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A REVIEW OF THE PATHOPHYSIOLOGY OF ENDOCRINE EXTRA HEPATIC MANIFESTSATIONS OF CHRONIC HEPATITIS C INFECTION

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Abstract

Chronic hepatitis C virus (HCV) infection causes progressive liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. It is also involved in the pathogenesis of many extrahepatic diseases manifesting as various autoimmune and rheumatic disorders (arthritis, vasculitis, sicca syndrome, porphyria cutanea tarda, lichen planus, nephropathies, thyroid diseases, metabolic disorders, and lung fibrosis; development of B-cell lymphoproliferative diseases. In this review we look at the endocrine extrahepatic manifestations including thyroid disorders and metabolic disorders (insulin resistance and diabetes mellitus) associated with chronic HCV infection.

The existence and severity of extrahepatic manifestations do not correlate with the severity of liver disease, and the mainstay of treatment is HCV eradication. Patients with systemic manifestations of HCV infection should be prioritized for treatment, especially in the era of new interferon-free therapies with fewer side effect.

Keywords: *Chronic hepatitis C infection, Extrahepatic manifestations, Thyroid disorder Metabolic disorders Interferon therapy Direct-acting antiviral agents*

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INTRODUCTION

Hepatitis C viral (HCV) infection is a serious infection, and results from the infection of hepatocytes by the Hepatitis C virus – which is a spherical, enveloped, single-stranded RNA virus, of the Flaviviridae family and genus Flavivirus, with 7 major genotypes and 67 subtypes.1 It causes both acute and chronic hepatitis and it is estimated by the World Health Organization (WHO) that about 71 million persons live with chronic Hepatitis C globally with mortality of 399,000, usually from liver cirrhosis and hepatocellular cancer.2 About 110million people have a history of HCV infection.3 HCV accounts for about 20% of all cases of acute hepatitis, and an estimated 30,000 new acute infection in the United States.4

In Nigeria, HCV has an estimated prevalence of 2.2%, with all the genotypes, save genotype 5, present in the population. 3

The routine pathophysiology to HCV-induced hepatitis involves the invasion of the hepatocytes and production of millions of new viral particles each day. The HCV genome is made up of a single, open reading frame and 2 highly conserved untranslated regions 5'-UTR and 3'-UTR at both ends of the genome.5

Upon infection, the virus undergoes proteolytic cleavage – resulting in 2 structural envelope glycoproteins (E1 and E2) and a core protein. The protein E2 contains binding sites for CD81 receptor in the hepatocytes and act as receptors/co-receptor for HCV, (6) and have a high rate of mutation due to its 2 hyper-variation regions – 1 and 2. The core protein of HCV modulate several signaling pathways in the liver cells affecting cell cycle regulation, promotion of cell growth, proliferation, apoptosis, lipid metabolism and oxidative stress.7 There are non-structural proteins which function as RNA-, helicase-, protein-dependent RNA polymerases (NS2, NS3, etc.) and play roles in viral propagation and replication, as well as assembly of cytoplasmic membrane-bound replication complex. 6 These viral replications modulated by these RNA polymerases lack proof-reading capabilities and leads to generation of several mutant viruses called quasi-species.

The resultant hepatic inflammation and fibrosis of varying degrees is what characterizes acute or chronic hepatitis C. Most patients are asymptomatic but may have non-specific symptoms such as arthralgia, pruritus, neuropathies, muscle pains and can progress to symptoms suggestive of hepatic decompensation – encephalopathy, ascites, variceal bleeding with attendant signs such as palmer erythema, fetor hepaticus, gynecomastia, testicular atrophy. 1

However, in addition to these hepatic disease, chronic infection with HCV have been demonstrated to also cause extra-hepatic disease – including dermatological, rheumatologic, metabolic and endocrine dysfunction.8

Some of these extra-hepatic manifestations of chronic HCV have been better described than others. The endocrine extra-hepatic manifestations have been extensively discussed in the literature and in case reports/studies.

This review shall focus only on the endocrine manifestation of chronic HCV infection and its proposed pathophysiology.

METHODS

This review was conducted by examining peer- review articles, case reports, and cohort studies indexed in Pub med, Scopus, and Web of Sciences. References were selected based on relevance to endocrine manifestations of HCV, with emphasis on studies published between 2000 and 2025. Key search terms included ''Hepatitis C virus'', "extra hepatic manifestations'', "thyroid diseases,"C "diabetes mellitus", "cryoglobulinemia" and "interferon therapy".

DISCUSSION

Endocrine Manifestations of HCV infection

Chronic HCV infection is associated with hypothyroidism, autoimmune thyroid diseases, and papillary thyroid carcinoma. Interferon therapy can exacerbate thyroid autoimmunity. It also increases the risk of insulin resistance and type 2 diabetes mellitus, with autoimmune features observed in some cases. Rare cases link HCV to Autoimmune Polyendocrine Syndrome (APS) type2, involving Addissson's disease, thyroid autoimmunity and type 1 diabetes. Finally HCV Virus infection has been associated with erectile dysfunction and hypoandrogenism in men.

Thyroid Disorders and HCV

In a study by Himoto and Masaki (2012) the link between HCV infection and the endocrine system dysfunction was evaluated. The paper demonstrated significant association between chronic HCV infection and hypothyroidism, thyroid autoimmunity and thyroid cancer as well as development of type 2 Diabetes Mellitus. 9

In a study by Antonelli et al published in the American Journal of Medicine (2004), 630 patients with chronic hepatitis due to HCV infection but free of cirrhosis, hepatocellular cancer and not on interferon (IFN) therapy were studied against a control group. Mean Thyroid Stimulating Hormone (TSH) levels were higher and free T3 In a study by Villanuera and Brau, dual thyroid antibodies – TSAb (thyroid-stimulating antibodies) and TBAb (thyroid-blocking antibodies) were noted in patients with chronic HCV and Grave's disease (ophthalmopathy), and patients were noted to experience both thyroid blocking and thyroid stimulating phenomenon. (12) The study reveals a TBAb predominance however such that patients presented with clinical hypothyroidism but had sufficient thyroid stimulating antibodies to also precipitate Grave's disease and ophthalmic adipogenesis. Introduction of Interferon-gamma for treatment of HCV was shown to tilt the equilibrium in favour of TSAb and this manifested in a progressive thyrotoxic biochemical profile. 12 This can be explained by the immune-modulatory effect of the interferon-gamma.

and free T4 levels lower in patients with chronic hepatitis C than in other patient groups. It was demonstrated that chronic HCV patients were more likely to have hypothyroidism, anti-thyroid antibodies and anti-thyroid peroxidase antibodies. (8)(10)

In another study involving 1400 chronic HCV patient reviewed at 3 separate hospitals in Egypt, it was found that 90% of the patients had insulin resistance, 24% had hyperglycemia (16% T2DM, 8% IGT) and 21% had dysthyroidism (13% hyperthyroidism, 6% hypothyroidism, 6% euthyroid goiter). (11)

Calvaruso amd Craxi, Italian physicians and researchers reported that Autoimmune thyroid disorder (AITD) and hypothyroidism were significantly more frequent in patients with chronic hepatitis compared to HBV-infected patients or normal subjects. The prevalence of aberrant levels of anti-thyroid antibodies in patients with chronic HCV ranged from 2-48%, and that of subclinical hypothyroidism were reported as 2- 9% with particular

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susceptibility to Grave's disease and Hashimoto's thyroiditis, upon commencement of interferon –gamma for HCV infection13

There is also evidence suggesting a causal relationship between chronic HCV and papillary thyroid cancer, especially in a setting of Mixed Cryoglobinemia. 13 In a 2002 study involving patients with HCV-related Mixed Cryoglobinemia, there was a marginal increased prevalence of papillary thyroid cancer in the study group compared to the control group. This was collaborated in another study involving 308 patients with chronic HCV and a control group, where more patients with chronic HCV were found to have papillary thyroid cancer than patients in the control group. These same patients with chronic HCV were also found to have increased circulating thyrotropin, anti-thyroglobulin and thyroperoxidase antibodies. 13

Diabetes Mellitus (DM) and HCV

The relationship between non-cirrhotic chronic HCV and Type 2 Diabetes Mellitus, compared to patients with other forms of liver disease have been repeatedly demonstrated in the literature. In a study by Antonio A, Ferri C, Fallahi P et al, involving 229 mixed cyroglobinemia-HCV patients versus 217 controls with HCV infection, there was demonstrably increased prevalence of T2DM in the study group.14 In another large study in 2005, T2DM was significantly more prevalent in HCV patients compared to control group or non-cirrhotic HBV patients. 13

In a case-control study in Italy, by Metwalley KA, and Farghaly HS, 564 HCV-infected non-cirrhotic patients were compared with 302 patients without viral hepatitis or alcohol dependence, and 82 patients with non-cirrhotic HBV infection, Type 2 diabetes mellitus was significantly more prevalent in HCV-infected non-cirrhotic patients compared to the control patients (12.6% vs 4.9% and 7% respectively; p = 0.008). In this study, a characteristic phenotype was noted – HCV-infected, non-cirrhotic patients with Type 2 DM were slightly older, had higher levels of triglycerides and were obese, but with lower levels of HDL cholesterol in contrast to non-diabetes HCV patients who were leaner and with lower levels of LDL.10

There is some vagueness in defining the diabetes mellitus in background of HCV infection. The classification as Type 2 is mostly traditional because of the pathognomic phenotype described. However, it has been noted that in HCV-infected Diabetes patients with Mixed Cryoglobinemia, an autoimmune pathogenesis is observed, suggesting a type 1 phenotype. (10)

Type 1 diabetes mellitus and anti-pancreas autoimmunity has also been associated with interferon-gamma treatment of HCV. 13

Autoimmune Polyendocrine Syndrome (APS)

In the Journal of Medical Case Reports (2012), researchers, Metwalley and Farghaly reported a rare case of Autoimmune Polyendocrine Syndrome type 2 in an Egyptian child with chronic HCV – characterized by autoimmune Addison's disease, autoimmune thyroid disease and Type 1 diabetes mellitus. 15 The patient was noted to have hyperkalemia, hyponatremia, low cortisol, high adrenocorticotropic hormone, slightly elevated thyroid stimulating hormones and anti-thyroglobulin and anti-thyroid peroxidase antibodies.15

Male Gonadal Dysfunction and HCV

Some studies have also found link between HCV and gonadal alterations manifesting in erectile dysfunction in male patients and hypo-androgenism 8 In an Italian study that compared 207 HCV-infected males with 207 non-infected controls, without confounding factors such as cardio-vascular, psychiatric, diabetes, hypothyroid or renal disorders, HCV-infected patients were noted to have a higher prevalence of erectile dysfunction and abnormal sex hormones compared to the control ($p < 0.001$). 10

PROPOSED THEORIES OF PATHOPHYSIOLOGY

A number of theories have been proposed, some of which have strong research-based evidence, to explain this abundant clinical correlation between chronic HCV and multiple endocrine morbidities, particularly thyroid dysfunction and Diabetes Mellitus.

1. Direct infection of thyrocytes
2. HCV-induced metabolic disturbance
3. Type 1 T-Helper cell mediated Immune response.
4. Interferon mediated immunomodulation.

Direct Infection of Thyrocytes

There is theorization that HCV can directly infect the thyroid cells, leading to HCV thyroiditis. This was confirmed in a study which was carried out in chronically infected HCV patients in whom HCV-RNA (anti-genome) were detected in their thyroid gland. 16 HCV genome is able to induce endogenous IFN within the thyroid cells. This indigenous IFN could cause thyroiditis in possibly similar ways as exogenous IFN used for HCV treatment. It has direct insulting effect on the thyrocytes, particularly the follicular cells, and causes inhibition of TSH-induced gene expression of Thyroglobulin, TPO and Na-Iodine Symporter (NIS). 17 The IFN could also enhance thyroid auto-antibody formation in genetically susceptible patients and mediate autoimmune thyroid disease.

HCV-Induced Metabolic Disturbance

There is theory that HCV induces significant changes in the metabolism of glucose and lipid, which could lead to Insulin Resistance, dyslipidemia and obesity, all of which contribute to the evolution and phenotypical presentation of type 2 Diabetes Mellitus. Inflammatory cytokines like the Tumor Necrosis Factor-alpha (TNF- a) being elaborated in the setting of chronic hepatitis C virus infection induce a chronic inflammatory state that interfere with glucose and lipid metabolism and ultimately result to Insulin Resistance (IR). Viral proteins have been noted to also play direct roles by interfering with intracellular signaling pathways for insulin, leading to significant metabolic disturbances. 10

Type 1 T-Helper Cell Role

Studies have suggested and indeed linked increased Th1 immune response with HCV infection and development of thyroid autoimmunity and type 2 Diabetes Mellitus. This is triggered ab initio by the infection of B-cells and thyrocytes by the Hepatitis C viruses causing a cytotoxic and chemotactic BURST for the purpose of containing viral replication and spread. One of the cytokines secreted is the CXCL10 and this upregulated CXCL10 is known to mobilize Th1 lymphocytes. Recruited Th1 lymphocytes stimulate IFN-gamma, TNF-a production that in turn stimulates more CXCL10 secretion from these B-cells and thyrocytes, and thus propagate tan immune cascade that may precipitate or trigger appearance of thyroid auto-immune disorders or Type 2 Diabetes Mellitus in persons who are already genetically predisposed8

There may also be instances of molecular mimicry between host components and viral proteins which perpetuates the autoimmune phenomenon brewing.

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The strong relationship between this CXCL10 and autoimmune thyroid disease is further collaborated by the presence of elevated CXCL10 in inflammatory cells and thyrocytes in patients who have Grave's disease. 18,19 In a study involving patients with Grave's disease, their thyrocytes were stimulated in vitro with IFN-gamma, and large amounts of CXCL10 was elaborated, and this further supports the evidence that CXCL10 elaborated by inflammatory cells and thyrocytes in the background of chronic HCV infection play significant causal role in the pathogenesis of autoimmune thyroid disease.19 Another study by Antonelli et al, demonstrated how radioiodine therapy or thyroidectomy respectively in the background of AITD is associated with depressed levels of CXCL10, suggesting the strong likelihood that these cytokines are produced by thyrocytes and/or intra-thyroid lymphocytes, and in the setting of chronic HCV infection could lead to AITD. 20,21

These studies buttress the fundamental or underlying role CXCL10, elaborated by the inflammatory cells and HCV-infected thyrocytes play in the evolution of autoimmune thyroid disease and hypothyroidism seen in patients with chronic HCV infection. 22

Other Auto-immune Pathways

a. Molecular mimicry or cross-reactivity between thyroidal antigens and viral antigens. The antibodies designated to target the viral antigens are mistaken and attack the thyroid antigens, leading to development of autoimmune thyroiditis. 23
b. Some studies have suggested activation of by-standing auto-reactive T-lymphocytes during the cytokine surge that follows the initial inflammatory response at the thyroid gland following infection. 24 These cells target the T-lymphocytes – leading to autoimmune thyroiditis.
c. Expression of special proteins known as heat shock proteins on the surface of thyrocytes that become target for cross-reactivity. 25
d. Other studies have suggested aberrant MCH class II molecules expressed by the thyrocytes in the background of chronic HCV infection which form a basis for autoimmunity.26,27
e. Recognition of cryptic epitopes on the thyroid cells by infiltrating lymphocytes and inflammatory cells due to the HCV infection which lead to autoimmune disease of the thyroid gland. 22

Role of Interferon

As early as the 1980's, an association was observed between interferon-a and thyroid disease in patients who were receiving IFN-a for their breast cancer, and this has received considerable attention. 28

IFN is the mainstay of treatment for HCV infection. Earlier prescribed as monotherapy for chronic HCV cases with clearance of <20%, it is currently practiced now to use pegylated IFN with Ribavirin, with viral clearance of 40% – 90%. (29) It binds to cell surface receptors and acts as a powerful anti-viral, anti-tumoral, anti-inflammatory and immunomodulatory agent, effective for viral clearance. IFN is known to have a significant side effect profile however, including neuro-psychiatric symptoms and thyroiditis30 It is for this reason that the thyroid function and antibody panel of patients starting IFN therapy must be done prior to commencement and must be monitored closely during treatment.

The mechanism of thyroid insult is both autoimmune and non-autoimmune. 31 The autoimmune mechanism, though not fully understood, have been suggested to be by its capacity to activate inflammatory cells (macrophages, lymphocytes, neutrophils) as a potent exogenous cytokine. It also has a positive feedback effect on other endogenous cytokines/chemokines leading to a cytokine storm, especially of Interleukin 6 (IL-6) – which has been demonstrated to be important in the pathogenesis of AITD. 32,33

IFN can also cause upregulation of MHC class I and II and CD40 on thyrocytes which results in activation and mobilization of cytotoxic T lymphocytes and overt immune response.34 This accumulated T-cell activation, mediated also in part by the CD40 and its attendant IL-6 surge, further aggravate an aggressive immune milieu.

IL-6 binding to thyroid cells have been shown to reduce TSH-mediated iodine uptake, TSH-sensitive thyroid peroxidase mRNA expression and thyroid hormone release leading to dysthyroidism.34,35 This exaggerated immune response lead to autoimmune disease of the thyroid and overt inflammation, especially in persons who are genetically susceptible to autoimmune thyroid disease or have pre-treatment anti-thyroid antibodies.22

IFN induced thyroiditis (IIT) have been found to cause Grave's disease, Hashimoto thyroiditis and subclinical hypothyroidism. Attack complexes found in IIT-associated Grave's disease or Hashimoto thyroiditis against follicular cells of the thyroid gland lead to prostaglandin (E2), IL-1a, IL-6 cross-reaction which further promote lymphocyte inflammation and thyroiditis. 35 IFN may also mediate thyroiditis by reducing Treg. cell function and Th1 cell upregulation which propagate inflammation of the thyroid gland. 37

The non-immune pathway by which IFN causes thyroid disease is similar to indigenous IFN. It causes a direct insult to the thyroid cells and inhibits several important steps in the production of thyroid hormones, including inhibition of the Na-Iodine Symporter (NIS) and the gene expression of Thyroglobulin and Thyroid peroxidase.17

CONCLUSION

Chronic hepatitis C virus (HCV) infection is a systemic disease where endocrine extrahepatic manifestations, such as thyroid disorders and type 2 diabetes, significantly contribute to overall morbidity and mortality. The pathophysiology involves direct viral effects on thyrocytes and pancreatic beta cells, chronic inflammatory signaling, and metabolic disturbances like insulin resistance.

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