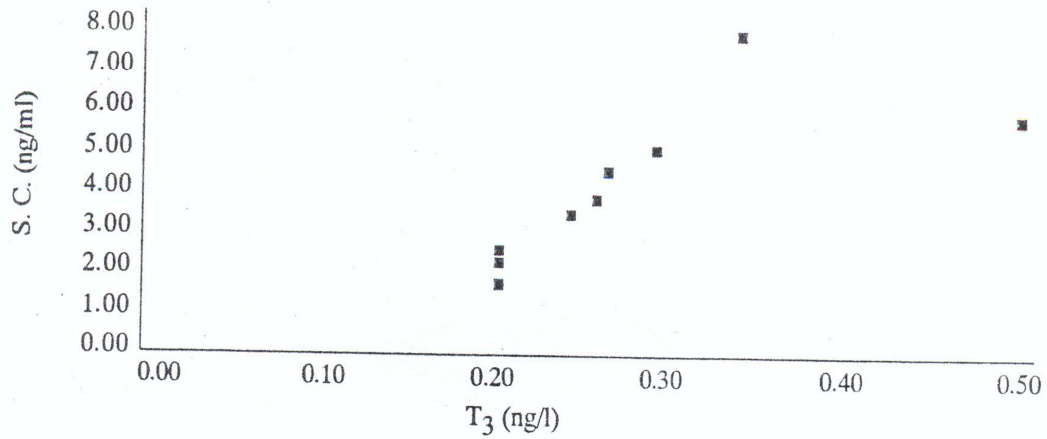


Fig. (1): Correlation study between somatomedin C and T<sub>3</sub> with R = 0.81

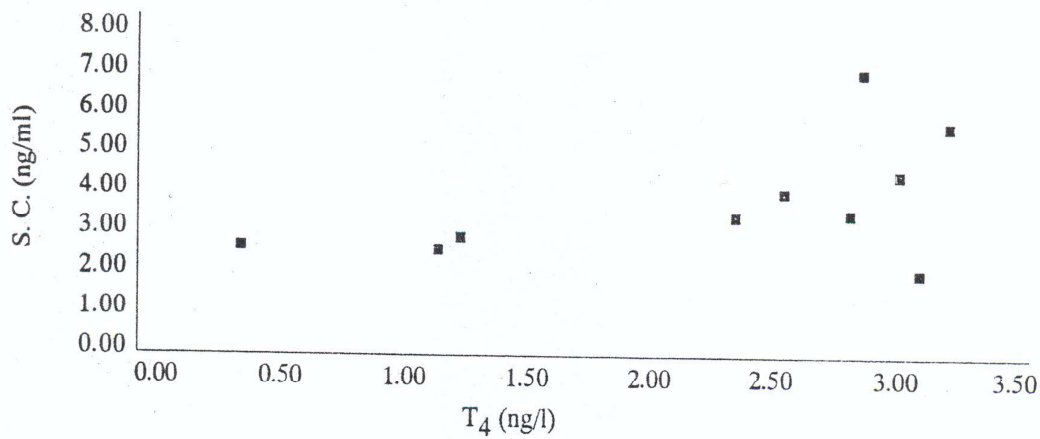


Fig. (2): Correlation study between somatomedin C and T<sub>4</sub> with R = 0.58

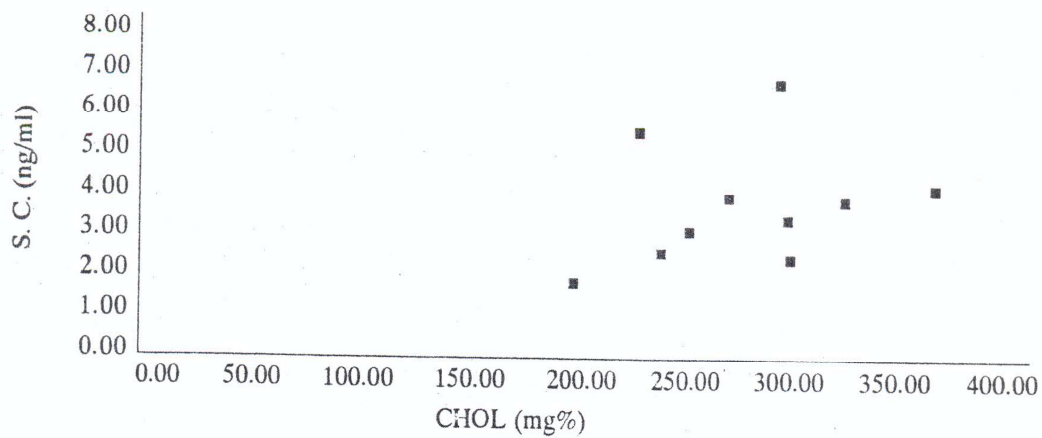


Fig. (3): Correlation study between somatomedin C and Cholesterol with R = 0.6

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