THYROID DYSFUNCTION IN PATIENTS TREATED WITH ANTI-HCV ORAL DIRECT ACTING ANTIVIRAL THERAPY

ABSTRACT:

Background: Hepatitis C is highly prevalent in Pakistan and direct acting antiviral agents have replaced interferon-based regimen due to better safety, however, its association with thyroid dysfunction remains unclear. This study was thus conducted to determine prevalence of thyroid dysfunction in patients treated for hepatitis C infection with oral direct acting anti-viral therapy.

Methods: This multi-centre prospective cohort study was conducted at MedicineDepartment of Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan, District Headquarter Hospital, Sargodha, Pakistan and Akbar Niazi Teaching Hospital, Islamabad, Pakistanfrom June-2023to February-2026.A total of 280 patientswith hepatitis C infectionwithout any prior thyroid dysfunction were included. All of these patients were treated with sofosbuvir 400mg and daclatasvir 60mg. At completion, patients were assessed for thyroid dysfunction. Association of thyroid dysfunction withage and gender was assessed using Chi-square test. Statistical analysis was done using SPSS software version 25.

Results: Mean age was 41.29 ± 13.53 years. There were 198 (70.70%) male and 82 (29.30%) female patients. Mean viral load was 868.33 ± 411.08 IU/ml.Prevalence of thyroid dysfunction in present study among hepatitis C patients given direct oral anti-viral treatment was 94 (33.60%) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid. Prevalence of thyroid dysfunction was significantly higher in female patients ($p = 0.018$).

Conclusion: Thyroid dysfunction was observed in 33.6% of the hepatitis C infected patients treated with oral direct acting anti-viral therapy with significantly high prevalence in females.

Keywords: Daclatasvir, Hepatitis C, Hyperthyroidism, Hypothyroidism, Sofosbuvir.

INTRODUCTION:

Hepatitis C virus (HCV) infection is a highly prevalent in Pakistan that has been reported to infect an estimate of 11.5% of the population. [1]According to the estimates of World Health Organization, if Pakistan wants to eliminate this disease from the society, minimum threshold for screening and treatment would require an increase of18 million and one million people per year, respectively. [2] HCV primarily spreads through blood contact and various other modes including repeat usage of shaving blades, needle stick injury, tattooing, sexual transmission, vertical transmission from mother to baby, vast spread quackery practices, unhygienic conditions of health care facilities providing dental and surgical care, and blood transfusion. [3, 4]

Primarily, HCV infects liver where it causes chronic inflammation leading to cirrhosis. [5, 6] This leads to a myriad of complications such as portal hypertension, hepatocellular carcinoma, hepatorenal syndrome and encephalopathy. [7]Classically, HCV was managed with peg-interferon but it was associated with high relapse,low compliance and high thyroid dysfunction rate. [8] To counter this, newer direct acting oral anti-viral agents (DAAs) are now used. In fact, DAA therapy is now used as standard of care in treating HCV patients globally, particularly in South Asian region. Despite a large set of population being on DAA therapy in this region, data regarding its potential effect on the thyroid function, particularly at regional level, is unavailable. Due to lack of this data, evidence regarding whether or not DAA use is associated with thyroid dysfunction or not is yet not clear. Therefore, present multi-centre study was conducted with the aim to determine prevalence of thyroid dysfunction among HCV affected patients treated with DAAs.

METHODOLOGY:

This multi-centre prospective cohortstudy was held at Medicine Department of Tehsil Headquarter Hospital, Sarai Alamgir, Pakistan, District Headquarter Hospital, Sargodha, Pakistan and Akbar Niazi Teaching Hospital, Islamabad, Pakistan from June-2023 to February-2026. A sample size of 280 patients was calculated by inputting 95% confidence interval, 5% absolute precision and anticipated prevalence ofthyroid dysfunction in DAA users of 23.8%[9], in WHO sample size calculator software. The sample selection process was based on non-probability consecutive sampling technique.

Male and female patients who were aged between 18 and 65yearswith HCV-RNA PCR based diagnosis of HCV(defined by > 20 IU/ml) without any prior thyroid dysfunction were included. Patients with prior exposure to any form of HCV treatment, non-compliant to medications course, thyroid dysfunction, thyroid surgery, medications interfering with thyroid function (like amiodarone, iodine), any comorbid condition, liver cirrhosis and its related complicationswere excluded.

Before inclusion, it was ensured that all the patients gave their explicit informed consent in written form for which a dedicated pre-printed form was used. In addition, pre-treatment screening for thyroid dysfunction was also done to ensure euthyroid status of the patients intended toget treatment. Pre-treatment patient related parameters including their age, gender andviral load were recorded. Patients were given monthly doses of medication (sofosbuvir 400mg and daclatasvir 60mg combination to be taken once daily) for three months. Patients were call one day before completion of one month to collect the next month dose and compliance was ensured by asking them to bring their empty bottles of medicines. At completion of three months, when patients were called to take sample for repeat HCV RNA PCR to assess for achievement of sustained viral load, additional blood sample was obtained to assess for thyroid dysfunction (defined by presence of any pattern of disturbance in free T4, free T3 and TSH levels). Hypothyroidism was defined by presence of TSH > 5.0, free T4 < 0.7 ng/dl and free T3 < 260 pg/ml.Hyperthyroidism was defined by presence of TSH < 0.35, free T4 > 1.53 ng/dl and fT3 > 480 pg/ml.

All the collected data was entered and analysed with SPSS version22. Qualitative variable(gender and thyroid dysfunction)was measured as frequency and percentage. Quantitative variables (age andviral load) were measured asmean ± standard deviation (SD). Association of thyroid dysfunction with age and gender was assessed using Chi-square test since cell count was more than five. A p-value ≤ 0.05 was considered statistically significant.

RESULTS:

A total of 280patients with HCV RNA PCR based HCV diagnosis were included. Mean age was 41.29 ± 13.53 years. There were 198 (70.70%) male and 82 (29.30%) female patients. Median viral load was 868.33± 411.08IU/ml. Pre-treatment patient demographic is given in Table-I:

Table-I: Pre-treatment patient demographic (n = 280)

Characteristic	Mean ± SD; n (%)
Median age (years)	41.29 ± 13.53
Age group	
<40 years	130 (46.40%)
≥ 40 years	150 (53.60%)
Gender	
Male	198 (70.70%)
Female	82 (29.30%)
Median viral load (IU/ml)	868.33± 411.08

Prevalence of thyroid dysfunction in present study among HCV patients given DAA treatment was94 (33.60%) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid. Association of thyroid dysfunction prevalence by age and gender is given in Table-II:

Table-II: Thyroid dysfunctionassociation withage and gender (n = 280)

Age stratification			
	<40 years (n = 130)	**≥ 40 years (n = 150)**	**p-value †**
Thyroid Dysfunction	39 (30.00%)	55 (36.67%)	0.239
Gender stratification			
	Male (n = 198)	**Female (n = 82)**	**p-value †**

Thyroid Dysfunction	58 (29.29%)	36 (43.90%)	0.018

† = Chi-square test

DISCUSSION:

Hepatitis C is a prevalent communicable disease wreaking havoc in the South Asian region of the world, particularly in Pakistan and India. According to recent estimates its prevalence has surged to 11.5% and3.23%, respectively. [1, 10] This burden is encountered by therapy through modern oral direct anti-viral agents (DAAs) which have now effectively replaced classically used injectable interferon-based therapy owing to better safety and efficacy profile. [11, 12]One of the factor that resulted in this this replacement was association of interferon therapy with dysfunction of thyroid hormone regulation. [13] At the same time, it is unclear whether DAAs also result in this pathology or not, which prompted conductance of this study.

In present study, prevalence of thyroid dysfunction in present study among HCV patients given DAA treatment was94 (33.60%) with 80 (28.6%) patients being hypothyroid and 14 (5.00%) patients being hyperthyroid.In comparison to this, Wahid *et al*. reported that among DAA users suffering from active HCV, prevalence of hypothyroidism and hyperthyroidism was 18.9% and 4.9%, respectively which were lesser yet comparable with present study findings. [9] Contrarily, Abdelrazik*et al.* reported that patients who were treated with DAA for presence of active HCV infection were found to have prevalence of dysfunction of thyroid hormone regulation was only 1% which was negligible in comparison to present study. [14] Similarly, in another study by Rodia*et al*. reported that none of the patients whose active HCV disease was treated with DAAs developed thyroid dysfunction, demonstrating high level of safety of DAAs. [15]In another study by Dyrka*et al*. who specifically reviewed the literature on DAA-related endocrine effects concluded that, unlike interferon-based regimens, DAAs were well tolerated and rarely resulted in dysfunction of thyroid hormone regulation.[16]

This high prevalence of dysfunction in the regulation of thyroid hormone in local population may be explained possible by higher burden of HCV-associated thyroid autoimmunity in local population rather than effect of the DAA regimen itself. This is evidenced by comparable or even

higher rates of dysfunction being documented in antiviral-naive HCV populations before any drug exposure in previous literature. Nazary*et al*.assessed treatment-naive HCV-positive patients and reported that hypothyroidism prevalence was 10.6% among these treatment naïve HCV patients even.[17]Similarly, in an antiviral-naive HCV cohort comprising of Pakistani population, Zhong *et al*. reported an overall thyroid dysfunction prevalence of 41%, with hypothyroidism alone accounting for 29%, closely approximating post-DAA prevalence being reported in prevalence study, despite their patients never having received treatment.[18]

With regards to demographic characteristics, one important finding was higher proportion of HCV infected patients being males accounting for more than 70% of the affected individuals with a mean age of 41.29 ± 13.53 years. In comparison to this, Hyppolito*et al.* in a large Brazilian DAA treated HCV infected cohort reported that mean age of study population was 56.6 ± 11 years with a similar male predominance reporting males making up 60.2% of the cohort. [19]Similarly, Brzdek*et al*. analysed a nationwide Polish DAA registry and found that the treated population wasprimarily male-dominated. [20]The younger median age of present cohort likely reflects the demographic profile of HCV transmission in Pakistan, where unsafe therapeutic injections propagate infection across a broader, younger age spectrum rather than in high-income settings where transmission historically concentrated in older cohorts. Similarly, the male predominance likely reflects differences in referral patterns between hospital-based Hepatitis Control Program clinics, where male patients often present earlier due to occupational screening they have to go through owing to their role of being the bread winner in underdeveloped societies.

Upon association analysis, it was observed that there was no significant difference of DAA associated thyroid dysfunction prevalence among different age groups ($p = 0.239$), however, the prevalence of this DAA use related morbidity was significantly higher among females in comparison to males ($p = 0.018$). This female preponderance mirrors a well-established and consistent finding across previous literature. Battheu*et al.* reviewed the basis of sex-related differences in thyroid disease and concluded that the interplay of sex hormones, X-chromosome-linked genetic factors, foetal microchimerism and the gut microbiota collectively predisposes women to a substantially higher burden of thyroid disease than men.[21] In a similar vein, Faria*et*

al. reviewed sexual dimorphism across the hypothalamic-pituitary-thyroid axis and noted that women carry a consistently higher prevalence of thyroid disease than men.[22]

In summary, the present study demonstrates that thyroid dysfunction is a clinically significant finding among HCV patients undergoing DAA therapy, with hypothyroidism predominating and females bearing a disproportionately higher burden. The discordance with several international reports suggests that this association may be driven more by underlying HCV-related thyroid autoimmunity in the local population than by a direct thyrotoxic effect of DAAs themselves. These findings support incorporating routine thyroid function screening into the pre- and post-treatment workup of HCV patients receiving DAA therapy, with particular vigilance for female patients.

Certain limitations of this study should be acknowledged. The absence of a treatment-naïve control arm limited our ability to definitively attribute thyroid dysfunction to DAA exposure rather than HCV infection itself. Thyroid autoantibody status was not assessed, precluding differentiation between autoimmune and non-autoimmune mechanisms. The non-probability consecutive sampling technique and single ethnic population may limit generalizability of findings to other populations. Additionally, the three-month follow-up period may not have captured delayed-onset thyroid dysfunction, and long-term outcomes following treatment completion were not evaluated.

CONCLUSION:

In conclusion,prevalence of thyroid dysfunction among HCV patients given DAA treatment was 33.6% with 28.6% patients being hypothyroid and 5% patients being hyperthyroid.Thyroid dysfunction was significantly more frequent in female than male patients, while age alone did not significantly affectedprevalence in this cohort. These findings support routine thyroid function screening before and after DAA therapy, particularly for female patients.

ETHICAL APPROVAL:

Obtained from the ethical committee of hospital(Ref No:EC-002/01; dated: 10/08/2024)

PATIENTS' CONSENT:

Informed consent in writing was taken from all participants

COMPETING INTEREST:

None

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