ORIGINAL ARTICLE

# Frequencies of Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome in Lean Individuals

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## Abstract

**Background:** Non-Alcoholic Fatty Liver Disease (NAFLD) prevalence has doubled in the last 20 years and is becoming a vital health concern due to its increasing prevalence. Lean patients having normal-weight central obesity with NAFLD may have increased morbidity and all-cause mortality and thus form an important target for lifestyle modifications and preventive strategies.

**Objective:** To determine frequencies of NAFLD and Metabolic Syndrome in lean individuals.

**Methods:** The present cross-sectional study was undertaken at the Medicine Department, Pakistan Ordinance Factories Hospital, Wah Cantonment Pakistan from July 2018 to June 2020 enrolling 230 patients aged 20 to 70 years, of both sex. Demographic information, co-morbid conditions, BMI, and waist circumference were recorded. An abdominal ultrasound was performed to determine hepatic fatty infiltration. Blood samples were collected for serum HDL-cholesterol (HDL-C) and serum triglyceride estimation. SPSS 22.0 was used for data entry and analysis.

**Results:** Mean age was 45.7+12.5 years with male predominance at 130 (56.5%). Diabetes mellitus was present in 104 (45.2%) and 102 (44.3%) were hypertensive. The mean BMI was 23.4+3.6 kg/m2. The mean serum triglyceride level was 209+10.1 mg/dl and elevated at 141 (61.3%). The mean serum HDL-C level was 23.1+4.2 mg/dl and was reduced by 142 (61.8%). NAFLD was seen in 38 (16.5%) patients and 24 (10.4%) had Metabolic Syndrome. Among the 38 lean NAFLD patients, 21 (55.3%) had Metabolic Syndrome.

**Conclusion:** NAFLD was seen in almost one-fifth of lean patients enrolled. Metabolic syndrome was reported in more than one-half of these lean NAFLD patients.

**Keywords:** *Metabolic syndrome, Non-Alcoholic Fatty Liver Disease (NAFLD), lean patients, hepatic malignancy, liver cirrhosis.*

## INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) prevalence has doubled in the last 20 years and is becoming a vital health concern due to its increasing prevalence [1]. Being the hepatic component of Metabolic Syndrome, NAFLD is important because the benign fatty liver can lead to steatohepatitis, liver cirrhosis, and hepatic malignancy [2]. NAFLD patients also have an increased risk for Diabetes Mellitus development [3] NAFLD is also associated with increased risk for cardiovascular and renal diseases, colorectal malignancy, atrial fibrillation, and thyroid dysfunction [4]. Obesity is associated strongly with various metabolic disorders including NAFLD [5]. However, NAFLD should not be neglected in normal-weight or lean patients with deranged hepatic enzymes [6]. Body Mass Index (BMI) measures lean and fat mass while Waist-Hip Ratio measures visceral fat accumulation which has a more potent association with adverse metabolic profile and mortality risk as compared to BMI [7]. Ha *et al.* [8] reported visceral adiposity in non-obese patients elevated the risk of NAFLD more than subcutaneous fat and BMI in the Asian population. It is therefore important to recognize fatty liver disease in the lean population.

It has been postulated that this lean phenotype has a worse metabolic and liver profile as compared to obesity-related fatty liver disease. Sahakyan *et al.* [7] demonstrated the risk for cardiovascular and all-cause mortality to be high in normal BMI patients having central obesity. In China, Feng *et al.* [9] showed NAFLD to be present in 18.3% of lean individuals having BMI <24 kg/m2 and 14.5% of these had Metabolic Syndrome. Furthermore, lean NAFLD had a strong association with diabetes mellitus, hypertension, and metabolic syndrome as compared to overweight and obese NAFLD indicating an elevated risk for metabolic disturbances, cardiovascular morbidity, and mortality [9]. Feldman *et al.* [10] showed NAFLD in up to 8% of lean patients and these patients were more likely to have impaired glucose tolerance and reduced adiponectin concentrations. Patients having normal-weight central obesity with NAFLD may have increased morbidity and all-cause mortality and thus form an important target for lifestyle modifications and preventive strategies.

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*Received: February 21, 2023; Revised: May 15, 2023; Accepted: May 23, 2023*
*DOI: https://doi.org/10.37184/lnjpc.2707-3521.5.42*

  ISSN: 2708-9134 (Online) Liaquat National Journal of Primary Care 2024; 6(1): 8-13

The objective of the present study was to find out the frequency of NAFLD in lean patients and its link with metabolic syndrome. Continued alcohol consumption can lead to serious disease, alcoholic hepatitis, or liver cirrhosis. In Denmark, increased mortality and increased cancer risk were seen in alcoholic fatty liver patients [11]. In NAFLD, steatohepatitis can progress to liver cirrhosis and its complications including variceal bleeding, ascites, and hepatic encephalopathy. The rate of progression is worse when more than one liver disease is present. Furthermore, diabetes mellitus and hypertriglyceridemia are also linked to fibrosis [12]. The risk of hepatic malignancy in NAFLD appears to be the same as with other forms of liver cirrhosis. However, NAFLD appears to elevate hepatic malignancy risk in non-cirrhotic patients. NAFLD also has a strong and independent association with pre-diabetes.

## METHODS

The present descriptive cross-sectional study was conducted at Medicine Department, Pakistan Ordinance Factories Hospital, Wah Cantonment Pakistan from July 2018 to June 2020 to determine the frequencies of Non-Alcoholic Fatty Liver Disease (NAFLD) and Metabolic Syndrome in lean individuals. Keeping a margin of error of 5% and 95% confidence interval, a sample size of 230 was required using expected frequencies of 18.3% of NAFLD and 14.5% of Metabolic Syndrome [9]. Patients with identifiable causes of the fatty liver such as significant alcohol consumption, use of steatogenic medication (estrogens, tamoxifen, or corticosteroids), hepatic malignancy, and pregnancy as assessed by history and examination were excluded from the study. Patient enrollment was done by the Outpatient Department of Medicine Department after taking approval from the Institutional Review Board of Pakistan Ordinance Factories Hospital, Wah Cantonment Pakistan. After taking informed consent and by using a non-probability consecutive sampling technique, 230 lean participants aged 20 to 70 years of both sex were enrolled.

Lean was labeled as a patient having BMI less than 23 kg/m2 using the cutoff for the Asian population [13]. Non-alcoholic Fatty Liver Disease (NAFLD) was labeled as hepatic steatosis on imaging having no cause for secondary hepatic fat accumulation. Metabolic syndrome was diagnosed according to the AHA criteria [14] as shown in Table **1**. After taking detailed history and examination, demographic information and the presence of co-morbid conditions (diabetes mellitus, hypertension) were recorded. Current weight in kilograms and height in meters was assessed and BMI was recorded as kg/m2 for each participant. Waist circumference (in inches) was assessed at the umbilical level. An abdominal ultrasound was conducted to determine hepatic fatty infiltration by a 3.5MHz probe by a Consultant Ultrasonographist. All patients were assessed for liver size, echogenicity, structure contour, and posterior beam attenuation. Blood samples after 10-hour fasting were collected for serum HDL-cholesterol (HDL-C) and serum triglyceride estimation.

**Table 1:** AHA Diagnostic criteria for metabolic syndrome [14].

| AHA Diagnostic Criteria for Metabolic Syndrome | |
|---|---|
| **Diagnosis of metabolic syndrome if three or more of the following are present:** | |
| 1. | A waistline of 40 inches or more for men and 35 inches or more for women |
| 2. | (measured across the belly) |
| 3. | A blood pressure of 130/85 mmHg or higher or are taking blood pressure medications |
| 4. | A triglyceride level above 150 mg/dl |
| 5. | A fasting blood glucose level greater than 100 mg/dl or are taking glucose-lowering medications |
| 6. | An HDL-cholesterol level less than 40 mg/dl (men) or under 50 mg/dl (women) |

SPSS version 22.0 was used for data entry and analysis. Mean and standard deviation was generated for quantitative variables. Frequency and percentage were used for qualitative variables. To control effect modifiers and confounders stratification was done. Post-stratification Chi-Square test was applied keeping p-value <0.05 as significant.

## RESULTS

The mean age of the patients was 45.7+12.5 years with 130 (56.5%) males and 100 (43.5%) females. One-hundred and thirty-two (57.4%) patients were aged 45 years or younger while 98 (42.6%) were aged 46 years or older. Diabetes mellitus was present in 104 (45.2%) patients and hypertension in 102 (44.3%) patients. The mean BMI was 23.4+3.6 kg/m2 and the mean waist circumference was 35.9+6.3 inches (91.1+16.0 cm) and 31.2+7.2 inches (79.2+18.2 cm) for males and females respectively. The mean serum triglyceride level was 209+10.1 mg/dl and was raised in 141 (61.3%) patients. The mean serum HDL-C level was 23.1+4.2 mg/dl and was reduced in 142 (61.8%) patients. Non-alcoholic Fatty Liver Disease (NAFLD) was seen in 38 (16.5%) patients and 24 (10.4%) patients had metabolic syndrome. Among the 38 lean patients with NAFLD, 21 (55.3%) patients had metabolic syndrome.

On data stratification, Non-alcoholic Fatty Liver Disease (NAFLD) in lean individuals demonstrated a significant association with Serum HDL-C level (p=0.015) but there was no association with age (p=0.097), sex (p=0.123), diabetes mellitus (p=0.089), hypertension (p=0.165) and serum triglycerides level (p=0.432) as shown in Table **2**. On data stratification, Metabolic Syndrome in lean individuals had a significant association with Serum HDL-C level (p=0.023) and lean NAFLD (p=0.013); however, no association was seen with age (p=0.897), sex (p=0.463), diabetes mellitus (p=0.089), hypertension (p=0.465) and serum triglycerides level (p=0.302) as shown in Table **3**.

**Table 2:** Comparison of demographic variables and Non-Alcoholic Fatty Liver Disease (NAFLD).

| Demographic Variables | Non-Alcoholic Fatty Liver Disease | | p-value |
|---|---|---|---|
| | Present n(%) | Absent n(%) | |
| **Age:** | | | |
| 20-45 years | 21 (15.9) | 111 (84.1) | 0.097 |
| 46-70 years | 17 (17.3) | 81 (82.7) | |
| **Sex:** | | | |
| Male | 24 (18.4) | 106 (81.6) | 0.123 |
| Female | 14 (14.0) | 86 (86.0) | |
| **Diabetes Mellitus:** | | | |
| Present | 11 (10.5) | 93 (89.5) | 0.089 |
| Absent | 27 (21.4) | 99 (78.6) | |
| **Hypertension:** | | | |
| Present | 13 (12.7) | 89 (87.3) | 0.165 |
| Absent | 25 (19.5) | 103 (80.5) | |
| **Serum Triglycerides Level:** | | | |
| Normal | 09 (10.1) | 80 (89.9) | 0.432 |
| Raised | 29 (20.5%) | 112 (79.5) | |
| **Serum HDL Level:** | | | |
| Normal | 11 (12.5) | 77 (87.5) | 0.015 |
| Decreased | 27 (19.0) | 115 (81.0) | |

**Table 3:** Comparison of demographic variables and metabolic syndrome.

| Demographic Variables | Metabolic Syndrome | | p-value |
|---|---|---|---|
| | Present n(%) | Absent n(%) | |
| **Age:** | | | |
| 20-45 years | 14 (10.6) | 118 (89.4) | 0.897 |
| 46-70 years | 10 (10.2) | 88 (89.8) | |
| **Sex:** | | | |
| Male | 15 (11.5) | 115 (88.5) | 0.463 |
| Female | 09 (9.0) | 91 (91.0) | |
| **Diabetes Mellitus:** | | | |
| Present | 14 (13.5) | 90 (86.5) | 0.089 |
| Absent | 10 (8.0) | 116 (92.0) | |
| **Hypertension:** | | | |
| Present | 16 (15.7) | 86 (84.3) | 0.465 |
| Absent | 08 (6.2) | 120 (93.8) | |
| **Serum Triglycerides Level:** | | | |
| Normal | 06 (6.7) | 83 (93.3) | 0.302 |
| Raised | 18 (12.7) | 123 (87.3) | |
| **Serum HDL Level:** | | | |
| Normal | 04 (4.5) | 84 (95.5) | 0.023 |
| Decreased | 20 (14.0) | 122 (86.0) | |
| **Non-Alcoholic Fatty Liver Disease:** | | | |
| Present | 21 (55.3) | 17 (44.7) | 0.013 |
| Absent | 03 (1.5) | 189 (98.5) | |

## DISCUSSION

NAFLD is becoming a vital health concern due to its increasing prevalence. The prevalence of NAFLD varies from 15% to 32% in Asian countries and Indian subcontinent [8, 9]. NAFLD patients are more prone to increased insulin resistance, dysfunctional glucose metabolism, and an elevated risk of diabetes mellitus development. NAFLD is also an independent risk factor for various chronic diseases including cardiovascular diseases, colorectal malignancy, atrial fibrillation, and thyroid dysfunction [4, 5]. NAFLD may be seen in normal-weight and lean individuals also, having distinct metabolic characteristics including higher serum transaminase levels, less insulin sensitivity, less severe necro-inflammatory activity, and liver fibrosis as compared to NAFLD in obese and overweight individuals [7, 11] Prevalence of NAFLD reported by Kim *et al.* [15] in non-obese, non-diabetic adults was 23.4% (16.1% normal-weight *versus* 34.4% overweight group). All-cause NAFLD was seen in 33.6% of the general Pakistani population [16]. The major cause of NAFLD, according to the National Health Survey of Pakistan conducted in 2006, was obesity seen in 25% [17]. A hospital-based study in Pakistan by Naiz *et al.* [18] showed NAFLD in 13.5%. NAFLD may be utilized as a predictor of various metabolic diseases and a cause of cryptogenic liver fibrosis in patients with normal weight.

There is very scarce literature about the natural history, therapeutic strategies, and prognosis of NAFLD in lean patients. It has been reported that mortality risk in Asians is more strongly associated with having low BMI than high BMI when compared to Cucasians [19] Cruz *et al.* [20] found cumulative survival to be significantly shorter in lean patients with NAFLD as compared to overweight or obese patients with NAFLD (p-value <0.02). Lean NAFLD is more associated with the male sex, non-Caucasian race, lower serum transaminase levels, lower prevalence of central obesity, diabetes, hypertriglyceridemia, hypertension, and Metabolic Syndrome; however, they had more severe lobular inflammation when compared to obese/overweight NAFLD patients. In the present study, 38 patients had NAFLD out of the 230 enrolled. Among these 38 patients with NAFLD, 11 (28.9%) had diabetes mellitus, 13 (34.2%) had hypertension, 29 (76.3%) had raised serum triglyceride levels and 27 (71.0%) had decreased HDL-Cholesterol levels. However, a significant association of NAFLD was only seen with serum HDL-Cholesterol level (p=0.015). Feng *et al.* [9] showed lean NAFLD was strongly associated with diabetes mellitus, hypertension, and Metabolic Syndrome as compared to overweight and obese NAFLD indicating an elevated risk for metabolic disturbances, cardiovascular morbidity, and mortality. In the present study, 24 patients had Metabolic Syndrome of the 230 enrolled. Among these 24 patients with Metabolic Syndrome, 21 (87.5%) had NAFLD showing a significant association (p=0.013).

In the present study, Diabetes Mellitus was seen in 104 (45.2%) patients. Out of these 104 patients, 11 (10.5%) patients had NAFLD while 14 (13.5%) had Metabolic Syndrome. There was no significant association of diabetes mellitus with either NAFLD (p=0.089) or Metabolic Syndrome (p=0.089) in the present study. However, it has been postulated that NAFLD may predict the development of diabetes mellitus and both these conditions serve to aid the progression of the other through shared genetic metabolic pathways [21,

22]. End-stage NAFLD leading to liver cirrhosis and hepatocellular carcinoma is a major indication of liver transplant globally [23]. Furthermore, the combined magnitude of diabetes mellitus and NAFLD is steadily increasing and requires better recognition both by the patients and their care providers [24]. Diabetes mellitus is a major chronic, often undiagnosed, global health problem that can affect all ages and either gender with an increased preponderance for a sedentary lifestyle. Various studies depict the disease burden of poorly-controlled diabetes mellitus in Pakistan and its association with cardiovascular disease and metabolic syndrome [25-27]. In Pakistan, diabetes mellitus was reported to be present in 11.2% of men and 9.1% of women with an urban population having a higher prevalence at 14.8% as compared to 10.3% in the rural population [28].

In China, Feng *et al.* [9] showed NAFLD to be present in 18.3% of lean individuals having BMI <24 kg/m2 and 14.5% of these had Metabolic Syndrome. Feldman *et al.* [10] showed NAFLD in up to 8% of lean patients. In the present study, 230 lean patients were enrolled and 38 (16.5%) patients had NAFLD while Metabolic Syndrome was seen in 24 (10.4%). Out of the 38 lean patients with NAFLD, 21 (55.3%) patients were aged 45 years or younger while 17 (44.7%) patients were 46 years or older. Twenty-four (63.2%) patients of lean-NAFLD were male as compared to 14 (36.8%) females. Metabolic syndrome represents a constellation of risk factors for type II diabetes mellitus and cardiovascular disease which occur simultaneously more frequently than by chance alone. These factors include hypertension, elevated fasting glucose, raised serum triglyceride, reduced HDL-cholesterol, and abdominal obesity [29]. It is becoming abundantly clear that these implications of metabolic disorders are related to insulin resistance and are seen more commonly in patients with abdominal obesity, especially those who have excess visceral or intra-abdominal adipose tissue [30]. Insulin Resistance leads to an inflammatory, atherogenic, and prothrombotic condition which not only increases the risk of Type II Diabetes Mellitus but also raises cardiovascular disease risk [31]. NAFLD has been linked strongly to insulin resistance, making NAFLD not only a consequence but also a cause of Metabolic Syndrome [32].

The treatment of NAFLD is challenging. The clinical practice relies on treating the components of Metabolic Syndrome [33]. Therefore lifestyle modifications based on weight loss, dietary changes, and exercise regimen are first-line. However, there is little reliable data that proves the usefulness of lifestyle changes in lean NAFLD [34]. Weight reduction may be especially helpful in lean NAFLD patients with visceral obesity. Jin *et al.* [35] found improvement in hepatic steatosis in up to 86% of patients at the time of follow-up biopsy in NAFLD patients following dietary modification and exercise regimen. Weight reduction of ≥5%, higher baseline steatosis, and total cholesterol reduction of ≥10% was significantly associated with steatosis improvement in non-obese patients with NAFLD [34]. High fructose or cholesterol diet restriction may also be beneficial. Another important step is the treatment for dyslipidemia which is commonly present in lean NAFLD. Furthermore, secondary causes of fatty liver should be ruled out. The role of genetic linkage and factors in metabolic pathways, insulin sensitizer agents, anti-oxidant therapy, and cytoprotective agents in lean NAFLD are being investigated [34, 35].

The current study has some limitations as well which need to be considered. Based in a single center, the present study had a relatively small sample size and enrolled patients taking Out-Patient care only. Furthermore, the risk of cardiovascular and renal disease, colorectal malignancy, atrial fibrillation, and thyroid dysfunction should also be seen in lean NAFLD patients. Case-control or cohort studies are better options but require more resources and time. Using the results of our study as baseline data, researchers could plan more studies and generate further evidence regarding the association of NAFLD in lean individuals and metabolic syndrome.

## CONCLUSION

NAFLD was not an uncommon finding in the present study seen in almost one-fifth of lean patients enrolled. However, metabolic syndrome was fairly common in these lean individuals of NAFLD and was reported in more than one-half of the lean NAFLD patients. We recommend using the presence of NAFLD to predict underlying metabolic syndrome in lean individuals so that early detection and management may lead to decreasing morbidity and mortality in this group of individuals.

Ethical Approval: Patient enrollment was done by the Outpatient Department of Medicine Department after taking approval (dated 17th November 2018) from the Institutional Review Board of Pakistan Ordinance Factories Hospital, Wah Cantonment Pakistan. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

## ETHICAL APPROVAL

ERC approval was taken from the Institutional Review Board of Pakistan Ordinance Factories Hospital, Wah Cantonment, Pakistan. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration.

## CONSENT FOR PUBLICATION

All authors provide their consent for the publication and take responsibility for the manuscript.

## AVAILABILITY OF DATA

The data of this study are available from the corresponding author upon reasonable request.

## FUNDING

Declared none.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

Declared none.

## AUTHORS' CONTRIBUTIONS

This study was conceived and designed by NIB, AR, and NK. NIB, AR, and KS did the initial literature research. AR, HA, FY, and KS did the data collection, assembly, and patient assessment. Data analysis and interpretation were done by NIB, NK, and FY. NIB, FY, and HA were involved in manuscript writing. AR, KS, and NK did the final critical review and corrections. NIB is the corresponding author on behalf of all other authors.

## REFERENCES

1. LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, *et al.* World Gastroenterology Organisation. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. J Clin Gastroenterol 2014; 48(6): 467-73. DOI: https://doi.org/10.1097/mcg.0000000000000116
2. Hashimoto E, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. J Gastroenterol Hepatol 2013; 28 Suppl 4: 64-70. DOI: https://doi.org/10.1111/jgh.12271
3. Lee YH, Cho Y, Lee BW, Park CY, Lee DH, Cha BS, *et al.* Nonalcoholic fatty liver disease in diabetes. Part I: Epidemiology and diagnosis. Diabetes Metab J 2019; 43(1): 31-45. DOI: https://doi.org/10.4093%2Fdmj.2019.0011
4. El Azeem HA, Khalek el-SA, El-Akabawy H, Naeim H, Khalik HA, Alfifi AA. Association between nonalcoholic fatty liver disease and the incidence of cardiovascular and renal events. J Saudi Heart Assoc 2013; 25(4): 239-46. DOI: https://doi.org/10.1016%2Fj.jsha.2013.07.004
5. Wong VW, Wong GL, Tsang SW, Fan T, Chu WC, Woo J, *et al.* High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut 2011; 60(6): 829-36. DOI: https://doi.org/10.1136/gut.2011.237974
6. Machado MV, Cortez-Pinto H. Fatty liver in lean patients: is it a different disease? Ann Gastroenterol 2012; 25(1): 1-2.
7. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, *et al.* Normal-weight central obesity: implications for total and cardiovascular mortality. Ann Intern Med 2015; 163(11): 827-35. DOI: https://doi.org/10.7326/m14-2525
8. Ha Y, Seo N, Shim JH, Kim SY, Park JA, Han S, *et al.* Intimate association of visceral obesity with non-alcoholic fatty liver disease in healthy Asians: A case-control study. J Gastroenterol Hepatol 2015; 30(11): 1666-72. DOI: https://doi.org/10.1111/jgh.12996
9. Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, *et al.* Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J Gastroenterol 2014; 20(47): 17932-40. DOI: https://doi.org/10.3748%2Fwjg.v20.i47.17932
10. Feldman A, Eder SK, Felder TK, Kedenko L, Paulweber B, Stadlmayr A, *et al.* Clinical and Metabolic Characterization of Lean Caucasian Subjects With Non-alcoholic Fatty Liver. Am J Gastroenterol 2017; 112(1): 102-10. DOI: https://doi.org/10.1038/ajg.2016.318
11. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, *et al.* Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005; 288(2): E462-8. DOI: https://doi.org/10.1152/AJPENDO.00064.2004
12. Deedwania PC, Hunninghake DB, Bays HE, Jones PH, Cain VA, Blasetto JW, *et al.* Effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia in patients with characteristics of the metabolic syndrome. Am J Cardiol 2005; 95(3): 360-6. DOI: https://doi.org/10.1016/j.amjcard.2004.09.034
13. Lim JU, Lee JH, Kim JS, Hwang YI, Kim TH, Lim SY, *et al.* Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients. Int J Chron Obstruct Pulmon Dis 2017; 12: 2465-75. DOI: https://doi.org/10.2147/copd.s141295
14. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009; 2(5-6): 231-7. DOI: https://doi.org/10.1242/dmm.001180
15. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, *et al.* Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 2004; 164(19): 2169-75. DOI: https://doi.org/10.1001/archinte.164.19.2169
16. Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, *et al.* Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000; 132(2): 112-7. DOI: https://doi.org/10.7326/0003-4819-132-2-200001180-00004
17. Akbar DH, Kawther AH. Nonalcoholic fatty liver disease in Saudi type 2 diabetic subjects attending a medical outpatient clinic: prevalence and general characteristics. Diabetes Care 2003; 26(12): 3351-2. DOI: https://doi.org/10.2337/diacare.26.12.3351-a
18. Niaz A, Ali Z, Nayyar S, Fatima N. Prevalence of NAFLD in healthy and young male individuals. ISRN Gastroenterol 2011; 2011: 363546. DOI: https://doi.org/10.5402%2F2011%2F363546
19. Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, *et al.* Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011; 364(8): 719-29. DOI: https://doi.org/10.1056/nejmoa1010679
20. Dela Cruz AC, Bugianesi E, George J, Day CP, Liaquat H, Charatcharoenwitthaya P, *et al.* 379 Characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology 2014; 146(5): S-909. DOI: http://dx.doi.org/10.1016/S0016-5085(14)63307-2
21. Zein CO, Unalp A, Colvin R, Liu YC, McCullough AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. J Hepatol 2011; 54(4): 753-9. DOI: https://doi.org/10.1016/j.jhep.2010.07.040
22. Lo L, McLennan SV, Williams PF, Bonner J, Chowdhury S, McCaughan GW, *et al.* Diabetes is a progression factor for hepatic fibrosis in a high fat fed mouse obesity model of non-alcoholic steatohepatitis. J Hepatol 2011; 55(2): 435-44. DOI: https://doi.org/10.1016/j.jhep.2010.10.039
23. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010; 51(5): 1820-32. DOI: https://doi.org/10.1002/hep.23594
24. Hebbard L, George J. Animal models of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2011; 8(1): 35-44. DOI: https://doi.org/10.1038/nrgastro.2010.191
25. Chowdhry MAT, Butt NI, Shakeel H, Gondal MNF, Saeed H. Tahir H. Is lack of patient knowledge a cause of poorly controlled diabetes mellitus? PJMHS 2021; 15(9): 2302-4. DOI: https://doi.org/10.53350/pjmhs211592302
26. Zia N, Aftab S, Butt NI, Ashfaq F, Anser A, Saeed S. Prevalence of silent cardiac ischemia in type II diabetes mellitus. Pak Heart J 2021; 54(2): 162-6. DOI: https://doi.org/10.47144/phj.v54i2.2093
27. Afzal H, Butt NI, Ashfaq F, Habib O, Anser A, Aftab S. Obstructive sleep apnea in type 2 diabetes mellitus. RMJ 2023; 48(1): 20-2.

28. Meo SA, Zia I, Bukhari IA, Arain SA. Type 2 diabetes mellitus in Pakistan: Current prevalence and future forecast. J Pak Med Assoc 2016; 66(12): 1637-42.

29. Radu F, Potcovaru CG, Salmen T, Filip PV, Pop C, Fierbințeanu-Braticievici C. The link between NAFLD and metabolic syndrome. Diagnostics (Basel) 2023; 13(4): 614. DOI: https://doi.org/10.3390/diagnostics13040614

30. Barale C, Russo I. Influence of cardiometabolic risk factors on platelet function. Int J Mol Sci 2020; 21(2): 623. DOI: https://doi.org/10.3390/ijms21020623

31. Lemieux I, Després JP. Metabolic syndrome: past, present and future. Nutrients 2020; 12(11): 3501. DOI: https://doi.org/10.3390%2Fnu12113501

32. 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. Lancet Gastroenterol Hepatol 2022; 7(9): 851-61. DOI: https://doi.org/10.1016/s2468-1253(22)00165-0

33. Anwar A, Butt NI, Ashfaq F, Aftab S, Nasim H, Khan FA. Elevated CRP level in metabolic syndrome. RMJ 2022; 47(4): 837-40.

34. Jin YJ, Kim KM, Hwang S, Lee SG, Ha TY, Song GW, *et al.* Exercise and diet modification in non-obese non-alcoholic fatty liver disease: analysis of biopsies of living liver donors. J Gastroenterol Hepatol 2012; 27(8): 1341-7. DOI: https://doi.org/10.1111/j.1440-1746.2012.07165.x

35. Xu R, Pan J, Zhou W, Ji G, Dang Y. Recent advances in lean NAFLD. Biomed Pharmacother 2022; 153: 113331. DOI: https://doi.org/10.1016/j.biopha.2022.113331