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STUDY OF EFFECT OF DIRECTLY ACTING ANTIVIRALS ON THYROID PROFILE IN CHRONIC HEPATITIS C PATIENTS

General Medicine

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ABSTRACT

Background and Aim: Chronic hepatitis C virus (HCV) infection often leads to liver cirrhosis, hepatocellular cancer, liver failure, and death. The advent of direct-acting antiviral agents (DAAs) in the recent years has revolutionized HCV treatment. Chronic Kidney Disease (CKD) affects the hypothalamus-pituitary thyroid axis and the peripheral metabolism of thyroid hormone. The purpose of this study was to analyse the thyroid profile of hepatitis C patients on DAA's as not many studies have been conducted on the same. **Methods:** Ours was a hospital based follow up observational study. The study was conducted with a sample size of 52. The subjects were followed up for 12 weeks and thyroid function of these patients were estimated at the beginning of treatment and at the end of 12 weeks. **Results:** Of the 52 patients, 27(51.9%) patients had CKD. A comparison amongst the total studied patients before and after treatment regarding thyroid function revealed no statistical significance regarding serum free T4, and serum free T3 – Free T3 pretreatment (3.092 ± 0.3391), post treatment (3.136 ± 0.3519), Free T4 pretreatment (0.8813 ± 0.1571), post treatment (0.8902 ± 0.1613)]. Statistically significant difference was observed for S.TSH values pretreatment (3.674 ± 2.465) and post treatment (3.185 ± 1.95) with a p value of 0.043. **Conclusion:** At the end of the study, it was concluded that thyroid function in patients with hepatitis C infection was not affected with treatment with new DAAs. Hypothyroidism is prevalent in patients with CHC, and after treating with DAAs, thyroid dysfunction slightly improved, especially subclinical, after achievement of Sustained Virological Response (SVR). Also, the prevalence of subclinical hypothyroidism increases consistently in patients who have a decline in GFR.

KEYWORDS

HCV infection, Directly Acting Anti- viral (DAA's), Thyroid profile, chronic kidney disease (CKD)

INTRODUCTION

Hepatitis C virus has become one of the major global causes of death and morbidity. A recent study shows an increase over the last decade to 2.8%, corresponding to > 185 million infections worldwide. Persistent hepatitis C is a gradually progressive disease. Chronic HCV infection often leads to liver cirrhosis, hepatocellular cancer, liver failure, and death.[1]. For many years, the standard of care for the treatment of chronic hepatitis C had been a combination of pegylated interferon (Peg-IFN) and ribavirin for 48 weeks. However, this combination had many drawbacks [2]. It has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted to each specific step within the HCV life cycle.

The side ramifications of IFN remedy on the thyroid gland were reported for the very first time ~2 decades ago, and since that time, numerous studies have been done in this area. Chronic kidney disease affects thyroid function in multiple ways, including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid content and increased iodine stores in thyroid glands. When compared to the general population, the CKD patients receiving hemodialysis, the incidence of HCV is much higher, ranging from 3 to 50 %.

The effect of IFN therapy on thyroid profile is an established fact. But, the era of IFN for the treatment of hepatitis C is over as it is replaced by the highly promising Directly Acting Antivirals (DAA's).[3] The DAA's show very promising results in attaining SVR. Our study hypothesized that the DAA's had no adverse effect over the patient's thyroid profile. On the other hand, in CKD patients undergoing treatment with DAA's, an improvement in thyroid profile was noticed. As not many studies have been done in this field, our study is of significance in modifying or establishing the safety of DAA's in the treatment of hepatitis C.

AIMS AND OBJECTIVES

1. To study the effect of DAAs on thyroid profile in HCV positive patient.
2. Evaluation of thyroid function in HCV positive patients without chronic kidney disease.
3. Evaluation of thyroid function in HCV positive patients with chronic kidney disease.
4. Comparison of thyroid function between HCV positive patients with and without chronic kidney disease.

MATERIALS AND METHODS

This study was conducted at the Department of Internal Medicine, J.L.N. Medical College & Hospitals, Ajmer, after approval from the institutional ethical committee. After taking informed consent, study was performed with 52 patients from January 2020 to October 2021.

The study included patients attending Medical OPD/IPD, HCV clinic, Dialysis unit. The study population was also divided into two groups for detailed evaluation:
Group A (Patients also suffering from chronic kidney disease)
Group B (Patients without chronic kidney disease).

The matter of interest was thyroid function of these patients which we compared with the reference values. The subjects were followed up for 12 weeks and thyroid function of these patients were estimated at the beginning of treatment and at the end of 12 weeks. None of the patients were lost to follow up.

Inclusion criteria

1. HCV positive patients taking directly acting antiviral therapy without CKD.
2. HCV positive patients with chronic kidney disease taking directly acting antiviral therapy.

Exclusion criteria

1. Hepatitis C positive patients already on medication for thyroid dysfunction.
2. Patient who is already a known case of thyroid dysfunction.
3. Patients on drugs like amiodarone, iodine and iodinated drugs, lithium, heparin, anti-epileptic drugs etc.
4. HBsAg/HIV positive patients.

Statistical Analysis

The data obtained was analyzed using SPSS Software 20.0 All the information were recorded in a separate proforma for each subject. Paired t test was used for the comparison of data summarized as mean and standard deviation. Continuous data was represented as mean ± standard deviation.

Categorical data was expressed as numbers in percentage. Statistical significance was set at P less than 0.05. Data was presented in the form of tables, figures, graphs, diagrams wherever necessary.

RESULTS

In our study, we included a total of 52 patients who fulfilled the eligibility criteria, The mean age of the group was 45.34 ± 11.95 years. Majority of the patients were male i.e., 38(73.1%). 14 (26.9%) were females.

Of the 52 patients, 27(51.9%) patients had CKD. The main outcomes of the study are summarised in tables 1,2 ,3 and 4

Table 1. shows laboratory data among the studied hepatitis C virus positive patients before and after receiving new direct-acting antiviral agents.

VARIABLE	PRE-TREATMENT	POST TREATMENT	PAIRED t TEST	p VALUE
FREE T3	3.092 ± 0.3391	3.136 ± 0.3519	0.72	0.475
FREE T4	0.8813 ± 0.1571	0.8902 ± 0.1613	0.29	0.767
TSH	3.674 ± 2.465	3.185 ± 1.95	2.08	0.043
AST	56.6 ± 27.18	43.98 ± 12.28	4.292	0.0001
ALT	68.75 ± 45.31	46 ± 14.19	4.016	0.0002
UREA	124.1 ± 83.05	123.5 ± 81.57	1.531	0.1320
CREATININE	4.148 ± 3.259	4.129 ± 3.201	2.594	0.0123

We then divided the entire study population into two:
The first group were those patients who also suffered from chronic kidney disease (Group A) and The next group consisted of patients without CKD (group B)

Table. 2 Laboratory data among hepatitis C virus positive patients with CKD (Group A)

VARIABLE	PRE-TREATMENT	POST TREATMENT	PAIRED t TEST	p VALUE
FREE T3	3.0815± 0.0656	3.1396± 0.0748	-0.609	0.548
FREE T4	0.8944± 0.1725	0.8741± 0.1761	0.444	0.660
TSH	3.7956± 2.6498	3.6081± 2.1130	0.532	0.599
AST	51.07± 28.731	43.93± 13.182	1.814	0.081
ALT	70.15± 53.395	46.74 ± 16.999	2.495	0.019
UREA	201.8 ± 21.96	199.9± 21.02	1.771	0.0882
CREATININE	7.167± 1.065	7.093± 1.052	1.768	0.0887

Table. 3 Laboratory data among hepatitis C virus positive patients with no CKD (Group B)

VARIABLE	PRE-TREATMENT	POST TREATMENT	PAIRED t TEST	p VALUE
FREE T3	3.1024± 0.3438	3.1328± 0.3152	-0.377	0.709
FREE T4	0.8672± 0.1405	0.9076± 0.1450	-1.074	0.293
TSH	3.5432± 2.2968	2.7276± 1.67945	2.704	0.012
AST	62.56± 24.592	44.04± 11.487	4.462	0.0001
ALT	67.24± 35.642	45.20± 10.669	3.539	0.002
UREA	40.16± 2.528	40.96± 2.282	-1.540	0.1367
CREATININE	0.8880± 0.1453	0.9280± 0.1339	-1.633	0.1155

Table 4: Distribution based on comparison of pre and post treatment thyroid profile.

	PRE-TREATMENT	POST TREATMENT		
	FREQUENCY	PERCENT	FREQUENCY	PERCENT
EUTHYROID	41	78.84%	46	88.4 %
SUBCLINICAL HYPOTHYROIDISM	11	21.15%	6	11.53 %
TOTAL	52	100 %	52	100 %

At the end of the study,46(88.4%) was euthyroid and 6(11.53%) patients were having sub clinical hypothyroidism. i.e., 5 (9.6%) patients became euthyroid from their initial sub clinical hypothyroidism state.

The mean TSH of the group pretreatment was 3.67 ± 2.46 and post treatment was 3.14 ± 1.941.

DISCUSSION

Our results portrayed thyroid dysfunction in 21.15% of the HCV-infected patients (subclinical hypothyroidism in 11 patients.). Rest were Euthyroid. Study by Batool et al. [4] showed that serum TSH level in 84.7% cases were normal ,9.0%had hypothyroidism, and 6.3% had hyperthyroidism. A subgroup analysis for thyroid disorders in HCV cases revealed that 4.7% had subclinical hypothyroidism, 4.3% had overt hypothyroidism,3.6% had overt hyperthyroidism, and 2.7% had subclinical hyperthyroidism.[7]

In our study 26% patients with HCV infection with CKD had thyroid disorder (subclinical hypothyroidism) at the beginning of the study. By the end of the treatment 2/7(28.5%) patients with subclinical hypothyroidism became euthyroid.

Recently, Quion-verde et al have also reported higher prevalence of up to 5% of frank hypothyroidism in patients with chronic renal failure, in comparison with hospitalized patients with normal renal function (0.6%). [5]

In our analysis, aspartate aminotransferase and alanine amino transferase were significantly improved by the end of treatment. This is in line with the findings of Elsharkawy et al. [6], as they noted decline in alanine aminotransferase and aspartate aminotransferase values after treatment, which may indicate the significant role of DAAs in improving hepatic inflammatory changes induced by viral infection.

Comparing the pre and post treatment lab parameters only serum ALT showed a statistically significant difference in this group.[8] In contrast, patients without CKD showed a significant improvement in the values of TSH, AST and ALT. On studying both the groups together (Group A + B) serum levels of TSH, AST, ALT and Creatinine were noticed to have statistically significant difference.[9] This could be attributed to the fact that both HCV and CKD cause impairment in thyroid functions.

Limitations Of The Study

- Small sample size
- Single center design
- Prevalence of hypothyroidism increases as the age advances. So, we have to consider the influence of age on hypothyroidism.
- Patients in various stages of CKD were not enrolled.

CONCLUSION

Thyroid function in patients with persistent hepatitis C infections was not affected with treatment with new DAAs for treatment of HCV. Hypothyroidism is prevalent in patients with CHC, and after treating with DAAs, thyroid dysfunction improved slightly, especially subclinical, after achievement of SVR. Also, the prevalence of subclinical hypothyroidism increases consistently in patients who have a decline in GFR. Therefore, more multicentric studies with a larger sample size needs to be conducted to fully understand the interplay between HCV and CKD in causing thyroid disorders.

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