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ORIGINAL ARTICLE

INTERLEUKIN-6 IN HYPOTHYROIDISM

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ABSTRACT

Background: Hypothyroidism means that the thyroid gland can't produce enough thyroid hormones. Interleukin 6 (IL-6) a cytokine of innate immunity is a soluble mediator with a pleotropic effect on inflammation. Interleukin 6 test is helpful to study the hypothyroid status and to assess the adverse effects of hypothyroidism, was not studied in a tertiary care center in Pokhara, Nepal. The aim of this study is to determine the levels of interleukin 6 and to correlate with hypothyroidism.

Methodology: This was a hospital based cross-sectional study on 100 hypothyroid patients where samples were collected by convenient sampling from patients visiting the Tertiary care Hospital in Pokhara, Nepal. Thyroid function tests fT3, fT4 and TSH were analyzed by Chemiluminiscence Immunoassay (CLIA) for hypothyroidism. Interleukin 6 test was estimated by Immunofluorescence Assay (IFA). Excel-2010 and SPSS V 16.0 were used for data analysis.

Result: Among the total hypothyroid population, 83(83.0%) were subclinical and 17(17.0%) were overt cases. The 31(31.0%) of the total population has increased level of IL-6 and 69(69.0%) were normal. In this study, out of the 17% overt cases IL-6 was increased in 82.35 % cases and 17.65% of them found normal. In case of 83% subclinical hypothyroidism, IL-6 was increased in only 20.48% of cases and 79.52% of them found normal. There was a significant association between inflammatory status and hypothyroid status. IL-6 was significantly correlated with fT3 ($r = -0.485$, $p<0.01$fT4 ($r = -0.521$, $p<0.01$) and TSH ($r = 0.547$, $p<0.01$).

Conclusion: This study suggests that hypothyroid patients may have increased level of Interleukin 6. The frequency of inflammatory cases and severity of inflammation have been increased when cases worsen from subclinical to overt. Therefore, hypothyroidism must be treated early to avoid the consequences of inflammation.

Keywords: ***Hypothyroidism, Interleukin-6, fT3, fT4***

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INTRODUCTION

Hypothyroidism or an underactive thyroid gland means that the thyroid gland can't make enough thyroid hormone to keep the body running normally [1]. Subclinical hypothyroidism is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (T4). This designation is only applicable when thyroid function has been stable for weeks or more, the hypothalamic-pituitary-thyroid axis is normal, and there is no recent or ongoing severe illness. An elevated TSH, usually above 10 mIU/L, in combination with a subnormal free T4 characterizes overt hypothyroidism [2]. Hypothyroidism affects up to 5% of the general population, with a further estimated 5% being undiagnosed [3]. The American Thyroid Association reported that 20 million Americans have some form of thyroid disease and that more than 12% of the US population will develop a thyroid condition during their lifetime [4]. The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4 ·6% in the USA [5]. In Nepal, about 4.32% of the general public have thyroid disorders [6]. The prevalence of thyroid dysfunction was 17.42% where females had more thyroid dysfunction than the males and the cases of overt hypothyroidism (2.26%) and subclinical hypothyroidism (10.50%) had higher prevalences as compared to hyperthyroidism (1.59%) and subclinical hyperthyroidism (3.05%) in the western region of Nepal [7]. Untreated hypothyroidism can lead to health conditions like hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction [8]. Iodine consumption was found higher in the central and western parts and the terai region of Nepal where mean iodine content for all salt samples was found as 44.1 ppm, and 67.5% samples had more than 40 ppm, well above the expected level at the retail (30 ppm) and household (15 ppm) levels [10].

Interleukin 6 (IL-6) a cytokine of innate immunity [11] is a soluble mediator with a pleotropic effect on inflammation, immune response and hematopoiesis [14]. The pleotropic effect of IL-6 on various cells derives due to broad range of gp-130 expression observed on cells [15]. IL-6 as a B-cell stimulatory factor 2(BSF-2) stimulates B-cell to produce antibody secreting plasma cells [17] and as a hepatocyte stimulating factor (HSF) stimulates hepatocytes to produce acute phase proteins: C-reactive protein, serum amyloid- A, fibrinogen, haptoglobin and α1-antichymotrypsin [18]. IL-6 has a crucial role in vascular inflammations that the concentration of IL-6 is increased in hypothyroid rats [25]. Levothyroxine (L-T4) treatment of hypothyroid rats markedly decreased the elevated serum levels of TNF-α and IL-6 [26]. Levothyroxine therapy has significant effect to normalize the increased serum level of IL-6 among hypothyroid patients [35]. Hyperlipidemia stimulates atherogenesis by providing more lipids for foam cell formation, some induced inflammatory mediators increase lipid oxidation, such as tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) [27]. An increase in IL-6 in atherosclerosis results in effects on different cells involved in lipid processing and atherosclerotic plaque formation, such as the activation of endothelial cells, smooth muscle cell proliferation, and accumulation of macrophage lipids [28].

How to Cite

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Subclinical hypothyroidism patients were characterized by higher C- reactive protein and interleukin 6 [31]. IL-6 release is stimulated by thyroid stimulating hormone in adipocytes through cAMP/protein kinase A pathway to activate IL-6 gene expression [32].

The information about IL-6 in hypothyroid cases are very limited and not studied in tertiary care center in Pokhara, Nepal. We aimed to estimate IL-6, fT3, fT4 and TSH levels to correlate IL-6 with hypothyroidism.

METHODS AND MATERIALS

This was the hospital based cross-sectional study among 100 hypothyroid patients conducted by the School of Health and Allied Sciences, Pokhara University in collaboration with Pokhara Academy of Health Sciences (PoAHS), Pokhara, Kaski, Nepal from a period of June 2022 to November 2022. Ethical approval was obtained from Institutional Review Committee (IRC), Pokhara University Research Center (PURC), Kaski, Nepal (Ref. No. 59/079/080). Hypothyroid confirmed cases of age greater than 18 years of all gender visiting the laboratory who obeys the ATA criteria were included whereas hypothyroid cases with bacterial or viral infections, febrile illness, chronic disease, auto-immune disease and patient under antiviral therapy were excluded.

All the subjects were informed about the study and were voluntarily participated. Informed consent was taken from each individual and questionnaire as well. Fasting serum sample was taken for analysis. Thyroid function tests were analyzed by automated Chemiluminescence Immunoassay (CLIA) analyzer (Shenzhen YHLO Biotech Co., Ltd) and IL-6 levels were measured by semi-automated Immunofluorescence assay (IFA) analyzer (Getein Biotech,Inc).

All the baseline characteristics and obtained results were entered in Microsoft Excel 2010. To see the Inflammatory status (normal range; IL-6=7.0 pg/ml) the subjects above the normal range were taken under inflammatory group and below the normal range were taken under normal group. To see the hypothyroid status individuals with normal level of fT4 (fT4=0.5-1.4ng/dl) and TSH>5.0 µIu/L were taken under subclinical group while the individuals with sub-normal fT4 level (fT4<0.5 ng/dl) and TSH>10 µIu/L were taken under overt group, according to the guidelines of ATA (American Thyroid Association). Descriptive statistics (frequency, mean, standard deviation) was calculated and the IL-6 was correlated with the thyroid function test (fT3, fT4, TSH) by Pearson correlation coefficient test in SPSS (Statistical Package for Social Sciences, full version 16.0). Chi-square test was done to see the association between inflammatory status and hypothyroid status. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 hypothyroid patients (34 males and 66 females) were incorporated in this study. The population was distributed with the age of Mean ± SD (47.81±12.22) years and weight of Mean ± SD (66.75±5.31) kg while the systolic blood pressure of Mean ± SD (124.5±9.25) mmHg and the diastolic blood pressure of Mean ± SD (82.70±8.39) mmHg. Among the total hypothyroid population, 83(83.0%) were subclinical and 17(17.0%) were overt cases (Figure 1.0). The 31(31.0%) of the total population has increased level of IL-6 and 69(69.0%) were normal. In this study, out of the 17% overt cases IL-6 was increased in 82.35 % cases and 17.65% of them found normal. In case of 83% subclinical hypothyroidism, IL-6 was increased in only 20.48% of cases and 79.52% of them found normal (Table 1.0). IL-6 was significantly correlated with fT3 (r= -0.485, p<0.01) fT4 (r= -0.521, p<0.01) and TSH (r= 0.547, p<0.01) where there was a positive correlation between IL-6 and TSH with moderate strength (Table 2.0). There was a significant association between inflammatory status and hypothyroid status (Figure 2.0).

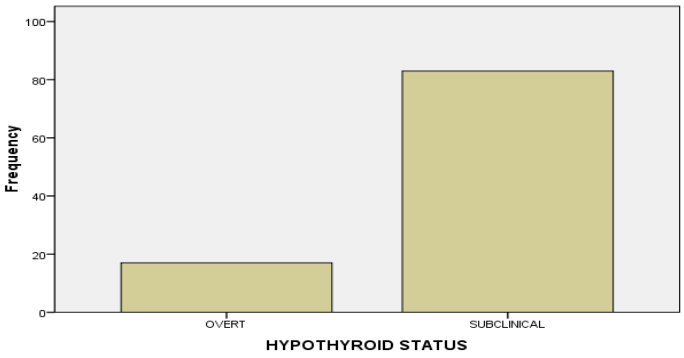

Figure 1: General distribution of population according to hypothyroid status

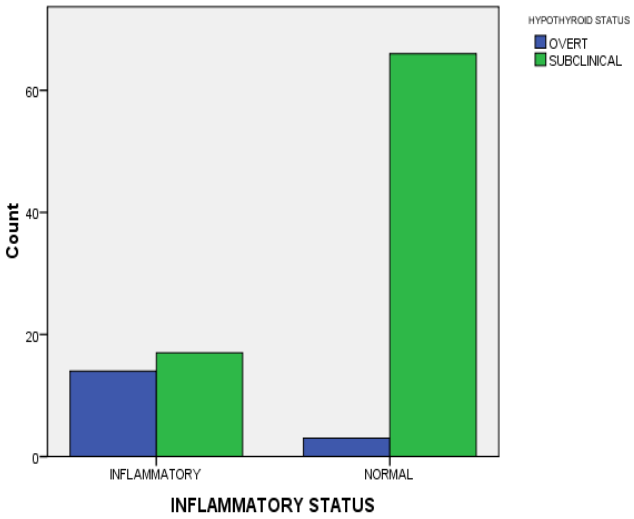

Figure2: Association between inflammatory status and hypothyroid status

Table 1: Distribution of inflammatory status and hypothyroid status. The values expressed represents number of subjects.

Inflammatory Status	Hypothyroid Status		Total
	Overt	Subclinical	
Inflammatory	14	17	31
Normal	3	66	69
Total	7	83	100

Table 2: Correlation between IL-6 and thyroid function tests.

Thyroid function tests	R-value	P-value
fT3	-0.485	< 0.01
fT4	-0.521	< 0.01
TSH	0.547	< 0.01

DISCUSSION

This study suggests that the hypothyroidism is correlated with the increased levels of IL-6 and may arise adverse inflammatory consequences. The inflammatory status is significantly associated with the hypothyroid status. The relationship of IL-6 with TSH was positive and statistically significant (p<0.01) where the mean concentration of IL-6 was 6.57±9.90. A similar cross-sectional study carried out by Gupta G. et.al in 154 hypothyroid patients found that average mean of IL-6 was 9.30±2.54 and the relationship between hypothyroidism and IL-6 was positive with statistical significance (p<0.05) [34].

In this study out of 100 hypothyroid patients 17.0 % were overt and 83.0% were subclinical which is supported by the study done by Naval Kishor Yadav et.al in western Nepal found that among the hypothyroid cases 17.7% were overt and 82.3% were subclinical [7]. These results build on existing evidence of hypothyroidism distribution in western part of Nepal. The 34.0% of the subjects were male and 66.0% were female

which gives the similar findings done in a study by Prabin Khatri et.al where 26.8% were males and 73.2% females [9], which contributes the clear understanding distribution of gender among Nepalese hypothyroid patients. Another experimental study done by Hajje et.al on Wister rats found that there was a significant ($p<0.05$) relationship between PTU (propyl thio-uracil) induced hypothyroidism and concentration of IL-6.(25). Similar study done by Taddei S. et.al in 53 subclinical hypothyroid patients with mean concentration of IL-6 1.12 pg/ml in compare to control which was 0.72 pg/ml with significant ($p < 0.01$) relationship (31).

IL-6 release is stimulated by thyroid stimulating hormone in adipocytes through cAMP/protein kinase A pathway (32). Levothyroxine therapy has significant effect to normalize the increased serum level of IL-6 among hypothyroid patients[35].

CONCLUSION

Based on the data this study suggests that hypothyroid patients may have increased levels of Interleukin 6. The association of IL-6 level with the hypothyroid status shows the risk of future development of cardiovascular disorders, metabolic disorders and chronic inflammation. If subclinical cases left untreated may progress to overt with relatively increased level of IL-6. These results build on evidence of growing adverse health status due to hypothyroidism. The outcomes of this study provided the light to all the laboratory scientists that interleukin 6 could be the potent marker of hypothyroid status. This study aware the clinicians that hypothyroidism must be treated early to avoid the consequences of inflammation. This study has limitations on sample size, bio markers range, study design, so a longitudinal case-control study with more variables, better tools and techniques are required to establish the generalized evidence.

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