ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 7, Issue – 3, May – 2022 , Page No. : 218 - 224

Correlation of Serum Cystatin C and Thyroid Hormones in Hypothyroid Patients

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Citation this Article: Dr. Suman Debnath, Dr. Tina Das, Dr. Davina Hijam, "Correlation of Serum Cystatin C and Thyroid Hormones in Hypothyroid Patients", IJMSIR- May - 2022, Vol – 7, Issue - 3, P. No. 218 – 224.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Thyroid disorders are the most common endocrine problems encountered in our laboratory. Cystatin C, a potent cysteine protease inhibitor, is considered as a novel marker for assessing glomerular filtration rate (GFR) and claimed to be superior to serum creatinine. Thyroid dysfunction has been demonstrated to have an impact on the serum concentrations of cystatin C. Compared with the euthyroid state, serum cystatin C concentrations are lower in the hypothyroid state. This study was done to estimate and compare the level of serum cystatin C in patients suffering from hypothyroidism as well as in normal healthy individuals, to find whether serum cystatin C and hypothyroidism is correlated and can serum cystatin C be used as a marker of peripheral thyroid hormone effect. This was a case control study, carried out in 50 hypothyroid patients presenting in different departments of Regional Institute of Medical Sciences, Imphal from Oct 2017 to Oct 2019. Another 50 patients were taken as healthy controls. Serum Cystatin C was measured by ELISA and serum TSH, T3 & T4 was measured by chemiluminescence enzyme immunoassay. The serum cystatin C level was low (0.84±0.42mg/L) in hypothyroid patients as compared to controls (1.22±0.65mg/L). The level of TSH is negatively correlated whereas levels of T3 & T4 are positively correlated with serum cystatin C level, both of which are statistically significant. This study concluded that the thyroid hormones influence the production of cystatin C and cystatin C is decreased in hypothyroid patients.

Keywords: Cystatin C, Hypothyroidism, Chemi luminescence, ELISA

Introduction

Thyroid disorders are the most common endocrine diseases in the world as well as the most common endocrine problems encountered in our clinical and endocrinology laboratory.[1] Thyroid diseases are very often misdiagnosed, misunderstood, and frequently overlooked and they affect almost every aspect of health. Most of them remain undetected because the clinical assessment alone has sensitivity and specificity and can suspect only up to 40% of symptomatic thyroid disorders. Only the biochemical tests can be used to confirm the

diagnosis.[2] Thyroid hormones have diverse cellular functions, including up-regulation of carbohydrate and lipid catabolism and stimulation of protein synthesis which results in increase in the basal metabolic rate. In areas where the daily iodine intake <25mg, congenital hypothyroidism is seen. In iodine-replete areas, most persons with thyroid disorders have an auto immune hypothyroidism, Hashimoto's thyroiditis to Thyrotoxicosis caused by Grave's disease.[3] Despite the coverage of National Iodine Deficiency Diseases Control Programme (NIDDCP) in India, iodine deficiency is still prevalent in many parts of India including the North Eastern States.[4] According to Garcia-Mayor RV et al,[5] current thyroid function tests may have limitations since they only measure the total or free T4 and/or T3 and TSH serum concentrations in peripheral blood and not the effect of T4 or T3 on different specific target tissues. Another topic of debate in this field is the reference values of TSH, with the suggestion that the upper reference limit should be reduced as the reference range is too high to include patients with thyroid antibodies that are destined for future hypothyroidism.[5]

As a consequence there is still great interest in new biomarkers that are more accurate, precise, also complement the existing diagnostic tools and may facilitate risk stratification in patients with thyroid diseases.

Cystatin C is a member of the Cystatin superfamily of potent cysteine protease inhibitors involved in the catabolism of proteins.[6] Cystatin C is produced by all nucleated cells at a constant rate which can be detected in the body fluids.[7] Because of its small size, cystatin C is freely filtered by the renal glomerulus but not secreted and is reabsorbed by renal tubular epithelial cells. Subsequently after reabsorption, it is catabolized by the tubular cells so that it does not return to the blood flow. [8,9] Serum cystatin C concentrations are independent of age, body weight and gender. [10,11] Even, the diurnal variation in cystatin C level is insignificant and the concentration is stable in stored seum. [12-14] Cystatin C measurement in serum is neither interfered by icterus nor by hemolysis.[15]

Although cystatin C concentrations are not influenced by many pathophysiological conditions other than those affecting GFR, thyroid dysfunction have been demonstrated to have an impact on the serum concentrations of cystatin C. Compared with the euthyroid state, serum cystatin C concentrations are lower in the hypothyroid state and higher in the hyperthyroid state. Restoration of euthyroidism is associated with normalization of cystatin C values. The mechanism for this may involve the stimulatory effects of thyroid hormones (T3, T4) on cystatin C production, [16-19] so serum cystatin C concentration may be used as a biomarker in thyroid disorders. Although most of the studies reported that the changes of serum cystatin C level are directly proportional to the thyroid hormonal changes but some of the studies also report contradictory results.[20] It is with this view that the present study has been carried out to evaluate the serum concentrations of cystatin C among the hypothyroid patients and compare with normal healthy individual without any thyroid disorders to find out the influence of thyroid hormones on serum cystatin C level and whether cystatin C can be used as a marker for peripheral thyroid hormone action in thyroid disorders.

Materials & Methods

This study is a case control study conducted in the Dept. of Biochemistry, RIMS in collaboration with Department of Medicine, RIMS, Imphal from September 2018 to

August 2020. The study population included 50 hypothyroid patients taken as cases and 50 normal healthy individuals who were free from any systemic diseases & thyroid diseases were taken as the control. Individuals with diseases such as- kidney disease, malignancies, hematopoietic disorders, infection with immunodeficiency virus, glucocorticoids treatment, rheumatoid arthritis, severe illness, physical trauma, psychological & physiological stress were excluded from the study. Serum cystatin C was measured by Bio vendor human cystatin C ELISA kit and serum TSH, T3 & T4 was measured by chemiluminescence enzyme immunoassay (CLIA). Ethical clearance was taken from Institutional Ethical Committee RIMS, Imphal.

Results

Table 1: Age wise distribution of cases and controls

Age Group (years)	Cases (n=50)		Controls (n=50)	
	Number	Percentage	Number	Percentage
20 and below	2	4%	2	4%
21 to 30	12	24%	11	22%
31 to 40	16	32%	18	36%
41 to 50	10	20%	10	20%
51 and above	10	20%	9	18%
Total	50	100%	50	100%

Table- 1 shows age-wise distribution of cases and controls. Maximum no. i.e., 16 (32%) cases were in the age-group of 31-40 years. This was followed up by age group of 21 – 30 years with 12(24%) cases, 10(20%) cases each in 41 -50 and 51 & above age groups, while 2(4%) cases were aged 20 years and below. Similarly, maximum no. i.e., 18(36%) controls were in the age-group of 31-40 years followed by 11(22%) cases in 21 - 30 years age group.

Table 2: Sex wise distribution of cases and controls

Sex	Cases		Controls	
	Number	Percentage	Number	Percentage
Male	8	16%	9	18%
Female	42	84%	41	82%
Total	50	100%	50	100%

Table-2 shows sex-wise distribution of the cases and controls. Numbers of females were more in both the groups. Among cases, 42 (84%) were females as compared to 8 (16%) males.

Table 3: Biochemical parameters in cases and controls.

Biochemical Parameters (Mean ± SD)	Cases	Controls	p-value
TSH (mIU/L)	31.62 ± 35.05	2.00 ± 1.05	<0.01
T3 (nmol/L)	1.06 ± 0.29	1.76 ± 0.42	<0.01
T4 (mmol/L)	52.71 ± 19.84	106.45 ± 23.03	<0.01
Cystatin C (mg/L)	0.84 ± 0.42	1.22 ± 0.65	<0.01

Table-3 shows the biochemical parameters in cases and controls. Mean value of TSH was more in hypothyroid (31.62 ± 35.05 mIU/L) compared to controls (2.00 ± 1.05 mIU/L). Mean T3 and T4 values were less in hypothyroid compared to the controls. The mean serum cystatin C level is less in hypothyroid (0.84 ± 0.42mg/L) as compared to controls (1.22 ± 0.65mg/L). The differences in all the values among the cases and controls are statistically significant. (<0.01)

Table 4: Correlation between Cystatin C and TSH, T3, T4 in all subjects

Parameters	Pearson's Correlation	
	R-value	p-value
Cystatin vs. TSH	-0.25	<0.01
Cystatin vs. T3	0.53	<0.01
Cystatin vs. T4	0.60	<0.01

Table-4 shows Pearson correlation between the biomarkers among all the study population. The level of TSH is negatively correlated with serum cystatin C level ($r = -0.25$) which is statistically significant (<0.01). Serum T3 and T4 levels are positively correlated with serum cystatin C level ($r = 0.53, 0.60$) which are also statistically significant (<0.01).

Discussion

In the present study, the common age group of having thyroid dysfunction is 20-40 years (table 1) which is comparable to study by Baral N et al [21] in eastern Nepal. But other similar studies showed that thyroid dysfunction was common in age group above 40 years.[19] this may be due to the fact that autoimmune disorders are more common in elderly populations and the causes of thyroid dysfunctions are mostly autoimmune. These prevalence differences between subjects in this study and others may be due to difference in case selection procedure, geographical area, family history and related pathophysiologic conditions. Results of this study, however, are within the prevalence limits established by other studies.

Among 50 thyroid disorder cases, 84% were females and 16% were males which showed that females were more prone to have thyroid disorders (table- 2). Our findings are in accordance to that of Khan A et al [22] and Mansoor R et al. [23]

The present study, to our knowledge, is the first study to report about the influence of thyroid hormones on serum cystatin C level in the adult population of Manipur. The pattern of change in serum cystatin C levels observed in our study i.e., decreased in hypothyroidism (0.84±0.42), may be due to various reasons. Thyroid hormones have significant effects on renal hemodynamic, renal handling of salt and water, and the active tubular transport processes for Na, K, and H resulting changes in kidney function. [24,25] Primary hypothyroidism results a reduction in GFR most likely due to decreased renal blood flow and T4 replacement results in an increase in GFR. [26-30] Thyroid dysfunction affects the metabolic processes in all organs and tissues, including the kidneys. The medical condition inflicts changes in the GFR, effective renal plasma flow and the kidney structure. Hypothyroidism decreases the GFR bby increasing the peripheral vascular resistance, decreasing the effective renal plasma flow, vasoconstriction of the renal blood vessels and the negative ino- and chronotropic effect.

In healthy subjects, if the kidneys work effectively and GFR is within normal range, serum Cystatin C values should remain normal. Negative correlation was established between Cystatin C values and GFR- high Cystatin C values indicate low GFR and vice versa.[31] Stojan Oski S et al[32] in their study suggests that the cellular production rate of Cystatin C has the dominant role of determination on its serum concentration. In hypothyroid patients, low cystatin C values can be observed even though the GFR is decreased. Den Hollander JG et al [17] in their study also concluded that thyroid hormone also affect the production rate of Cystatin C, increasing it in hyperthyroidism and decreasing it in hypothyroidism.

Schmid C et al [33] in their study showed that T3 stimulates cells to increase the release of cystatin C into the culture medium. Indeed, T3 has been reported to increase cystatin C production in Hep G2cells (kept in thyroid hormone-stripped medium), as assessed by RT-PCR of the cells and a nephelometric immunoassay of the media, by about 30%.[34] Rather than being dominated by renal catabolism and clearance (where cystatin C production is considered constant), decreased plasma cystatin C in hypothyroidism (GFR decreased in hypothyroidism) and increased plasma cystatin C in hyperthyroidism (GFR increased in hyperthyroidism) appear to reflect an important impact of thyroid hormones on the production of cystatin C.[33]

In this study, all cases of hypothyroidism showed decreased level of cystatin C. The level of serum cystatin C is negatively correlated with TSH (r= -0.25) and positively correlated with T3 (r= 0.53) and T4 (r= 0.60) which are found to be statistically significant and in accordance with the previous studies, [19,24,35] indicating that cystatin C can be used as a marker of thyroid function.

Conclusion

The findings of this study suggest that alterations in thyroid status can change serum cystatin C concentration. The study does not provide any information on the mechanism underlying serum cystatin C variation in patients with thyroid disorder but it is conceivable that thyroid hormone definitely affects the production rate of cystatin C. This mechanism appears more likely than a modification of cystatin C metabolic clearance rate. So, determination of serum cystatin C concentration may correctly give some idea about peripheral thyroid hormone action and diagnosis of thyroid disorders. Cystatin C which is presently used as a superior tool for the kidney function tests may also be cautiously done in thyroid disorder patients and specially in critically ill or ICU patients where the thyroid hormones level are highly dysregulated. However, more work is needed to be done to determine whether cystatin C concentration is affected in all cases of thyroid dysfunction (especially in subclinical cases) and whether restoration of euthyroidism brings back serum cystatin C level to normal.

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