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CLINICAL PROFILE OF YOUNG PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE AND ITS CORRELATION WITH METABOLIC SYNDROME

Medicine

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ABSTRACT

The term NAFLD is used to describe a spectrum of liver diseases ranging from simple steatosis to steatohepatitis in the absence of significant alcohol intake which can result in cirrhosis and hepatocellular carcinoma.1. Abnormal deposition of triglycerides in hepatocytes is the basic pathology in NAFLD.2 Central obesity, type 2 diabetes mellitus, hypertension and dyslipidemia are the main risk factors of NAFLD.Non-alcoholic fatty liver disease (NAFLD) is closely associated with obesity, insulin resistance, and dyslipidaemia, and comprises non-alcoholic fatty liver (NAFL) and less commonly, non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma. Patients with NASH have an increased risk of death from cardiovascular disease, non-hepatic malignancies, and cirrhosis, which may be complicated by hepatocellular cancer.Excessive accumulation of hepatic triacylglycerol (TAG) stores (steatosis) results from a combination of increased delivery of non-esterified fatty acids from uncontrolled lipolysis in adipose tissue, increased de novo lipogenesis from carbohydrates, and increased delivery of diet derived free fatty acids (FFAs).Weight loss through diet and exercise remains the cornerstone of optimal management .

KEYWORDS

INTRODUCTION:

The term NAFLD is used to describe a spectrum of liver diseases ranging from simple steatosis to steatohepatitis in the absence of significant alcohol intake which can result in cirrhosis and hepatocellular carcinoma.[1]. Abnormal deposition of triglycerides in hepatocytes is the basic pathology in NAFLD.[2] Central obesity, type 2 diabetes mellitus, hypertension and dyslipidemia are the main risk factors of NAFLD.[3]

NAFLD is now the most common chronic liver disease in many developed countries[4,5]and is closely associated with obesity and cardiovascular disease[6,7]and is one of the leading cause of liver transplantation. Furthermore, NAFLD is expected to become an even more serious public health issue because of the increasing prevalenc of obesity and aging[8,9,10]. Metabolic syndrome (Mets) is a cluster of metabolic abnormalities that is a precursor to cardiovascular disease and predicts the risk of type 2 diabetes mellitus, and patients with NAFLD have a higher rate of MetS than those without NAFLD[11-13]Both MetS and NAFLD involve interactions of adipokines, cytokines, inflammatory factors and insulin resistance, and some researchers have proposed that NAFLD can be regarded as a hepatic manifestation of MetS[21]. The increasing prevalence of NAFLD, specifically non-alcoholicsteatohepatitis (NASH) with fibrosis, is concerning, because patients appear to experience higher mortality from liver-related and non-liver-related causes compared with the general population.

AIMS AND OBJECTIVES:

The aim of the study is to evaluate clinical profile of young patients having non-alcoholic fatty liver disease and find the prevalence of metabolic syndrome in patients having NAFLD.

THE METABOLIC SYNDROME

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus.. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL)

TABLE 401-1 NCEP-ATPIII[a] 2001 and Harmonizing Definition Criteria for the Metabolic Syndrome

NCEP:ATPIII 2001	HARMONIZING DEFINITION[b]		
Three or more of the following:	**Three of the following:**		
• Central obesity: waist circumference >102 cm (M), >88 cm (F)	Waist circumference (cm)		
	Men	**Women**	**Ethnicity**
	≥94	≥80	Europid, sub-Saharan African, Eastern and Middle Eastern
	≥90	≥80	South Asian, Chinese, and ethnic South and Central American
	≥85	≥90	Japanese
• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication	• Fasting triglyceride level >150 mg/dL or specific medication		
• Low HDL[c] cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication	• HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication		
• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication	• Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication		
• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes	• Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)		

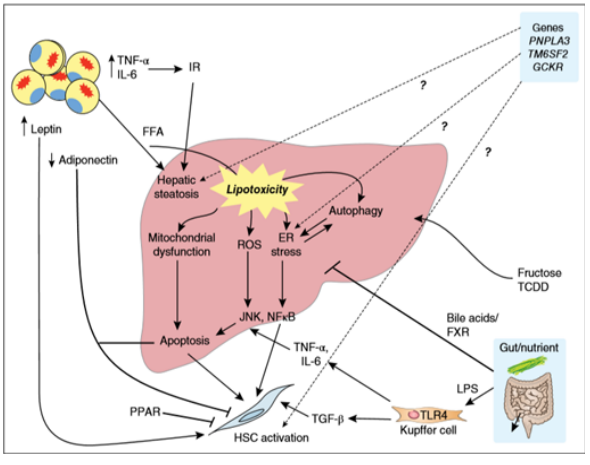
[a]National Cholesterol Education Program and Adult Treatment Panel III. [b]In this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used. [c]High-density lipoprotein.

Patients with metabolic syndrome frequently have an increase in fat (triglyceride) accumulation in the liver and hepatic insulin resistance[23] This increase in liver fat, which is associated with insulin resistance but not with other known causes of steatosis (e.g., alcohol, viruses, drugs), is called non-alcoholic fatty liver disease (NAFLD). The liver is the site of production of two of the key components of metabolic syndrome, fasting plasma glucose and VLDL, which contains most of the triglycerides present in serum. In patients with NAFLD, the ability of insulin to normally suppress production of glucose and VLDL is impaired.[24]

PATHOGENESIS OF NAFLD:

The mechanisms underlying the pathogenesis and progression of NAFLD are not entirely clear. The best-understood mechanisms pertain to hepatic steatosis[26]. This is proven to result when hepatocyte mechanisms for triglyceride synthesis (e.g., lipid uptake and de novo

lipogenesis) overwhelm mechanisms for triglyceride disposal (e.g., degradative metabolism and lipoprotein export), leading to accumulation of fat (i.e., triglyceride) within hepatocytes. Obesity stimulates hepatocyte triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest from dietary sources and intestinal permeability. Reduced intestinal barrier function increases hepatic exposure to gut-derived products, which stimulate liver cells to generate inflammatory mediators that inhibit insulin actions. Obese adipose depots also produce excessive soluble factors (adipokines) that inhibit tissue insulin sensitivity. Insulin resistance promotes hyperglycaemia. This drives the pancreas to produce more insulin to maintain glucose homeostasis. However, hyperinsulinemia also promotes lipid uptake, fat synthesis, and fat storage. The net result is hepatic triglyceride accumulation (i.e., steatosis). Triglyceride per se is not hepatotoxic. However, its precursors (e.g., fatty acids and diacylglycerols) and metabolic by-products (e.g., reactive oxygen species) may damage hepatocytes, leading to hepatocyte lipotoxicity. Lipotoxicity also triggers the generation of other factors (e.g., inflammatory cytokines, hormonal mediators) that deregulate systems that normally maintain hepatocyte viability. The net result is increased hepatocyte death. Dying hepatocytes, in turn, release various factors that trigger wound healing responses that aim to replace (regenerate) lost hepatocytes. Such repair involves transient expansion of other cell types, such as myofibroblasts and progenitor cells, that make and degrade matrix, remodel the vasculature, and generate replacement hepatocytes, as well as the recruitment of immune cells that release factors that modulate liver injury and repair. NASH is the morphologic manifestation of lipotoxicity and resultant wound healing responses



METHODS AND MATERIALS

Source of data: The cases of the study were taken from the patients who were admitted in the department of general medicine in Shardaben hospital and V.S.Hospital.

Duration of study: August 2018 to September 2020

Inclusion criteria:

- All the patients with age between 18-45 years.
- All the patients with fatty liver on routine ultrasonography findings.

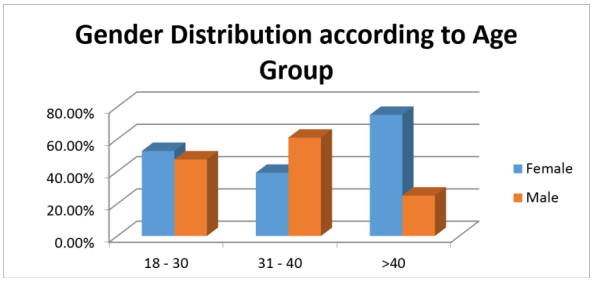
EXCLUSION CRITERIA:

- History of significant alcohol consumption
- Viral hepatitis
- Autoimmune hepatitis
- Metabolic diseases (e.g. hemochromatosis, Wilson, alpha 1-antitrypsin deficiency) and Hepatotoxic medication (e.g. amiodarone, corticosteroids, methotrexate, tamoxifene etc.)

OBSERVATION AND DISCUSSION

TABLE:1 Age distribution of patients studied

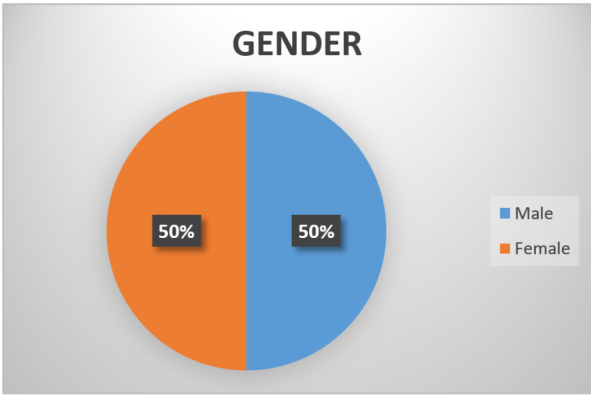
Age Group	GENDER				Total
	Female	%	Male	%	
18 – 30	10	52.63%	9	47.37%	19
31 – 40	9	39.13%	14	60.87%	23
>40	6	75.00%	2	25.00%	8
Total	**25**	**50.00%**	**25**	**50.00%**	**50**



In our study max no of patients were from age group 31-40 years(46%).

TABLE: 2 Gender distribution of patients studied

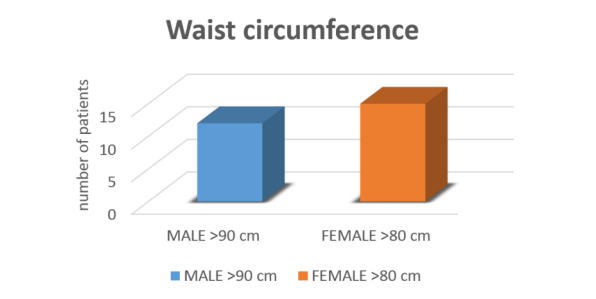
Gender	Present Study	Marchesini et al study
Female	25 (50.00%)	52 (82.89%)
Male	25 (50.00%)	252 (17.11%)
Total	**50 (100.00%)**	**304 (100.00%)**



In our study there were 25 male patients and 25 females patients.

TABLE:3 Waist Circumference (cms) of patients studied

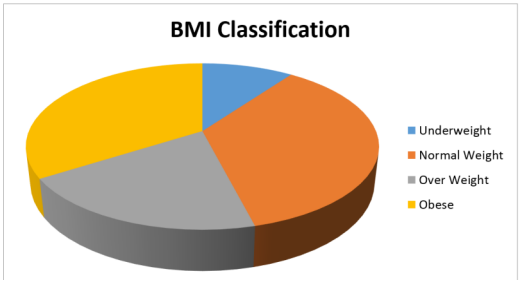
Waist Circumferences	N	%	p value	MARCHESINI et al(n=43)	p value	Uchil et al (n=225)	p value
Normal	23	46.00%	**0.047**	43%	<0.001	53%	<0.05
Abnormal	27	54.00%		57%		47%	
Total	**50**	**100.00%**		100%		100%	



In our study,there were 14 male patients whose waist circumference was more than 90cm and 18 female patients whose waist circumference was more than 80cm.So in total there were 32 patients(64%) who had abnormal waist circumferences making our results consistent with Marchesini et al and Uchil et al study results. Our results are suggestive that there is significant correlation between raised waist circumference and NAFLD.

TABLE:4 BODY MASS INDEX of patients studied

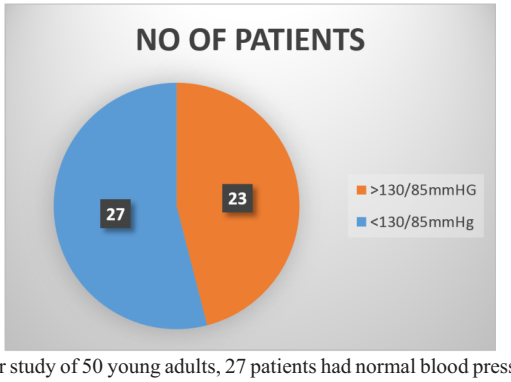
BMI Classification	N	p value	Marchesini et al	P value
Underweight	5 (10.00%)	**0.029**	0 (0.00%)	**0.034**
Normal Weight	18 (36.00%)		68 (22.00%)	
Over Weight	10 (20.00%)		161 (53.00%)	
Obese	17 (34.00%)		75 (25.00%)	
Total	**50 (100.00%)**		**304 (100.00%)**	



Inour study, 5 patients were found to be underweight, 18 patients had normal weight,10 patient were having overweight and 17 patients were obese. So there were 27 patients who were either overweight or obese. Among 27 patients who were obese or overweight, 19 patients were having metabolic syndrome which is indicative of significant correlation between obesity and MetS. Our study results are similar to Marchesini et al (2003) study results as they also found that more than half of the study population were either overweight or obese.

TABLE:5 Blood pressure of patients studied

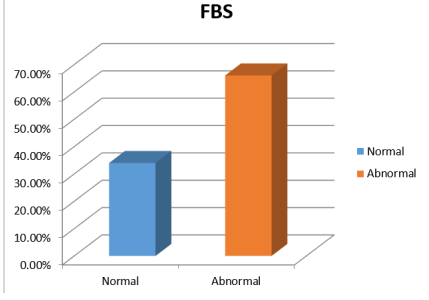
Blood Pressure	N	%	MARCHESINI et al(n=43)	Uchil et al(n=225
Normal(<130/85)	27	54.00%	47%	72%
Abnormal (>130/85mmHg)	23	46.00%	53%	28%
Total	**50**	**100.00%**	100%	100%



In our study of 50 young adults, 27 patients had normal blood pressure and 23 had blood pressures above 130/85mmHg.Our findings are similar to Uchil et al but are inconsistent with MARCHESINI et al study.

TABLE:6 Fasting blood sugar of the patients studied

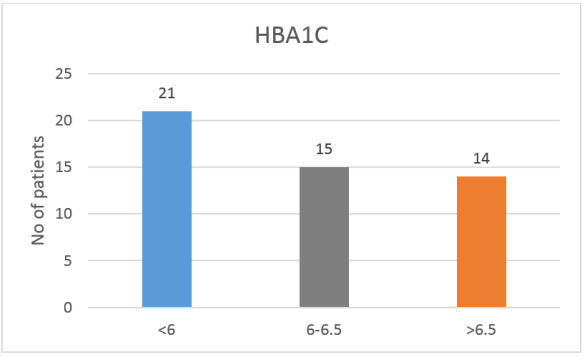
FBS	N	%	p value	MARCHESINI et al(n=43)	p value	Uchil et al (n=225)	p value
Normal (<100mg/dl)	17	34.00%	**0.024**	40%	0.004	28%	<0.05
Abnormal (>100mg/dl)	33	66.00%		60%		72%	
Total	**50**	**100.00 %**		100%		100%	



In our study of study of 50 patients, 33patients(66%) had their fasting blood sugar above 100mg/dl and 17 patients had them less than 100mg/dl making our study findings consistent with to Marchesini et al and Uchil et al study results.

TABLE:7 Prevalence of diabetes(HBA1C and FBS) of the patients studied

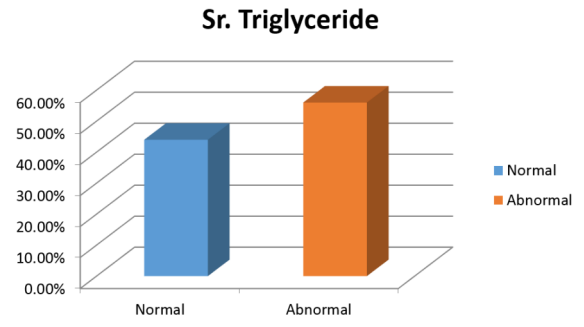
HBA1C	No of patients	%	FBS	No of patients	%
• <6	21	42	<126mg/dl	36	72
• 6-6.5	15	30	>126mg/dl	14	28
• >6.5	14	28		50	100



Considering HBA1C and FBS>126mg/dl as the criteria to classify the patients as diabetics, 14 patients(28%) were having diabetes according to our study.

TABLE:8 S.Triglycerides of the patients studied

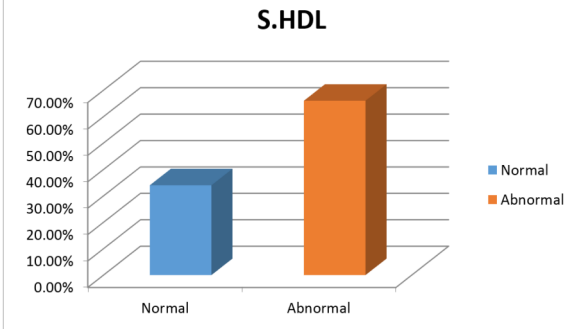
S.Triglyceride	N	%	MARCHESINI et al(n=43)	Uchil et al(n=225
Normal(<150mg/dl)	22	44.00%	42%	56%
Abnormal(>150mg/dl)	28	56.00%	58%	44%
Total	**50**	**100.00%**	100%	100%



In our study of 50 patients, 28 patients (56%) had abnormal S.Triglyceridelevels and 22 patients had normal S.triglyceride levels.

TABLE:9 S.HDL of the patients studied

S.HDL	N	%	p value	MARCHESINI et al(n=43)	p value
Normal(>40mg/dl)	17	34.00%	**0.024**	43%	0.019
Abnormal (<40mg/dl)	33	66.00%		57%	
Total	**50**	**100.00%**		100%	



In our study of 50 patients, 33 patients(66%) had abnormal S.HDL levels and 17 patients had normal S.HDL levels making our findings were consistent with MARCHESINI et al study. Our study is suggestive that low S.HDL levels are consistent with NAFLD.

TABLE:10 Comparing parameters of metabolic syndrome with NAFLD

Patients having NAFLD	Number of patients	%	MARCHESINI et al(n=43)	Uchil et al(n=225)
Waist circumference >90cm in males and >80cm in females	27	54	57%	47%
Fbs>100	33	66	60%	72%
S.Triglycerides>150	28	56	58%	44%
S.Hdl<40	32	64	57%	30%
Blood pressure>135/80	23	46	53%	28%

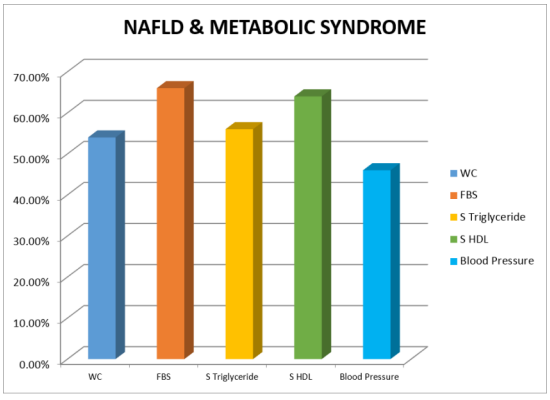


TABLE:11 Comparison of Metabolic syndrome with NAFLD

Patients having NAFLD	Prevelance of metabolic syndrome	P value
MY STUDY(n=50)	64%	0.047
MARCHESINI et al(n=43)	53%	<0.0001
Uchil et al(n=225)	47%	<0.05

In our study the prevalence of metabolic syndrome among NAFLD was 64% (32/50patients). The prevalence in MARCHESINI et al study was 53% and in Uchil et al was 47%.Considering these, there is significant correlation between the prevalence of metabolic syndrome and NAFLD and our findings are consistent with MARCHESINI et al and Uchil et al studies.

RESULT:

- A total of 50 patients having fatty liver on ultrasonography were enrolled for the study which included 25 males (50%) and 25 females(50%).
- Maximum number of patients were from age group 31-40(46%).
- In our study,the number of patients having increased waist circumference was 27(54%),having high blood pressure were 23 patients(46%), 33(66%)patients were having high fasting blood sugar,28(56%)patients having high S.Triglycerides, and low S.Hdl was seen in 33(66%) patients.
- A total of 27 patients (54%) were either overweight or obese and a 14 patients (28%) were having diabetes.
- In our study, out of 50 patients 32 patients (64%) were having Metabolic Syndrome.
- Among the 27 overweight and obese patients we found the prevalence of metabolic syndrome was seen in 19 patients (70%).
- Our results were found to be consistent with the results of MARCHESINI et al and Uchil et al studies proving the increasing prevalence of metabolic syndrome in patients of NAFLD.

CONCLUSION:

The relationship between NAFLD and MetS is complex and may be bi-directionally associated and NAFLD is strongly associated with the components of MetS and the prevalence of MetS is higher in patients with NAFLD.

Considering insulin resistance playing a critical role in the pathogenesis of NAFLD and MetS, it seems that NAFLD is the hepatic manifestation of MetS.

As obesity is having significant correlation with NAFLD & metabolic syndrome, dietary and lifestyle modifications must be taken to prevent and cure this epidemic of non-communicable disease.

USG evidence of fatty liver should be taken seriously as a predictor of MetS and NAFLD on USG should alert us of preventing MetS. So all measures should be undertaken in preventing it.

So screening for NAFLD should be performed in individuals who are either obese,diabetic or having MetS.

NAFLD is the object of significant scientific and clinical interest which is going to increase in the following years and thus further large scale prospective studies are needed to support these correlation of NAFLD and MetS.

REFERENCES:

1. Angulo P. Non-alcoholic fatty liver disease. N Engl J Med. 2002;346:1221-31.
2. Farrell GC, Larter CZ. Non-alcoholic fatty liver disease: from steatosis to cirrhosis. Hepatol. 2006;43:S1-112.
3. Scaffner F, Thaler H. Non-alcoholic fatty liver disease: a progressive liver disease. Scandinavian J Gastroenterol. 1986;8:283-93.
4. Farrell, G. C., Wong, V. W.-S. &Chitturi, S. NAFLD in Asia-as common and important as in the West. Nat Rev GastroenterolHepatol 10, 307–318 (2013).
5. Younossi, Z. M. et al. Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. Hepatology, doi: 10.1002/hep.28431 (2015).
6. Lonardo, A. et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. Dig Liver Dis. 47, 997–1006 (2015).
7. Lonardo, A., Sookoian, S., Pirola, C. J. &Targher, G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metabolism, doi: 10.1016/j.metabol.2015.1009.1017 (2015).
8. Wong, R. J. & Ahmed, A. Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations. World J Hepatol 6, 263–273 (2014).
9. Bertolotti, M. et al. Nonalcoholic fatty liver disease and aging: epidemiology to management. World J Gastroenterol 20, 14185–14204 (2014).
10. Amarapurkar, D. N. et al. How common is non-alcoholic fatty liver disease in the Asia? Pacific region and are there local differences? J GastroenterolHepatol 22, 788–793 (2007).
11. Shen, Y.-H. et al. Bright liver and alanine aminotransferase are associated with metabolic syndrome in adults. Obes Res. 13, 1238–1245 (2005).
12. FAN, J.-G. et al. Fatty liver and the metabolic syndrome among Shanghai adults. J GastroenterolHepatol 20, 1825–1832 (2005).
13. Ballestri, S. et al. Nonalcoholic fatty liver disease is associated with an almost two-fold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J GastroenterolHepatol, doi: 10.1111/jgh.13264 (2015).
14. Privitera, G. et al. Hepatic insulin resistance in NAFLD: relationship with markers of atherosclerosis and metabolic syndrome components. ActaDiabetol, doi: 10.1007/s00592-00015-00816-y (2015).
15. Al Rifai, M. et al. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 239, 629–633 (2015).
16. Pisto, P., Santaniemi, M., Bloigu, R., Ukkola, O. &Kesäniemi, Y. A. Fatty liver predicts the risk for cardiovascular events in middleaged population: a population-based cohort study. BMJ open 4, e004973 (2014).
17. Targher, G., Day, C. P. &Bonora, E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 363, 1341–1350 (2010).
18. Arulanandan, A. et al. Association Between Quantity of Liver Fat and Cardiovascular Risk in Patients With Nonalcoholic Fatty Liver Disease Independent of Nonalcoholic Steatohepatitis. ClinGastroenterolHepatol 13, 1513–1520.e1511 (2015).
19. Younossi, Z. M., Otgonsuren, M., Venkatesan, C. & Mishra, A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism 62, 352–360 (2013).
20. Ong, J. P., Pitts, A. &Younossi, Z. M. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease J Hepatol 49, 608–612 (2008).
21. Vanni, E. et al. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis. 42, 320–330 (2010).
22. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. Circulation. 2002;106:3143–3421.
23. Kotronen A, Westerbacka J, Bergholm R, Pietilainen KH, Yki-Jarvinen H. Liver fat in the metabolic syndrome. J ClinEndocrinolMetab 2007; 92: 3490–97.
24. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J ClinEndocrinolMetab 2002; 87: 3023–28.
25. Targher G, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. SeminThrombHemost 2009; 35: 277–87.
26. Angulo P et al: Fibrosis in nonalcoholic fatty liver disease: Mechanisms and clinical implications. Semin Liver Dis 35:132, 2015.
27. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J PhysiolEndocrinolMetab 2005; 288: E462–68.
28. Park SK, Seo MH, Shin HC, Ryoo JH. Clinical availability of nonalcoholic fatty liver disease as an early predictor of type 2 diabetes mellitus in Korean men: 5-year prospective cohort study. Hepatology 2013; 57: 1378–83.
29. Kotronen A, Johansson LE, Johansson LM, et al. A common variant in PNPLA3, which encodes adiponutrin, is associated with liver fat content in humans. Diabetologia 2009; 52: 1056–60.
30. Gastaldelli A, Cusi K, Pettiti M, et al. Relationship between hepatic/ visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology 2007; 133: 496–506.
31. Adiels M, Olofsson SO, Taskinen MR, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. ArterioscIerThrombVascBiol 2008; 28: 1225–36.
32. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013; 93: 359–404.
33. Sung KC, Wild SH, Byrne CD. Development of new fatty liver, or resolution of existing fatty liver, over fi ve years of follow up, and risk of incident hypertension. J Hepatol 2014; published online Jan 18. DOI:10.1016/j.jhep.2014.01.009.
34. Cabrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. ProcNatlAcadSci USA 2009; 106: 15430

35. Cabrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. ProcNatlAcadSci USA 2009; 106: 15430–
36. Farrell, G. C., Wong, V. W.-S. &Chitturi, S. NAFLD in Asia-as common and important as in the West. Nat Rev GastroenterolHepatol 10, 307–318 (2013).
37. Younossi, Z. M. et al. Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. Hepatology, doi: 10.1002/hep.28431 (2015)
38. Lonardo, A. et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. Dig Liver Dis. 47, 997–1006 (2015).
39. Lonardo, A., Sookoian, S., Pirola, C. J. &Targher, G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metabolism, doi: 10.1016/ j. metabol. 2015. 1009. 1017 (2015)
40. Wong, R. J. & Ahmed, A. Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations. World J Hepatol 6, 263–273 (2014).
41. Bertolotti, M. et al. Nonalcoholic fatty liver disease and aging: epidemiology to management. World J Gastroenterol 20, 14185–14204 (2014).
42. Amarapurkar, D. N. et al. How common is non-alcoholic fatty liver disease in the Asia? Pacific region and are there local differences? J GastroenterolHepatol 22, 788–793 (2007).
43. Shen, Y.-H. et al. Bright liver and alanine aminotransferase are associated with metabolic syndrome in adults. Obes Res. 13, 1238–1245 (2005).
44. FAN, J.-G. et al. Fatty liver and the metabolic syndrome among Shanghai adults. J GastroenterolHepatol 20, 1825–1832 (2005).
45. Ballestri, S. et al. Nonalcoholic fatty liver disease is associated with an almost two-fold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J GastroenterolHepatol, doi: 10.1111/jgh.13264 (2015).
46. Privitera, G. et al. Hepatic insulin resistance in NAFLD: relationship with markers of atherosclerosis and metabolic syndrome components. ActaDiabetol, doi: 10.1007/s00592-00015-00816-y (2015).
47. Al Rifai, M. et al. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 239, 629–633 (2015).
48. Pisto, P., Santaniemi, M., Bloigu, R., Ukkola, O. &Kesäniemi, Y. A. Fatty liver predicts the risk for cardiovascular events in middleaged population: a population-based cohort study. BMJ open 4, e004973 (2014)
49. Targher, G., Day, C. P. &Bonora, E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 363, 1341–1350 (2010).
50. Arulanandan, A. et al. Association Between Quantity of Liver Fat and Cardiovascular Risk in Patients With Nonalcoholic Fatty Liver Disease Independent of Nonalcoholic Steatohepatitis. ClinGastroenterolHepatol 13, 1513–1520.e1511 (2015).
51. Younossi, Z. M., Otgonsuren, M., Venkatesan, C. & Mishra, A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism 62, 352–360 (2013).
52. Ong, J. P., Pitts, A. &Younossi, Z. M. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease.
53. J Hepatol 49, 608–612 (2008). 18. Vanni, E. et al. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis. 42, 320–330 (2010).
54. Lonardo, A., Ballestri, S., Marchesini, G., Angulo, P. &Loria, P. Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome. Dig Liver Dis. 47, 181–190 (2015).
55. Kotronen A, Westerbacka J, Bergholm R, Pietilainen KH, Yki-Jarvinen H. Liver fat in the metabolic syndrome. J ClinEndocrinolMetab 2007; 92: 3490–97.
56. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J ClinEndocrinolMetab 2002; 87: 3023–28.
57. Targher G, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. SeminThrombHemost 2009; 35: 277–87.
58. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J PhysiolEndocrinolMetab 2005; 288: E462–68.
59. Park SK, Seo MH, Shin HC, Ryoo JH. Clinical availability of nonalcoholic fatty liver disease as an early predictor of type 2 diabetes mellitus in Korean men: 5-year prospective cohort study. Hepatology 2013; 57: 1378–83.
60. Kotronen A, Johansson LE, Johansson LM, et al. A common variant in PNPLA3, which encodes adiponutrin, is associated with liver fat content in humans. Diabetologia 2009; 52: 1056–60.
61. Chen LY, Qiao QH, Zhang SC, Chen YH, Chao GQ, Fang LZ. Metabolic syndrome and gallstone disease. World J Gastroenterol 2012; 18: 4215–20
62. 36 Adiels M, Olofsson SO, Taskinen MR, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. ArterioscIerThrombVascBiol 2008; 28: 1225–36.
63. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013; 93: 359–404.
64. Sung KC, Wild SH, Byrne CD. Development of new fatty liver, or resolution of existing fatty liver, over fi ve years of follow up, and risk of incident hypertension. J Hepatol 2014; published online Jan 18. DOI:10.1016/j.jhep.2014.01.009.
65. Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. ProcNatlAcadSci USA 2009; 106: 15430–35.
66. Chalasani N et al: The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 142:1592, 2012.