

VIRAL HEPATITIS C AND THYROID ABNORMALITIES

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Infection associated with hepatitis C virus (HCV) is a major health problem and is one of the most important causes of chronic liver diseases and the most common causes of end stage liver diseases. After a long-time of discussions, the link between HCV and autoimmune disorders was proven. Interferon treatment may also play a huge role in these processes. To prevent this, analysis of thyroid gland's hormones, including antibodies, must be done before, during and after 6 months of IFN therapy, to find any abnormalities timely. New therapy is safer, with less side effects, but still are very expensive and a large proportion of patients may not have access to them.

Keywords: Hepatitis C virus, autoimmune thyreoiditis, Interferon-induced thyreoiditis

Introduction. According to the World Health Organization (WHO) at least 170 million people are infected with HCV worldwide and 3 to 4 million new infections occur per year [1]. The conventional treatment of chronic hepatitis C consists the injection of Peg-IFN- α 1.5 mkg/kg once a week and a daily oral dose of ribavirin 15 mg/ kg. The main goal of this review is to study whether thyroid abnormalities develop on the basis of HCV or more on IFN therapy. The estimated prevalence of thyroid disorders induced by CHC and its treatment with Peg-IFN- α based therapy ranges between 2.5% to 35% in different countries [12, 21, 23, 26, 27].

Liver diseases are known to induce thyroid disorders and abnormal serum concentrations of thyroid hormones. Hypothyroidism and thyroid autoimmunity are more common in patients with CHC, even in the absence of cirrhosis, HCC, or IFN- α treatment in comparison with normal individual or those who are infected with hepatitis B infection [14, 15].

Thyroiditis can also be associated with interferon and it is known as interferon induced thyroiditis (IIT), which can be classified as autoimmune and non-autoimmune types [24, 25]. This variability can be attributed either to an underestimation of the true prevalence of thyroid disorders or to the diverse genetic predisposition of the subjects [12, 15].

Epidemiology. In a recent study from Turkey showed that *de novo* incidence of thyroid dysfunction (TD) was found to be 16.8% among the 119 chronic HCV patients receiving pegylated-interferon plus ribavirin. Similarly, a clinical study also showed that at 11.5% of patients developed TD, 85.3% of these patients presented with subclinical TD, and 14.7% of them developed overt thyroiditis, at the end of the IFN- α based therapy (Table 1). The study also showed that 67.8% of them the thyroid function spontaneously returned to normal in the six months of follow-up and only 4.4% had persistent overt TD symptoms after the 24 month follow-up period. The likelihood of TD development during the treatment varies between 5.5% and 27.8% according to different studies [16-19]. Turkey, as a genetically affine country, demonstrates predisposed incidences in Kazakhstan.

Table 1 - Worldwide statistic data shows percentage in thyroid dysfunction and thyroid antibodies development among HCV patients treated by IFN [13].

Country	Treatment	No. (M/F)	Newly developed thyroid antibody n (%)	Newly developed thyroid dysfunction n (%)
France	IFN- α	68 (39/29)	4 (5.9)	8 (12)
Japan	IFN- α	109 (77/32)	2 (1.9)	9 (8.2)
Italy	IFN- α	114 (79/35)	36 (31.5)	8 (7)
Spain	IFN- α	144 (95/49)	7 (4.9)	4 (2.8)

Risk factors that may contribute or prevent autoimmune thyroid diseases.

Genetic factors contribute for about 70% to 80% and environmental factors for about 20% to 30% to the pathogenesis of autoimmune thyroid disease (AITD). Relatives of AITD patients carry a risk to contract AITD themselves. The 5-year risk can be quantified by the so-called Thyroid Events Amsterdam-score, based on serum thyroid-stimulating hormone, thyroid peroxidase (TPO)-antibodies and family history.

IIT is more common in females than in males. According to different studies, females appeared to have a 4.4 times higher risk of developing secondary thyroid disease to IFN- α based therapy in comparison with males. Females' susceptibility may be due to the effects of estrogenic sex steroids in promoting autoimmunity, or it could be due to the susceptibility gene on the X-chromosome, since females have two X-chromosomes, so males are less likely to inherit the gene. IIT is considered a major

complication for those who are treated with IFN- α based therapy. IIT is classified mainly into two types: either autoimmune (i.e., Hashimoto's thyroiditis and Grave's disease) or non-autoimmune (e.g. destructive thyroiditis and non-autoimmune hypothyroidism) [15, 23, 30]. The postpartum period is associated with an increased risk of AITD. Taking together, preventive interventions to diminish the risk of AITD are few, not always feasible, and probably of limited efficacy. [3]

To stop smoking decreases the risk on Graves disease but increases the risk on Hashimoto disease.

Moderate alcohol intake provides some protection against both Graves and Hashimoto disease.

Low selenium intake is associated with a higher prevalence of thyroid autoimmunity, but evidence that selenium supplementation may lower TPO antibodies and prevent subclinical hypothyroidism remains inconclusive.

Low serum vitamin D levels are associated with a higher prevalence of TPO antibodies, but intervention studies with extra vitamin D have not been done yet.

Stress may provoke Graves hyperthyroidism but not Hashimoto thyroiditis.

Estrogen use have been linked to a lower prevalence of Graves disease.

The most active natural vitamin D metabolite, 1,25-Dihydroxyvitamin D₃, effectively prevents the development of autoimmune thyroiditis. 1,25(OH)₂D₃ exerts its immunomodulatory actions by inhibiting HLA class II expression on endocrine cells, proliferation of T cell and secretion of inflammatory cytokines.

Vitamin D has recently been reported to play significant roles in the regulation of immune system, the process of erythropoiesis and thyroid functions. Deficiency of vitamin D was also found to correlate with an increased incidence of autoimmune diseases. Vitamin D supplementation enhances innate immunity and reduces the severity of autoimmunity. Vitamin D levels were found to be lower in patients with AITDs than in healthy people. Deficiency of vitamin D was also linked to the presence of anti-thyroid antibodies and abnormal thyroid functions. [2]. Several studies have indicated that VitD supplementation is useful for the prevention/treatment of anemia and thyroid disorders. However, little is known about the potential effect(s) for vitamin D as a prophylactic/treatment agent against these side effects during the treatment of CHC with Peg-IFN- α based therapy. Further studies with large number of patients are required to determine whether supplementation with vitamin D during the treatment of CHC with Peg-IFN- α based therapy is useful in increasing the rates of SVR and preventing the development of associated adverse effects.

According to Poupak et al, all risk factors may be collected in 7 groups with own influence on development of autoimmune thyroid diseases:

1. Age: the prevalence of disease tends to increase with age.
2. Genetic: a significant association between Hashimoto's thyroiditis and some histocompatibility antigens (HLA-DR, HLA-DR5, and some DQ alleles) is demonstrated. Many other susceptibility genes have been associated with AT; for example, specific CTLA4 gene polymorphisms are linked to a possible development of antithyroid antibodies .
3. Iodine: an increased AT prevalence is observed in areas of iodine sufficiency, compared with iodine-deficient areas.
4. Selenium: a selenium deficit is linked to a higher AT prevalence.
5. Irradiation: AT occurs more frequently after the exposure to low doses of radiations
6. Cytokine: the treatment with Interferon- (IFN-) α , or with Interleukin- (IL-) 2, can promote the onset of AT in predisposed patients
7. Infections: it was seen that several viral infections can predispose to an AT in animals. Moreover, different studies tried to associate AT with viral infections in humans with conflicting results [4]

Immunopathogenesis of HCV Infection and AITD.

Several molecular mechanisms have been suggested for the association of CHC with AT:

- a) molecular mimicry or cross-reactivity which may occur between viral antigens and thyroidal antigens (Figure 1).
- b) heat shock proteins expression in thyroid gland.
- c) abnormal expression of MHC class II molecules by thyrocytes.
- d) Changes in self-antigen expression due to viral infection, or recognition of cryptic epitopes; bystander activation of auto reactive T-cells by cytokine release during the local inflammatory response caused by virus.
- e) IL-6 influence.

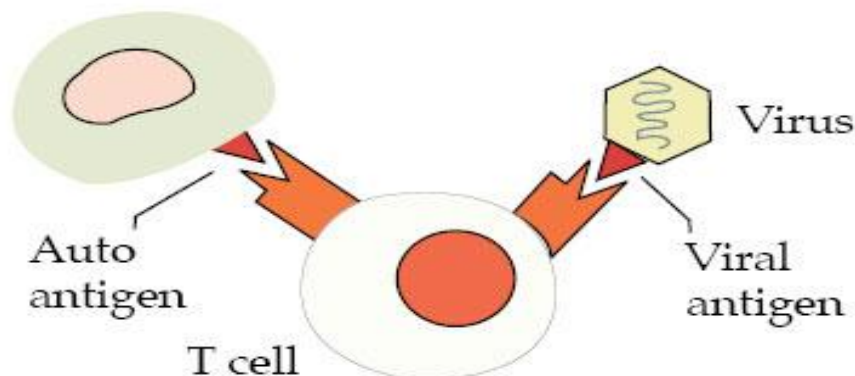


Figure 1 - Diagram showing Molecular Mimicry Hypothesis

The molecular mimicry hypothesis suggest that a certain AG has a great degree of similarity with endogenous structures. Mistaken identity triggers the host immune system (autoantibodies) to attack foreign as well as endogenous targets when infected with organism.

d) Cytokines, chemokines and their receptors may contribute either directly or indirectly in above-mentioned mechanisms. These factors are low molecular weight, function as chemical messengers and are interact with one another in complex ways. They are synthesized by multiple cell types and can have various functions depending upon the cell that produces it and the cell upon which the cytokine acts. Therefore, it is difficult to draw conclusions with regard to the specific role of each cytokine in mediating the observed pathophysiological effects. However, there is, a growing recognition that aberrant cytokine expression appears to play an important role in the pathogenesis of many human autoimmune diseases, including virus-induced thyroid autoimmunity. Consequently, the involvement of these mediators in disease cannot be ignored.

An increased expression of IFN- γ and IFN- γ inducible chemokines, in particular (C-X-C motif) ligand 10 chemokine (CXCL10), has been shown in hepatocytes and in lymphocytes of HCV infected patients, directly related to the degree of inflammation and to an increase in circulating levels of IFN- γ and CXCL10. CXCL10 is one of chemokines with C-X-C motif. IP-10 activates specifically CXCR3 receptor that is a G protein-coupled receptor with seven transmembrane domains mainly expressed in T activated lymphocytes, natural-killer cells (NKs), macrophages, and B cells. Recent studies showed that CXCL10 expression in serum and/or tissue levels is increased in autoimmune organ-specific diseases, such as type 1 diabetes, or systemic rheumatological diseases like rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, sarcoidosis, and psoriatic arthritis. High levels of CXCL10 are present in patients with AT, in particular in the presence of hypothyroidism, and an involvement of T-helper (Th)1 immune response in the induction of AT, GD, and Graves' ophthalmopathy has been demonstrated, suggesting that intrathyroidal lymphocytes and/or thyrocytes may be the source of CXCL10. Furthermore, the presence of HCV in the thyroid of chronically infected patients has been recently shown.

e) Also, IL-6 was modestly but significantly increased in patients with AT, which may suggest another way of pathogenesis. Specific IL-6 binding sites have been also identified in thyroid cells, which reduces TSH-mediated iodine uptake, thyroid peroxidase mRNA expression in response to TSH, and thyroid hormone release through the TSH-dependent mechanism. Both in GD and in HT, membrane attack complexes of complement occur around thyroid follicles. Formation of these complexes may result in prostaglandin E₂, IL-1 α , and IL-6 production, which promote infiltration of lymphocytes leading to cell destruction. In GD, proinflammatory cytokines such as IL-6 may further induce the synthesis of external thyroid-stimulating antibodies that bind to TSHR. IFN α can also contribute to an autoimmune inflammatory response via a variety of mechanisms, such as reducing T regulatory cell function and alterations in immunoglobulin production. Th1 polarization may constitute a potentially important therapeutic effect of IFN α and may contribute in the pathogenesis of IIT. This deduction depends partly on observations such as greater increase in type 1 helper T cells in hepatitis C patients who developed IIT. However, there are some conflicts regarding these results and several studies indicated that IFN α could influence the production of type 2 cytokines.

On the above mentioned bases, it has been speculated that HCV thyroid infection may act by upregulating CXCL10 gene expression and secretion in thyrocytes recruiting Th1 lymphocytes that secrete IFN- γ and tumor necrosis factor- (TNF-) α . These cytokines induce CXCL10 secretion by thyrocytes, thus perpetuating the immune cascade, which may lead to the appearance of AITD in genetically predisposed subjects (Figure 2).

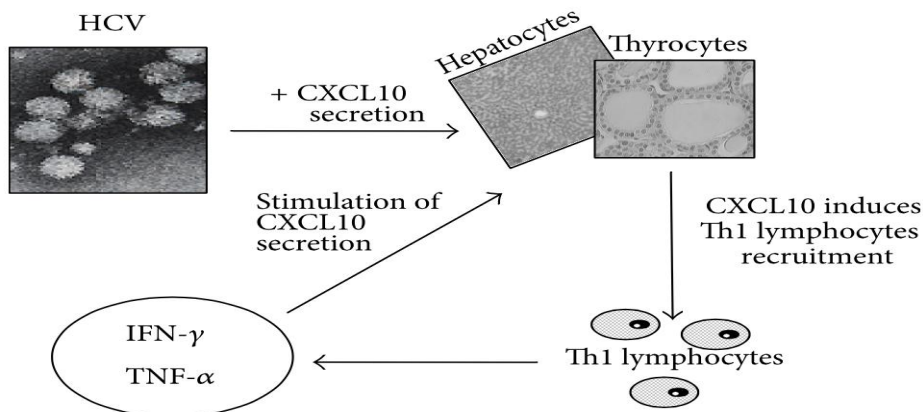


Figure 2 - HCV thyroid infection may act by upregulating CXCL10 gene expression and secretion in thyrocytes recruiting Th1 lymphocytes that secrete IFN- γ and TNF- α . These cytokines induce CXCL10 secretion by thyrocytes, thus perpetuating the immune cascade [4]

Treatment of CHC.

The traditional treatment for CHC is a combination of a weekly injection of pegylated interferon- α (Peg-IFN- α) with daily oral ribavirin (RBV) and the duration of the treatment is based on the viral genotype [1]. Although new direct acting antiviral (DAA) drugs have been developed, the treatment of CHC could still be based on a weekly injection of Peg-IFN- α -2a or -2b plus a daily weight-based dose of RBV with or without the new antiviral therapy depending on the progression of liver damage and the presence of other extrahepatic manifestations [2, 6-8]. Furthermore, the new antiviral drugs are expensive and therefore Peg-IFN- α based therapy could still be the standard of care especially for treatment naïve patients with no liver cirrhosis and/or for those living in developing countries and for whom access to the new drugs is not definite due to its high cost.

Several disadvantages are associated with Peg-IFN- α based therapy during the treatment of CHC. These include low response rate (e.g. 50% for genotypes 1 and 4) and the development of several drug induced side effects that could lead to dose reduction or termination of treatment [6, 10-14]. CHC and its treatment with Peg-IFN- α based therapy are associated with

several extra-hepatic complications including hematological and endocrinological abnormalities. The most prevalent side effects associated with the traditional treatment of CHC are anemia and thyroid disorders

Thyroiditis associated with CHC and IFN- α therapy.

Strong correlations between liver damage and thyroid disorders have been also reported [20]. Non-alcoholic fatty liver diseases (NAFLD) and abnormal liver enzymes are significantly associated with hypothyroidism and the prevalence of liver diseases and enzymes increase steadily with increasing grades of hypothyroidism [20]. Furthermore, a decrease in serum triiodothyronin (T3) concentration and thyroxine (T4) ratio is frequently observed in patients with liver cirrhosis probably due to impaired conversion of T4 to T3 in the liver [21].

Thyrotoxicosis is also associated with a variety of abnormalities of liver function [22] and results from a recent study suggests that low free T4 (FT4) concentrations are associated with hepatic steatosis [24]. Serum thyroid stimulating hormone (TSH) level was also significantly higher in NAFLD and it has also been suggested that measurement of free T3 and T4 levels may all be useful as predictors of mortality in intensive care patients who have cirrhosis [20]. Thyroiditis is a major clinical problem especially for patients with chronic HCV infection [25-28] (Figure 3).

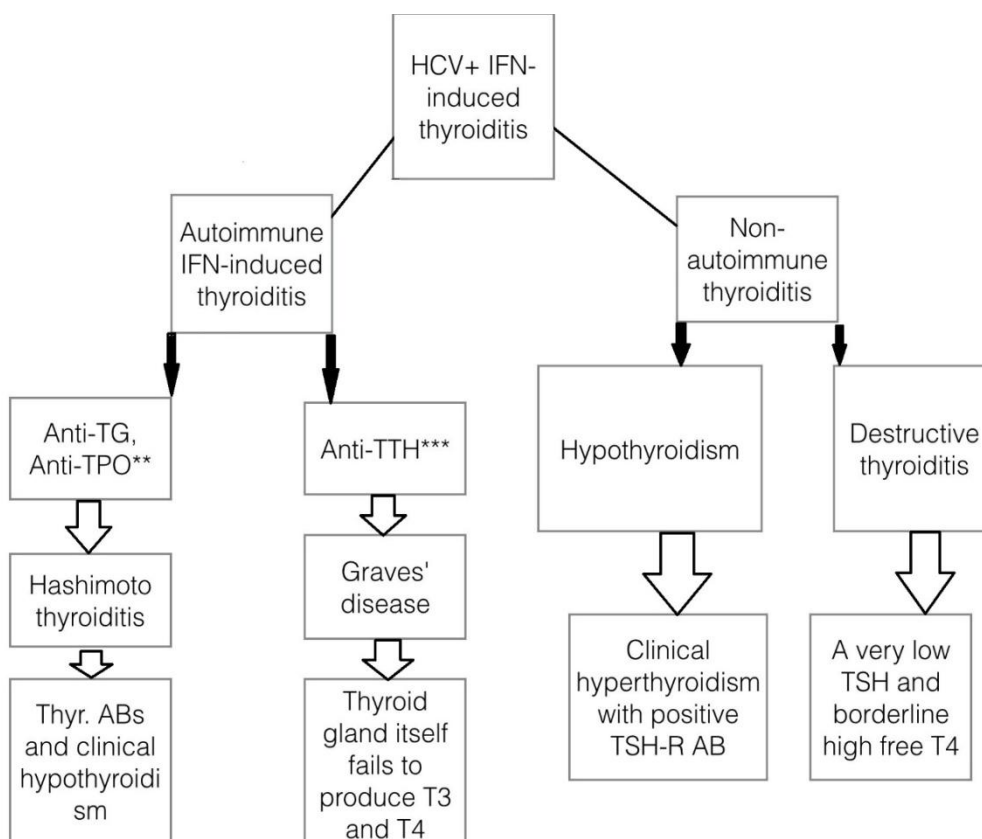


Figure 3 - Types of thyroid dysfunctions in HCV and IFN treatment. [2]

** anti-Tg and anti-TPO autoantibodies are observed most frequently in Hashimoto disease, they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers.

*** anti-TTH level may show the activity of Graves' disease.

Thyroid abnormalities following interferon therapy have also been described in children receiving interferon for hepatitis C infection [32]. Some of these complications of IFN therapy, especially thyrotoxicosis, can be severe and may interfere with adequate interferon therapy in patients with hepatitis C infection [24, 28]. Moreover, because the symptoms of hypothyroidism such as fatigue, hair loss, myalgia, and weight gain may be attributable to hepatitis C or IFN therapy, the diagnosis of hypothyroidism in these patients may be delayed [29]. This delay may lead to development of further complications. Thus, IIT represents a major clinical problem for patients with chronic HCV infection and who receive interferon for treatment that may interfere with their treatment course [27, 28].

Autoimmune thyroid diseases (AITD) are strongly influenced by genetic factors and therefore they are likely to affect the etiology of IIT.

Actually, the presence of HCV infection and IFN- α therapy might induce thyroiditis in genetically inclined individuals [30]. IFN- α and RBV could also act against thyroid cells by inducing a direct toxic effect [27, 31]. While it is not clear which factors contribute to the susceptibility to IIT, recent evidence suggests that genetic factors, gender, and hepatitis C virus infection may play a role [31]. However, viral genotype and therapeutic regimen do not influence susceptibility to IIT [32].

Another way of treatment:

Recently, new antiviral drugs have been developed. These medicines, called direct antiviral agents (DAA) are much more effective, safer and better-tolerated than the older therapies. Therapy with DAAs can cure most persons with HCV infection and treatment is shorter (usually 12 weeks) and safer. Although the production cost of DAAs is low, these medicines remain

very expensive in many high- and middle-income countries. Prices have dropped dramatically in some countries (primarily low-income) due to the introduction of generic versions of these medicines.

Hashimoto, Graves or autoimmune- which one is more common?

The commonest of autoimmune IIT is Hashimoto's thyroiditis (HT) and it is more likely in people who are positive to thyroid antibodies (TAb) before starting the therapy with Peg-IFN- α based therapy [27]. However, development of HT could also occur in CHC patients and who are negative to TABs during the course of therapy [31]. A less common manifestation of autoimmune IIT is Graves' disease (GD) [31, 34]. In a retrospective study, 321 patients diagnosed with hepatitis B or C and treated with IFN- α , 10 patients developed thyrotoxicosis, which was characterized by a completely de-created TSH [30]. Six of those patients developed GD and all of them had symptomatic thyrotoxicosis, which failed to resolve even after IFN- α cessation [34].

GD and HT are both known of formation of thyroid-reactive T cells that infiltrate the thyroid gland [28, 36]. HT is characterized by Th1 switching of the thyroid infiltrating T cells, which induce apoptosis of thyroid follicular cells and clinical hypothyroidism. In GD, most of T cells undergoes a T helper (Th) 2 differentiation and activates B cells to produce antibodies against the thyroid stimulating hormone receptors, which are the hallmark of GD, and eventually they will cause clinical hyperthyroidism as a result of thyroid stimulation [37]. Indeed, IFN- α therapy in patients with hepatitis C has been strongly associated with both GD and HT, as well as the production of thyroid antibodies without clinical disease [28, 38].

Several studies have shown that the treatment of hepatitis C with IFN can induce the production of Tabs *de novo*, or cause a significant increase in TABs levels in individuals who were positive for TABs prior to interferon therapy [31]. The incidence of *de novo* development of thyroid autoantibodies secondary to IFN therapy varied widely in different studies from 1.9% to 40% [27]. The wide variations in the reported incidence of TABs in interferon treated patients could be related to the used detection assays and different cut-off values applied in the different studies [39].

However, up to 50% of patients who develop thyroid abnormalities during IFN- α therapy do not develop autoantibodies, which suggests that thyroid dysfunction may be caused by a direct effect on thyroid cells [40]. A previous *in vitro* study reported that TSH-induced gene expression of thyroglobulin was inhibited following the culture of human thyroid follicular cells with interferon type I.

Destructive thyroiditis is a self-limited inflammatory disorder is another form of thyroid abnormality associated with Peg-IFN- α based therapy during the treatment of CHC. This disorder consists of three phases: hyperthyroidism, followed by hypothyroidism phase, and finally normalization of thyroid function and usually it takes weeks to months to resolve [25, 31, 40].

Subacute thyroiditis due to IFN therapy for hepatitis C infection is usually benign. In addition, a subset of these patients may progress to permanent hypothyroidism, usually accompanied by the development of TABs suggesting an underlying autoimmune thyroiditis [28]. Alternatively, the hypothyroidism may be due to a direct toxic effect of IFN on the thyroid. Clinical and subclinical hypothyroidism without TABs during IFN therapy have been described and in many of these cases thyroid insufficiency is transient but permanent hypothyroidism is likely to develop if patients were positive for thyroid antibodies [41].

Thyroid cancer as a complication?

Montella et al. have carried out a case- controlled study on the different oncological pathologies. Among 495 patients with HCV 130 had developed thyroid cancer, with association: OR = 2.8, 95% CI 1.2–6.3, $P = 0.01$. [5]

Other studies have confirmed an association between AT and thyroid cancer. Accordingly, features of AT were observed more frequently in HCV patients than in controls suggesting that AT may be a predisposing condition for thyroid cancer. Since about 15–30% of HCV patients may show an aggressive disease, for example, lung metastases, difficult to treat, the finding of an increased prevalence of thyroid cancer in these patients is clinically relevant [5].

Antonelli et al. studied the prevalence of thyroid cancer in 308 unselected HCV+ patients in comparison to two population-based, gender- and age-matched control groups: 1) 616 subjects from an iodine deficient area; 2) 616 subjects from an iodine-sufficient area. Thyroid status was assessed by measurement of circulating thyroid hormones and autoantibodies, thyroid ultrasonography, and when indicated, fine-needle aspiration cytology.

Circulating thyrotropin, anti-thyroglobulin, and anti-thyropoxidase antibodies levels, and the prevalence of hypothyroidism were significantly higher in HCV+ patients ($p < 0.001$ for all). Six patients with papillary thyroid cancer were detected among HCV+ patients, whereas no case was observed in control 1 ($p = 0.001$), and only one case was observed in control 2 ($p = 0.003$). In HCV+ patients 83% with thyroid cancer had evidence of thyroid autoimmunity vs 31% of the other HCV+ patients ($p = 0.02$). [9]

These data suggest a high prevalence of thyroid papillary cancer in HCV+ patients, overall in presence of thyroid autoimmunity; careful thyroid monitoring is indicated during the follow-up of these patients [9].

Conclusion.

1. There is a proved link between thyroid gland's autoimmune pathologies, i.e. hypo- and hyperthyroidism, and viral hepatitis C.
2. Interferon treatment also influences on the development of autoimmune disorders in thyroid gland.
3. Other remedies (Direct Antiviral Agents) are safer, with less side effects, but still are very expensive and a large proportion of patients may not have access to them.
4. Another findings suggest that vitamin D supplementation could have a potential role in improving the success rate of Peg-IFN- α during the treatment of CHC merit further research especially that it is widely available and inexpensive, and it could provide an alternative option to treat those patients who have limited financial support and/or access to the new antiviral treatment.
5. Monitoring of thyroid gland's hormones, including antibodies, must be done before, during and after 6 months of IFN therapy, to find any abnormalities timely.

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С ВИРУСЫ ГЕПАТИТ ЖӘНЕ ҚАЛҚАНША БЕЗДІҢ БҰЗЫЛУЛАР

Түйін: С вирусы гепатитін (HCV) жұқтыру Денсаулық сақтау министрлігінің негізгі мәселелерінің бірі және бауырдың созылмалы ауруларының ең маңызды себептерінің бірі болып табылады. Көп уақыт аралығында айтылған аутоиммундық ауруларының вирус гепатитінің механизмдік дамуы мен патогенезі зерттелінді. Интерферонның емделуі бұл процесте көп қызмет атқарады. Оның дамуының байланысты қалқанша безінің гормондарына терапияға дейін, терапияның кезінде, терапиядан 6 ай кейін анализ жүргізіледі. Жаңа терапия яғни ол зиянды емес аз кері әсер ету механизмімен сипатталады, бірақ бәрібір өте қымбат: бәрі пациенттерде өзіне жаңа терапия тауып алуы мүмкін емес.

Түйінді сөздер: С вирусы гепатит, аутоиммунды тиреоидит, интерферон терапиясынан дамып жатқан тиреоидит

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ВИРУСНЫЙ ГЕПАТИТ С И ЗАБОЛЕВАНИЯ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

Резюме: Инфицирование вирусом гепатита С (HCV) является одной из основных проблем здравоохранения и является одним из наиболее важных причин хронических заболеваний печени. После долгих дискуссий механизм развития и патогенез аутоиммунных заболеваний при вирусном гепатите С были доказаны. Лечение интерфероном также играет немаловажную роль в этом процессе. Для предотвращения этого необходимо проводить мониторинг гормонов щитовидной железы и аутоантитела к ним, до, во время и после 6 месяцев терапии интерфероном. Альтернативой интерферонотерапии является лечение препаратами прямого противовирусного действия, эти схемы более безопасны, с меньшими побочными эффектами, но, тем не менее, очень дорогостоящие: не все пациенты могут позволить себе новую терапию.

Ключевые слова: Вирус гепатита С, аутоиммунный тиреоидит, интерферон-индуцированный тиреоидит