

Hypothyroidism and Depression: Are Cytokines the Link?

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Abstract

Context: Primary hypothyroidism has been thought of as an inflammatory condition characterized by raised levels of cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). Depression is also well known to occur in hypothyroidism. Depression is also characterized by elevated inflammatory cytokines. We planned to study whether cytokines play an important part in linking these two conditions. **Objectives:** (1) To know the prevalence of depression in overt hypothyroidism due to autoimmune thyroid disease. (2) To correlate the levels of inflammatory markers with the occurrence of depression. (3) To study the effect of levothyroxine on inflammatory markers and depression. **Materials and Methods:** In this longitudinal, case-controlled study, 33 patients with autoimmune hypothyroidism (thyroid-stimulating hormone >10 uIU/ml) were included with 33 age-, sex-, and body mass index-matched healthy controls. Individuals were tested for Serum TNF- α , IL-6, high-sensitivity-CRP (hs-CRP). They were assessed for depression using Montgomery Asberg Depression Rating Scale (MADRS) and World Health Organization Quality of Life (QOL) Scale. Patients received L Thyroxine titrated to achieve euthyroidism and were reassessed for inflammatory markers and cognitive dysfunction. **Results:** Nineteen patients (57%) had mild to moderate depression (MADRS >11). After 6 months of treatment, eight patients (42%) had remission of depression with significant improvement in QOL scores ($P < 0.05$). TNF- α , IL-6, and hs-CRP were significantly elevated in patients compared with controls and reduced with therapy but did not reach baseline as controls. The change in inflammatory markers correlated with improvement in QOL scores in social and environmental domains ($P < 0.01$). **Conclusions:** Primary autoimmune hypothyroidism is an inflammatory state characterized by elevated cytokines which decline with LT4 therapy. It is associated with depression and poor quality of life. Treatment of hypothyroidism results in alleviation of depression in the majority of patients. Similarly, patients with mild to moderate depression should be tested for hypothyroidism as simple treatment may ameliorate their depression and improves MADRS score and QOL.

Keywords: Depression, high-sensitivity C-reactive protein, hypothyroidism, interleukin-6, Montgomery Asberg Depression Rating Scale, tumor necrosis factor alpha, World Health Organization Quality of Life Scale

INTRODUCTION

Primary hypothyroidism is a commonly encountered clinical problem. Treatment is indicated if thyroid-stimulating hormone (TSH) is more than 10 uIU/ml.^[1] The most common cause of hypothyroidism is autoimmune thyroiditis.

Hypothyroidism has been thought of as an inflammatory condition characterized by raised levels of inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL 6), and tumor necrosis factor-alpha (TNF- α).^[2] These inflammatory markers may have a role in the pathogenesis of many complications associated with hypothyroidism by causing endothelial dysfunction, smooth muscle cell proliferation and migration, and recruiting and activating

inflammatory cells.^[3] In addition, they induce the production of interferon-gamma and also mediate apoptosis.

Depression and cognitive impairment are also well known to occur in overt hypothyroidism.

According to the review by Boswell *et al.*^[4] the prevalence of depressive symptoms in hypothyroidism was nearly 50%.

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Clinical depression occurs in more than 40% of people suffering from hypothyroidism.^[2]

Interestingly, elevated titers of antithyroid antibodies have been documented in patients with clinical depression. The prevalence of antithyroid antibody positivity in depressed patients is 20% as opposed to 5%–10% in general population.^[5-7] The finding that depression often co-exists with autoimmune subclinical thyroiditis suggests that depression may also be caused by alterations in the immune system or vice versa or that in fact, it could be an autoimmune disorder itself.^[8] Patients with depression have been found to have increased biomarkers of inflammation, including innate immune cytokines, acute-phase proteins, chemokines, and adhesion molecules.^[9] It is a possibility that depression could belong to the spectrum of inflammatory and degenerative disorders.^[10] Similarly, hypothyroidism is a proinflammatory state characterized by elevated cytokines and multiple depressive symptoms.

This brings in forefront several questions – Could depression and hypothyroidism be linked? Are cytokines the missing link between the two? Can treatment with levothyroxine improve depression and reduce the level of cytokines? There are no Indian studies about the association of both thyroid function and inflammatory markers with depression. To seek an answer to these questions, this study was planned.

Aims and objectives

The aim of this study was to estimate the prevalence of depression in patients of hypothyroidism, to study the inflammatory markers in hypothyroidism and correlate them with the occurrence of depression and to study the effect of levothyroxine treatment on inflammatory markers and resolution of depression.

MATERIALS AND METHODS

This prospective open label case–control study was carried out at Endocrinology and Psychiatry Departments in a tertiary care hospital in Mumbai, after approval from the Institutional Ethics Committee. Patients visiting the thyroid clinic who were diagnosed to have antithyroid peroxidase (TPO) positive and TSH >10 m IU/ml (newly diagnosed and treatment naïve) qualified for the study if they were 18–45 years old, after informed consent.

The exclusion criteria were:

- Patients with any acute or chronic systemic disease
- Any autoimmune disease
- Any malignant condition
- Alcoholism
- Tobacco use
- Hypertension
- Diabetes mellitus
- Renal failure
- Underlying known cardiac disorder
- Pregnancy

- History of previous thyroxine therapy or antidepressant medication.

These stringent exclusion criteria were used to avoid the source of confounding factors which could influence the clinical or laboratory data.

We included 33 consecutive patients with overt hypothyroidism, and 33 age-, sex-, and body mass index (BMI)-matched volunteers as controls. The patients underwent a detailed clinical evaluation, followed by a collection of a venous blood sample obtained after an overnight fast of 10 h. Samples were taken at baseline and after 6 months of levothyroxine treatment.

The laboratory evaluation included measurements of thyroid function tests, anti-TPO antibody, serum TNF- α , IL-6, and high-sensitivity-CRP (hs-CRP). The hormonal evaluation was performed by chemiluminometric assay on the Advia Centaur platform manufactured by Siemens and the inflammatory markers by enzyme-linked immunosorbent assay kit from Krishgen Biosystems. The details of the kits and inter- and intra-assay coefficient of variations are given in Table 1.

The blood samples from controls were taken at baseline to get normative values of inflammatory markers. They did not receive any treatment.

Psychiatric evaluation

Patients were assessed for depression clinically using a semi-structured pro forma. This part of the study was carried out by a qualified and experienced psychiatrist who was unaware of the patient's thyroid status. Montgomery Asberg Depression Rating Scale (MADRS) was used to rate the severity of depression. This scale was validated in the local language. Participants were also asked to fill a questionnaire in the language that the participant best understood to assess the quality of life, i.e., the World Health Organization Quality of Life scale (WHO QOL).

MADRS is a very simple scale for even nonpsychiatric physicians to use. This scale assigns a score from 0 to 60. Score <10 is considered normal. A score of 10–35 is suggestive of mild to moderate depression, whereas a score more than 35 denotes severe depression.^[11] This scale consistently has the highest Cronbach's alpha levels reaching 0.92.^[12]

Table 1: Assays used and their coefficient of variation

	Method	Inter assay CV (%)	Intra assay CV (%)
TNF alpha	ELISA	9	3.3
IL-6	ELISA	6.5	7.8
hsCRP	ELISA	7.2	6
T3	CLIA	5.9	7.6
T4	CLIA	4.6	5.4
TSH	CLIA	2.6	2.9

TNF: Tumor necrosis factor, IL-6: Interleukin-6, hs-CRP: High-sensitivity C-reactive protein, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, CV: Coefficient of variation, CLIA: Clinical Laboratory Improvement Amendments

The quality of life was assessed by the WHO quality of life scale.^[13] This scale has a very broad focus beyond traditional health indicators to measures the actual impact of disease on impairment of daily activities and behavior in relation to the social background, thus actually giving the “the missing measurement in health.”

This scale has 4 domains, physical, psychological, social, and environmental. Each domain has a raw score which is then expressed as a transformed score ranging from 0 to 100.

Treatment

Thirty-three patients with hypothyroidism received treatment with L-thyroxin with the standard dose of 1.6 µ/kg bodyweight. Titration of the dose was done at 6 weeks and 3 months to achieve euthyroid status. After 6 months, patients were also reassessed and scores on depression scale (MADRS) and WHO QOL were recorded.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS statistical software 18.0 (SPSS Inc., Chicago, IL, USA). Demographic data were analyzed using descriptive statistics. Means were calculated for inflammatory markers. The mean values of pre- and post-treatment inflammatory markers were compared using paired *t*-test after evaluating assumption of normality. Furthermore, the mean values of inflammatory markers of controls (normal healthy volunteers) were compared with post-treatment mean values of inflammatory markers in treatment arm using independent *t*-test.

The proportion of depression among overt hypothyroidism before levothyroxine treatment and after treatment was compared using Chi-square test. The change in the inflammatory markers and depression scores and WHO QOL score was compared with the baseline and the control group. To find a correlation between inflammatory markers and depression prediction models were built using simple linear regression.

RESULTS

In this study, we included 33 patients, 28 female (85%) and 5 male patients (15%) with primary hypothyroidism, and 33 age-, sex-, and BMI-matched healthy controls. There was

Table 2: Baseline characteristics: Group statistics (mean±standard deviation)

Parameters	Cases (33)	Controls (33)	P
Age (years)	33.66±6.23	33.75±6.29	0.95
Height (cm)	159.3±6.4	159.3±6.3	0.98
Weight (kg)	67.49±9.14	67.45±9.16	0.98
BMI (kg/m ²)	26.64±4.1	26.63±4.1	0.99
T3 (ng/dl)	115.73±31.24	107.90±19.5	0.22
T4 (ug/dl)	7.49±2.7	8.8±1.73	0.023
TSH (uIU/ml)	44.77±33.2	2.69±1.05	<0.001
Anti TPO (U/ml)	1072±451	37±0.00	<0.001

BMI: Body mass index, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, TPO: Thyroid peroxidase

no significant difference between the cases and controls at the baseline except for the levels of TSH and anti-TPO antibody levels which were significantly elevated in the cases [Table 2].

Table 3 shows the levels of inflammatory markers in cases pre- and post-treatment and controls. The markers are significantly elevated in cases compared to controls. After the treatment with levothyroxine for 6 months and achieving euthyroidism all the markers reduced significantly. Figure 1 shows the change in the profile of inflammatory markers.

Table 4 and Figure 2 show the comparison of MADRS score and WHO quality of life scores in pre- and post-treatment groups. The MADRS score declined suggesting improvement in overall depressive symptoms whereas WHO QOL analysis reveals that all the domains of quality of life were positively impacted by the levothyroxine treatment.

Nineteen patients (57%) had mild to moderate depression (MADRS >11). After 6 months of treatment eight patients (42%) had remission of depression. With treatment, quality of life improved significantly in physical, psychological, social, and environmental domains (*P* < 0.05) [Table 4].

Nineteen patients of hypothyroidism had mild to moderate depression on MADRS. Patients who had remission of

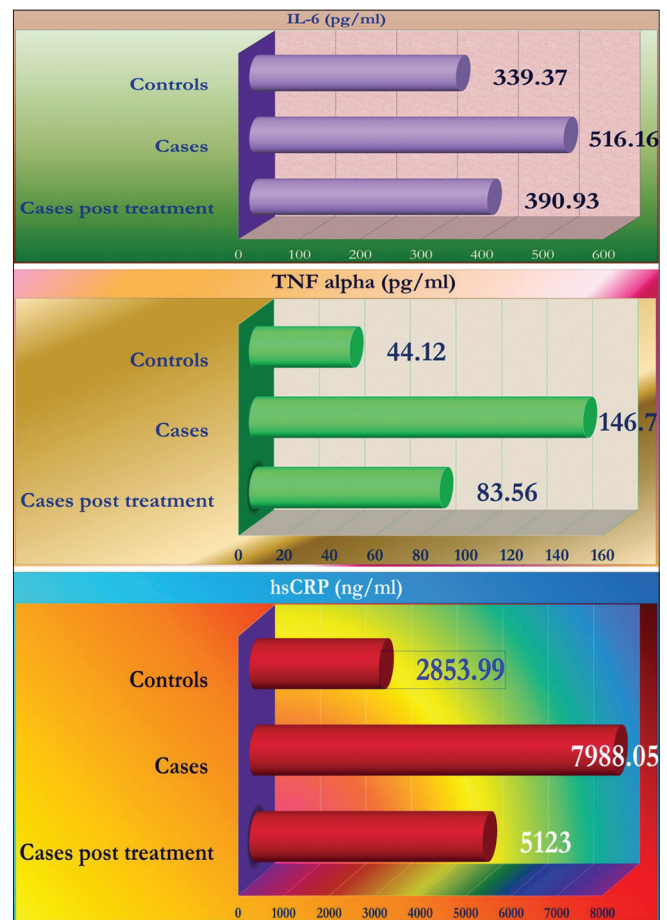


Figure 1: Inflammatory markers in cases and controls, before and after treatment

Table 3: Effect of treatment with levothyroxine on inflammatory markers (n=33)

	Controls (SE)	Cases (SE)	P	Cases (posttreatment)	P
TNF alpha (pg/ml)	44.12 (8.61)	146.72 (32.25)	0.003	83.56 (13.37)	<0.01
IL-6 (pg/ml)	339.37 (87.62)	516.16 (99.97)	0.074	390.93 (100.93)	<0.01
hsCRP (ng/ml)	2853.99 (528.16)	7988.06 (594)	<0.01	5123 (691.8)	<0.01

TNF: Tumor necrosis factor, IL-6: Interleukin-6, hsCRP: High-sensitivity C-reactive protein, SE: Standard error

Table 4: Montgomery Asberg Depression Rating Scale and World Health Organization Quality of Life scale

	Cases		P
	Pretreatment	Posttreatment	
MADRS	12.9±8.12	8.40±6.76	<0.001
D1-physical domain	57.80±23.41	73.03±20.43	<0.001
D2-psychological domain	53.37±21.54	67.73±18.79	<0.001
D3-social domain	61.73±21.30	79.57±17.40	<0.001
D4 environmental domain	66.40±18.98	82.97±14.24	<0.001

MADRS: Montgomery Asberg Depression Rating Scale

Table 5: Comparison of inflammatory markers in responders and nonresponders to levothyroxine therapy

	Responders (8)	Nonresponders (11)	P
TNF alpha			
Pretreatment	64.6±19.1	198.4±73.9	0.128
Posttreatment	62.4±11.5	93.2±20.1	0.226
IL-6			
Baseline	428.4±157.3	737.9±192.9	0.273
Posttreatment	285.7±110.4	552±192.1	0.272
hsCRP			
Baseline	6884.8±1685	7903.1±840.7	0.57
Posttreatment	4466.6±1545	6141.2±879	0.33
TSH			
Baseline	43.9±13.1	30.2±8.1	0.36
Posttreatment	1.8±0.4	2.04±0.5	0.72

TNF: Tumor necrosis factor, IL-6: Interleukin-6, hs-CRP: High-sensitivity C-reactive protein, TSH: Thyroid-stimulating hormone

depression were grouped as responders and compared with nonresponders. The nonresponders had elevated levels of inflammatory markers compared to responders; however, this difference is not statistically significant due to a small number [Figures 4, 5 and Table 5].

To find out the correlation between inflammatory markers and depression prediction models were built using simple linear regression. As shown in Figure 3, levels of TNF-α had positive correlation with baseline MADRS score and lower scores in the social domain of quality of life scores. The decline in TNF-α posttreatment correlated with improvement in score in social domain. Elevated TSH at baseline significantly correlates with elevated CRP. Change in the levels of IL 6 significantly correlated with improvement in social and environmental domains.

Thus, there is a positive correlation of hypothyroidism with elevated inflammatory markers and higher MADRS scores.

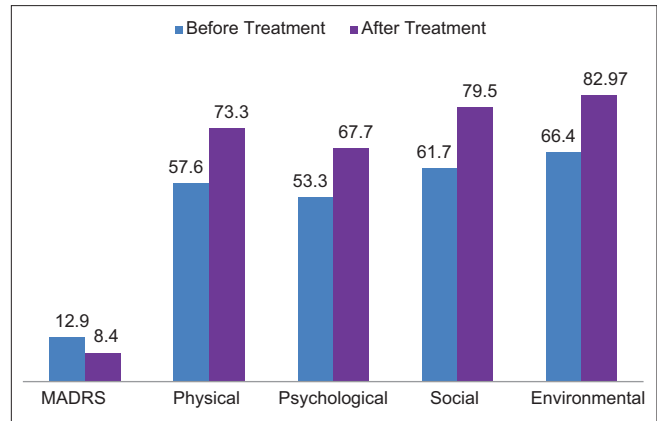


Figure 2: Montgomery Asberg Depression Rating Scale and World Health Organization Quality of Life scale - before and after treatment

It negatively impacts the quality of life. Treatment with levothyroxine improves the functional scores which are most obvious in the social and environmental domains [Figure 6].

DISCUSSION

In this study, the prevalence of mild to moderate depression among patients with overt hypothyroidism was 57% at the baseline. After 6 months of treatment with levothyroxine and achieving euthyroidism, 42% of the cases had remission of depression.

The levels of inflammatory markers such as TNF-α, IL 6, hs-CRP were significantly elevated in cases of hypothyroidism compared to controls at baseline. Levothyroxine therapy resulted in significant decline in the levels of these inflammatory cytokines. However, the levels remained elevated as compared to healthy controls.

It was also observed that the levels of inflammatory markers were higher in those who did not have remission of depression, but the difference was not statistically significant, which could be due to limited sample size.

With treatment, the quality of life improved significantly in physical, psychological, social, and environmental domains ($P < 0.05$)

The relationship between thyroid dysfunction and psychiatric disorders has long been recognized.

Historically, it was described more than 200 years ago. Parry in 1825 reported an increased incidence of “nervous affectations” in thyroid disorders., Gull in 1873 showed the relation between

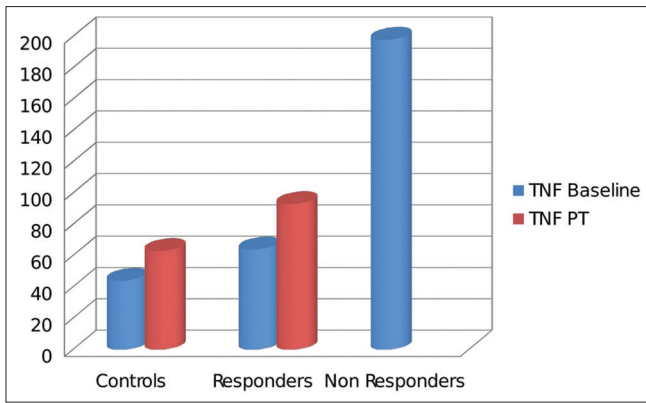


Figure 3: Comparison of inflammatory markers in responders and nonresponders: Tumor necrosis factor-alpha

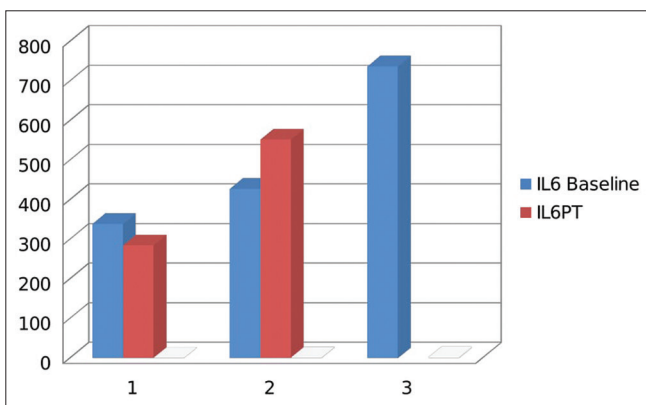


Figure 4: Comparison of inflammatory markers in responders and nonresponders: Interleukin-6

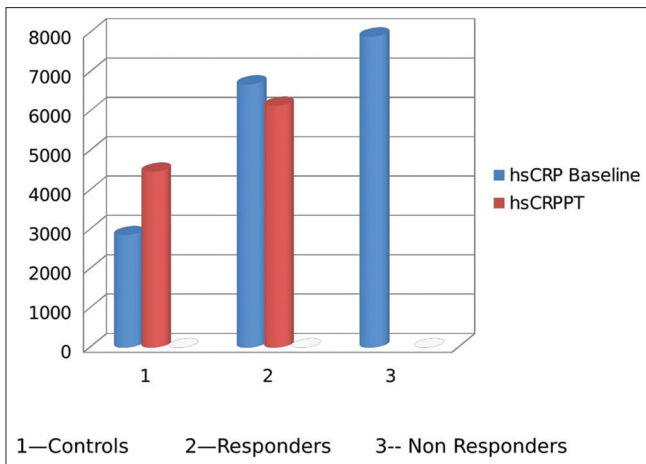


Figure 5: Comparison of inflammatory markers in responders and nonresponders: High-sensitivity C-reactive protein

myxedema and psychosis. It was confirmed in 1888 by the Committee of the Clinical Society. In 1949, Asher coined the term “myxedema madness” to describe the psychiatric status of subjects with hypothyroidism.

In last 100 years, this subject has been extensively evaluated and we have gained new insights in the association of these

two conditions. The effects of hypothyroidism on disturbances in emotion and cognition are well known.

These abnormalities are generally reversible with adequate thyroid treatment.

In this study, hypothyroid patients frequently demonstrated features of depression, cognitive dysfunction, apathy, and there was significant impact of this condition on the quality of life.

These findings were consistent with earlier studies by Türemen *et al.*, Ramazan *et al.*, and Tuzcu *et al.*^[14-16]

After treatment with levothyroxine and achievement of euthyroidism the levels of inflammatory markers decreased significantly. Similar observations were noted by Kebapcilar *et al.*^[17]

Marfella *et al.* observed a reduction in CRP in levothyroxine treated patients, but CRP was still significantly increased compared to the control group. He further observed significantly lower plasma TNF- α , IL-6, and IL-18 levels in treated with subclinical hypothyroidism compared to controls.^[18]

Guclu *et al.* demonstrated a significant decrease in serum IL-12, a statistically nonsignificant decrease in interferon-gamma (INF- γ) and no change in serum IL-2 or IL-4 in patients with hypothyroidism due to Hashimoto’s thyroiditis that underwent 12 weeks of levothyroxine treatment.^[19]

Similar findings were replicated in the recent study by Marchiori *et al.* in which proinflammatory and anti-inflammatory cytokines before and after thyroxin treatment were studied. There was a significant decrease in the levels of IL-1, IL-6, INF- γ , and TNF- α and with a significant increase in IL-10 (anti-inflammatory cytokine) with levothyroxine therapy.^[20]

In the current study, the levels of TNF- α , IL-6, and hs-CRP all showed significant decline ($P < 0.01$) after achieving euthyroidism in 6 months with levothyroxine therapy. However, the levels in the patients remained elevated as compared to the normal control population.

MADRS score of 11 was used as a cutoff to define mild to moderate depression.^[11] With this cutoff 19 patients (57%) were recognized to have depression. The WHO quality of life scale was used at baseline and after 6 months on follow-up. There was significant improvement in the quality of life, after levothyroxine treatment. After 6 months of treatment eight patients (42%) had remission of depression. The quality of life improved significantly in physical, psychological, social, and environmental domains ($P < 0.05$).

Our study has several strengths. We studied patients with autoimmune hypothyroidism who constitute a majority of cases in an outpatient setting. The patients did not have obvious symptoms of depression but on screening a large number of them had mild to moderate depression. Thus we could study the impact of disease in its subclinical stage

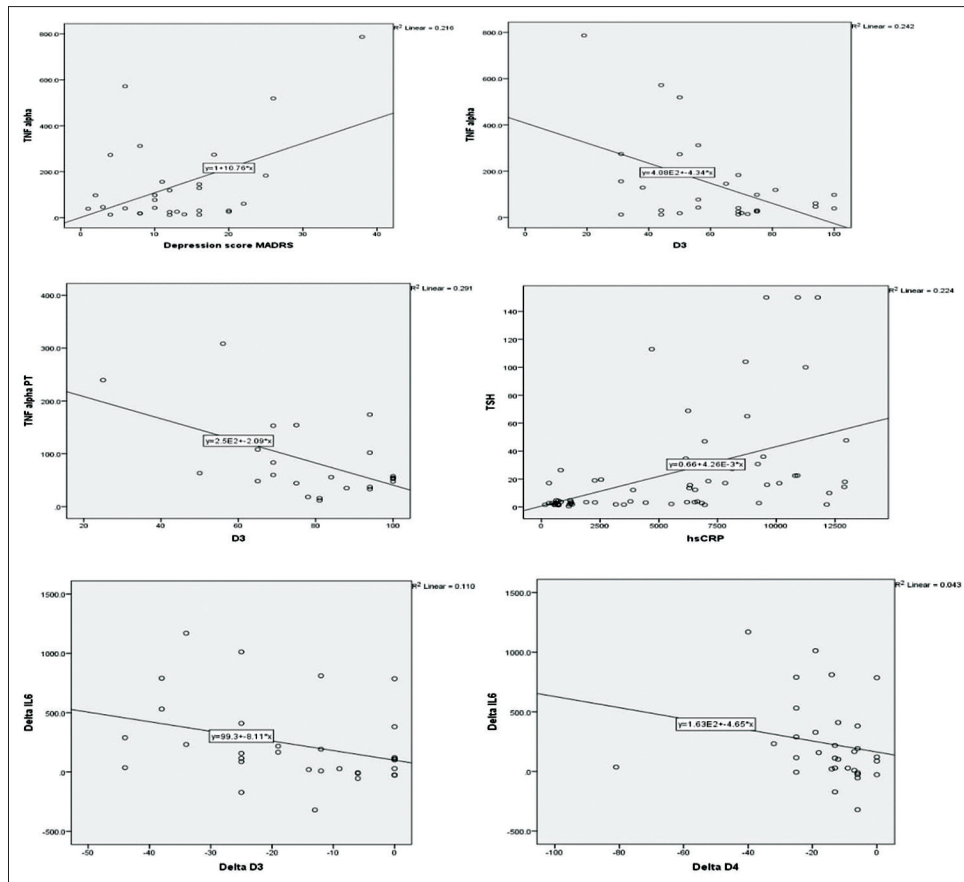


Figure 6: Correlation of inflammatory markers with Montgomery Asberg Depression Rating Scale and World Health Organization Quality of Life

and how it adversely impacted the quality of life, which often goes unnoticed.

We could also document objectively that patients with primary hypothyroidism have elevated levels of cytokines and with appropriate treatment these levels also come down significantly as does the depression score, which parallels the improvement in quality of life. The study could provide consistent scientific evidence for depressive disorders and thyroid dysfunction. These findings may give novel insights in the pathogenesis of depression in general and cognitive affection in particular in patients with hypothyroidism.

The limitations of our study are the number of patients and duration of follow-up.

The role of antidepressant therapy in nonresponders and assessment of its impact on further improvement in quality of life remains an area for future research.

CONCLUSIONS

Primary autoimmune hypothyroidism is an inflammatory state characterized by elevated cytokines. A possible role for thyroid autoimmunity and inflammatory markers in the pathogenesis of depression can be elucidated. It may be associated with depression and poor quality of life. Levothyroxine therapy leads to significant decline in the level of inflammatory cytokines.

Levothyroxine therapy significantly improves the MADRS scores. It significantly improves the quality of life. Physical, psychological, social, and environmental domains show significant positive impact of the therapy. A patient with mild to moderate depression should have thyroid functions evaluated as achieving euthyroidism improves the depression and quality of life. The impact of antidepressant therapy on nonresponders remains an area for future research.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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