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Prevalence of Hypothyroidism in Non-Alcoholic Fatty Liver Disease (NAFLD) Patients

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ABSTRACT

Non-alcoholic fatty liver disease is a leading cause of chronic liver disease and has a high prevalence globally. The principal causes range from obesity, hypertriglyceridemia, diabetes mellitus and other endocrinopathies to drugs and certain metabolic disorders. Hypothyroidism associated with non-alcoholic fatty liver disease has raised concerns over recent years but there is limited substantive data to support this evidence. **Objective:** To ascertain the existing prevalence of hypothyroidism in non-alcoholic fatty liver disease patients presenting to a tertiary care hospital. **Methods:** It was a descriptive cross-sectional study that was executed in the Medical Department of King Edward Medical University, Mayo Hospital, Lahore from 30th July 2022 to 29th July 2023. A total of 215 patients with diagnosed non-alcoholic fatty liver disease on ultrasound were enrolled after taking informed consent and their Thyroid profile i.e., measurement of serum thyroid stimulating hormone, free tri-iodothyronine and free thyroxine was done. **Results:** From a total of 215 patients, 7 (3.3 %) belonged to the age bracket of 20-40 years and 208 (96.7 %) in the age range of 41-60 years with a female preponderance of 118 (54.9%) and male 97 (45.1%). Mean age was reported to be 50.79 ± 3.95 years and BMI was 23.09 ± 3.93 kg/m2.The overall prevalence of hypothyroidism was reported in 42 (19.5%) patients. **Conclusions:** It was concluded that there is a high prevalence (19.5%) of hypothyroidism in patients with non-alcoholic fatty liver disease.

INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) known as Metabolic dysfunction-associated steatosis Liver Disease (MASLD) is one of the major determinants of chronic liver disease and has an approximate global prevalence of about 32% that varies substantially geographically [1]. The rise is attributed to varying degrees of obesity, Type 2 Diabetes mellitus (T2DM), and other metabolic, genetic, environmental and socio-economic factors. NAFLD entails a diverse clinical range spanning from asymptomatic disease to a relatively benign nonalcoholic fatty liver (NAFL), plain steatosis to steatosis with varied levels of inflammation and fibrosis [2...]. An estimated 20% of simple steatosis progresses to non-alcoholic steatohepatitis (NASH) which further progresses to cirrhosis and is labelled as an accelerating determinant of hepatocellular carcinoma worldwide [3, 4]. The triggering factors that contribute to the advancement from simple steatosis to NASH are manifold but are mainly attributed to the liver-related complications of metabolic syndrome, mainly hyperinsulinemia [5]. NAFLD is usually an incidental finding on imaging such as ultrasound or CT scan. Liver biopsy remains the definitive benchmark for diagnosis of NAFLD and NASH [6]. Hypothyroidism, marked by a decreased level of thyroid hormone (free T4) in the blood, is believed to have an association with NAFLD [7]. It is strongly related to metabolic syndrome which comprises three main components insulin resistance, dyslipidemia and obesity [8, 9]. The impact of thyroid hormones on hepatic physiology and fat metabolism is a complex phenomenon that involves cross-level cellular and molecular interactions [10]. Increased circulating levels of thyroid stimulating hormone (TSH) lead to decreased lipoprotein lipase activity further enhancing the accumulation of triglycerides within the liver and higher

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levels of proinflammatory adipokines are also contributors to hepatic inflammation and fibrosis [11]. Growing evidence suggests a plausible relationship between hypothyroidism and NAFLD. Various epidemiological studies conducted globally have proved a positive association between the two conditions [12]. Limited local data involving a smaller sample size also approves of this association [13]. Owing to the scarcity of local data showing a relationship between low levels of thyroid hormones and NAFLD.

This study aims to ascertain the magnitude of this problem in our population to guide policymakers about this escalating peril.

METHODS

This descriptive cross-sectional study was carried out in the Medical Department of King Edward Medical University, Mayo Hospital, Lahore from 30th July 2022 to 29th July 2023. A sample size of 215 patients was calculated employing Epi – the info software of Centers for Disease Control (CDC), using 16.8 % frequency of hypothyroidism [14], 5 % margin of error and 95% confidence level. Patients of both genders, in the age range of 18 - 60 years with ultrasound-proven NAFLD and having any of the symptoms like weight gain, constipation, muscle weakness or pain, joint pains, pale, dry skin, unusual tiredness etc. were selected via non-probability consecutive sampling technique. Patients with a prior history of hepatitis B virus (HBV), hepatitis C virus (HCV), liver cirrhosis, thyroid surgery, cerebrovascular accidents of both ischemic and hemorrhagic nature, ischemic heart disease, congestive cardiac failure and active alcohol consumption of 30grams/day for men and 20grams/day for women were not taken into consideration. After getting acceptance from the College of Physicians and Surgeons Pakistan (CPSP) Research Evaluation Unit (REU), reference number CPSP/REU/MED-2020-066-16666, and ethical approval from the Institutional Review Board (IRB) of King Edward Medical University, Reference No 585/RC/KEMU, all patients conforming to the selection criteria were enrolled after taking informed written and verbal consent. Following registration, a complete medical history was taken and a clinical examination was done. 3ml of venous blood was collected and the sample was submitted to the hospital's main laboratory for estimation of serum TSH and free T4 levels. The reported results were recorded in a specially designed proforma. On completion of the desired sample size, the collected data was submitted and evaluated by computer software SPSS Version 25.0. Age, serum TSH, FT4 and BMI of the patients were calculated as mean and standard deviation (Mean ± SD). Nominal data like gender, hypothyroidism, hypertension, diabetes, obesity, smoking and geographical area were presented in the form of frequencies and percentages. Stratification using the Chi-square test was employed for demographic as well as clinical variables and a p-value less than or equal to 0.05 ($p \leq 0.05$) was taken as statistically significant.

RESULTS

Out of a total of 215 patients, a female preponderance was noted i.e., 118 (54.9%) compared to 97 (45.1%) male with a mean age of 50.79 ± 3.95 years, out of which 7 (3.3%) had age range of 18-40 years and 208 (96.7%) were in the 41-60 years' age group. BMI was calculated to be 23.09 ± 3.93 kg/m2. Mean TSH was calculated to be 4.1 ± 2.3 mU/L and mean Free T4 levels were reported to be 5.7 ± 2.9 µg/dl (Table 1).

Table 1: Distribution of Demographic and Clinical Variables

Variables		Frequency (%)	Mean ± SD
Demographic Variables			
Age (Years)	18-40	7 (3.3%)	50.79 ± 3.95
	40-60	208 (96.7%)	
Gender	Male	97 (45.1%)	-
	Female	118 (54.9%)	
Geographical Location	Rural	85 (39.5%)	-
	Urban	130 (60.5%)	
Clinical profile			
BMI (kg/m^2)		0 (0%)	23.09 ± 3.93
TSH (mU/L)		0 (0%)	4.1 ± 2.3
Free T4 (µg/dl)		0 (0%)	5.7 ± 2.9
Diabetes		57 (26.5%)	-
Hyperlipidemia		39 (18.1%)	-
Hypertension		74 (34.4%)	-
Smoking		39 (18.1%)	-
Obesity		49 (22.8%)	-
Hypothyroidism		42 (19.5%)	-

Out of the total enrolled patients, 42(19.5%) had hypothyroidism (Figure 1).

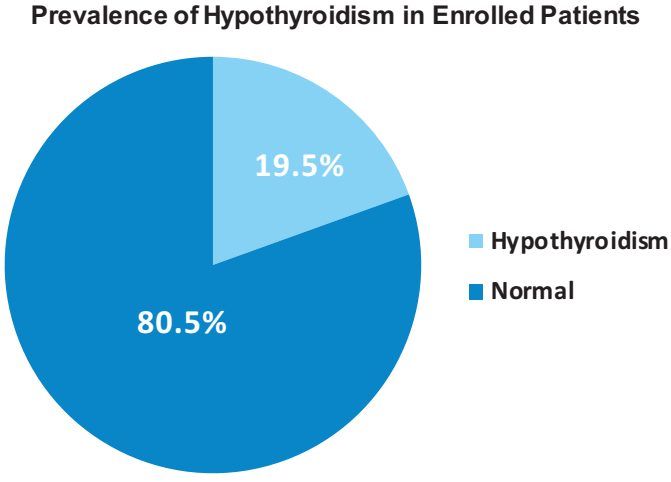

Figure 1: Prevalence of Hypothyroidism in Enrolled Patients

Prevalence of hypothyroidism comprised mostly male i.e., 23 (10.7%) and in the 40-60-year age range i.e., 39 (18.1%). A

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very significant proportion of the patients were found to be hypertensive i.e., 74 (34.4%) of which 29 (13.5%) had hypothyroidism (p<0.000) whereas 13 (6.1%) normotensive patients also had hypothyroidism. This was followed by diabetics who comprised 57(26.5%) of patients whereas 39 (18.1%) patients had hyperlipidemia. Smoking and obesity were also the major determinants of hypothyroidism in the sampled population i.e., 39 (18.1%) were smokers and 49 (22.8%) were obese. Based on geographical distribution, 85 (39.5%) patients belonged to rural areas whereas 130 (60.5%) were residents of urban areas (Table 2).

Table 2: Stratification of Hypothyroidism in NAFLD Patients concerning Demographic Variables Using Chi-Square Test (n=215)

Variables		Hypothyroidism		Total	p-Value
		Yes	No		
Age (Years)	18-40	3 (42.8%)	4 (57.2%)	7	0.35
	40-60	39 (20.2%)	169 (79.8%)	208	
Gender	Male	23 (23.7%)	74 (76.3%)	97	0.17
	40-60	19 (16.1%)	99 (83.9%)	118	
Geographical location	Rural	15 (17.6%)	70 (82.4%)	85	0.603
	Urban	27 (20.8%)	103 (79.2%)	130	
Total		42 (19.5%)	173 (80.5%)	215	-

Stratification of hypothyroidism in NAFLD patients concerning the clinical variables was analyzed (Table 3).

Table 3: Stratification of Hypothyroidism in NAFLD Patients Concerning comorbidities Using Chi-Square Test (n=215)

Variables		Hypothyroidism		Total	p-Value
		Yes	No		
Diabetes	Yes	10 (17.5%)	47 (82.5%)	57	0.846
	No	32 (20.3%)	126 (79.7%)	158	
Hyperlipidemia	Yes	9 (23.1%)	30 (76.9%)	39	0.511
	No	33 (18.8%)	143 (81.2%)	176	
Hypertension	Yes	29 (39.2%)	45 (60.8%)	74	0.000
	No	13(9.2%)	128 (90.8%)	141	
Smoking	Yes	8 (20.5%)	31 (79.5%)	39	0.509
	No	34 (19.3%)	142 (80.7%)	176	
Obesity	Yes	9 (18.4%)	40 (81.6%)	49	1.000
	No	33 (19.9%)	133 (80.1%)	166	
Total		42 (19.5%)	173 (80.5%)	215	-

DISCUSSION

NAFLD, one of the chief contributors of chronic liver disease and a precursor to cirrhosis, has a varied clinical spectrum with progression to hepatocellular carcinoma in certain cases [3, 4]. Mainly attributed to a sedentary lifestyle, genetics, obesity, insulin resistance, hypertension, dyslipidemias, endocrinopathies like type 2 diabetes mellitus, hypothyroidism, hypopituitarism etc., the list is long. The etiopathogenesis involves a complex interplay of genetic, molecular and cellular mechanisms that mostly revolve around lipid metabolism and insulin resistance [10]. Le and colleagues ascertained a 35.3% prevalence of NAFLD in North America whereas a prevalence of 47.8% was found in a meta-analysis conducted by Riazi et al., involving 15,178 patients [15, 1]. Among North American patients, NAFLD was prevalent in 63.7% of Hispanics, 56.8% of non-Hispanic whites and 46.2% of non-Hispanic blacks [16]. In Asia, the highest number of pre-existing cases of NAFLD reported to be 42% were found in Southeast Asia, with the greatest combined prevalence determined in Iran (38.07%) and the lowest in Japan (22.28%) [17, 1]. In 2022, a study was carried out by Fan et al., who reported lower FT4 levels in NAFLD patients compared to controls (8.93 µg/dl versus 8.76 µg/dl). Mean TSH levels were also found to be higher in patients having NAFLD i.e., 1.97mIU/L versus 2.52 mIU/L in the healthy individuals [18]. The result showed that in 47,217 patients of NAFLD/NASH from 11 studies, there were statistically significant higher levels of TSH compared to healthy controls. Another meta-analysis conducted in 2021 on 14,514 participants from 17 different studies labelled elevated TSH to be an isolated risk determinant for NAFLD, with free T4 being significantly associated and no association of free T3 [19]. In our cohort, the prevalence of hypothyroidism was found in 42 (19.5%) patients, although a female preponderance of 54.9% was observed in our study population only 8.8% were found to be hypothyroid whereas 10.7% of male had hypothyroidism and more in the 40 –60 years' age group. Our findings were somewhat by Vidal-Cevallos et al., who demonstrated that male were more likely to have NAFLD (72.8%) compared to female (50.8%). Their cohort also included more patients in the 41-50 years' age group (80.7%). A prevalence of 22.4% of hypothyroidism in NAFLD patients was observed by Vidal-Cevallos et al., which was congruent with our results [20]. The results of our study greatly differed from Memon et al., who calculated the prevalence of sub-clinical hypothyroidism to be 34.62% and overt hypothyroidism to be 6.92% out of a total of 130 patients with 83 (63.8%) of the patients having NAFLD and NASH [13]. This wide variation in results may be attributed to different geographical locations and ethnicity. Our cohort mainly belonged to Lahore, an urban area whereas Memon conducted his study on the rural population of Tandu Muhammad Khan, a division of Hyderabad in Sindh province. In our study, 96.7% of the patients had an age range of 41-60 years of which 18.1% had hypothyroidism whereas only 1.4% of NAFLD patients in the 18-40 years' age group had hypothyroidism. Obesity, characterized by a BMI of ≥25kg/m2 for Asians and ≥30kg/m2 for the remaining parts of the world, also serves as a strong predictor of NAFLD, implying a poorer prognosis. In our study, 49 (22.8%) patients were obese and the mean BMI of the entire cohort was found to be 23.09 ± 3.93 kg/m2. The correlation between high BMI in hypothyroid patients and NAFLD was also observed by Zeng who calculated a mean difference of 3.39 and a p-value of <0.000001 [19]. There were certain limitations of our study. The study was conducted on a relatively small cohort, belonging to a certain geographical area and with low socio-economic status with limited access to healthcare facilities. The cohort also included fewer

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patients in the 18-40 years' age group. So we recommend large, multi-centred studies from all provinces of Pakistan, of different ethnicities and geographical areas, with extended age groups and all socio-economic classes. The pooled data will give a better overview of the prevalence of hypothyroidism in NAFLD patients in our population. Since a significant prevalence is reported in our study, we need to take measures to ensure and stress the significance of a well-balanced diet and active lifestyle achieved through consistent physical activity to be introduced in all government and public sector educational institutions and workplaces. Timely intervention by educating the masses about the hazards associated with this disease will not only curb the rising incidence of NAFLD and NASH but will also help prevent cirrhosis which will lessen the healthcare burden on the government.

CONCLUSIONS

It was concluded that the prevalence of hypothyroidism in our study population was higher in male, in the older age group, having a higher BMI >23kg/m2 and inhabitants of urban areas. The frequencies of observed variables like smoking, hypertension, diabetes and obesity were also high but post-stratification results yielded significance only for hypertension ($p<0.0000$).

Authors Contribution

Conceptualization: MKH
Methodology: MKH, BA, TF
Formal analysis: TN, AR
Writing review and editing: TN, BA, FS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

[1] Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE *et al*. The Prevalence and Incidence of NAFLD Worldwide: A Systematic Review and Meta-Analysis.The Lancet Gastroenterology and Hepatology.2022 Sep; 7(9):851-61.doi:10.1016/S2468-1253(22)00165-0.

[2] Cai J, Zhang XJ, Li H. Progress and Challenges in the Prevention and Control of Nonalcoholic Fatty Liver Disease. Medicinal Research Reviews.2019 Jan; 39(1): 328-48. doi: 10.1002/med.21515.

[3] Tan DJ, Setiawan VW, Ng CH, Lim WH, Muthiah MD, Tan EX *et al*. Global Burden of Liver Cancer in Males and Females: Changing Etiological Basis and the Growing Contribution of NASH. Hepatology.2023 Apr; 77(4): 1150-63. doi: 10.1002/hep.32758.

[4] Huang DQ, Singal AG, Kono Y, Tan DJ, El-Serag HB, Loomba R. Changing Global Epidemiology of Liver Cancer from 2010 To 2019: NASH Is the Fastest Growing Cause of Liver Cancer. Cell Metabolism. 2022 Jul; 34(7): 969-77. doi: 10.1016/j.cmet.2022.05.003.

[5] Younossi ZM, Golabi P, Price JK, Owrangi S, Gundu-Rao N, Satchi R *et al*. The Global Epidemiology of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis among Patients with Type 2 Diabetes. Clinical Gastroenterology and Hepatology. 2024 Mar; 22(10): 1999-2010. doi: 10.1016/j.cgh.2024.03.006.

[6] Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W *et al*. Non-Alcoholic Fatty Liver Disease (NAFLD): A Review of Pathophysiology, Clinical Management and Effects of Weight Loss. BioMed Central Endocrine Disorders.2022 Mar; 22(1): 63. doi:10.1186/s12902-022-00980-1.

[7] Kizivat T, Maric I, Mudri D, Curcic IB, Primorac D, Smolic M. Hypothyroidism and Nonalcoholic Fatty Liver Disease: Pathophysiological Associations and Therapeutic Implications. Journal of Clinical and Translational Hepatology. 2020 Sep; 8(3): 347. 10.14218/JCTH.2020.00027.

[8] Gariani K, Jornayvaz FR. Pathophysiology of NASH in Endocrine Diseases. Endocrine Connections.2021 Feb; 10(2): R52-65. doi: 10.1530/EC-20-0490.

[9] Tanase DM, Gosav EM, Neculae E, Costea CF, Ciocoiu M, Hurjui LL *et al*. Hypothyroidism-Induced Nonalcoholic Fatty Liver Disease (HIN): Mechanisms and Emerging Therapeutic Options. International Journal of Molecular Sciences.2020 Aug; 21(16): 5927. doi: 10.3390/ijms21165927.

[10] Mavromati M and Jornayvaz FR. Hypothyroidism-Associated Dyslipidemia: Potential Molecular Mechanisms Leading to NAFLD. International Journal of Molecular Sciences. 2021 Nov; 22(23): 12797. doi: 10.3390/ijms222312797.

[11] Gor R, Siddiqui NA, Fernando RW, Nair AS, Illango J, Malik M *et al*. Unraveling the Role of Hypothyroidism in Non-Alcoholic Fatty Liver Disease Pathogenesis: Correlations, Conflicts, and the Current Stand. Cureus. 2021 May; 13(5). doi: 10.7759/cureus.14858.

[12] Qiu S, Cao P, Guo Y, Lu H, Hu Y. Exploring the Causality Between Hypothyroidism and Non-Alcoholic Fatty Liver: A Mendelian Randomization Study. Frontiers in Cell and Developmental Biology. 2021 Mar; 9: 643582. doi: 10.3389/fcell.2021.643582.

[13] Memon MA, Suthar RK, Bai K. Association of Nonalcoholic Fatty Liver Disease with Thyroid Functions. The Professional Medical Journal.2022 Apr; 29(05): 595-600. doi: 10.29309/TPMJ/2022.29.05.6044.

DOI: https://doi.org/10.54393/pjhs.v5i10.2145

[14] Parikh P, Phadke A, Sawant P. Prevalence of Hypothyroidism in Nonalcoholic Fatty Liver Disease in Patients Attending a Tertiary Hospital in Western India. Indian Journal of Gastroenterology. 2015 Mar; 34: 169-73. doi: 10.1007/s12664-015-0541-z.

[15] Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y *et al.* 2019 Global NAFLD Prevalence: A Systematic Review and Meta-Analysis. Clinical Gastroenterology and Hepatology. 2022 Dec; 20(12): 2809-17. doi: 10.1016/j.cgh.2021.12.002.

[16] Zhang X, Heredia NI, Balakrishnan M, Thrift AP. Prevalence and Factors Associated with NAFLD Detected by Vibration Controlled Transient Electrography among US Adults: Results from NHANES 2017–2018. PloS One. 2021 Jun; 16(6): e0252164. doi: 10.1371/journal.pone.0252164.

[17] Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH *et al.* Prevalence, Incidence, and Outcome of Non-Alcoholic Fatty Liver Disease in Asia, 1999–2019: A Systematic Review and Meta-Analysis.The Lancet Gastroenterology and Hepatology.2019May;4(5): 389-98. doi: 10.1016/S2468-1253(19)30039-1.

[18] Fan H, Liu Z, Zhang X, Wu S, Shi T, Zhang P *et al.* Thyroid Stimulating Hormone Levels Are Associated with Genetically Predicted Nonalcoholic Fatty Liver Disease. The Journal of Clinical Endocrinology and Metabolism.2022 Sep; 107(9): 2522-9. doi: 10.1210/clinem/dgac393.

[19] Zeng X, Li B, Zou Y. The Relationship Between Non-Alcoholic Fatty Liver Disease and Hypothyroidism: A Systematic Review and Meta-Analysis. Medicine. 2021 Apr; 100(17): e25738. doi: 10.1097/MD.0000000000025738.

[20] Vidal-Cevallos P, Murúa-Beltrán Gall S, Uribe M, Chávez-Tapia NC. Understanding the Relationship Between Nonalcoholic Fatty Liver Disease and Thyroid Disease. International Journal of Molecular Sciences.2023 Sep; 24(19): 14605. doi: 10.3390/ljms241914605.