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Research paper

Non-alcoholic fatty liver disease in asymptomatic young adults: association with HOMA, metabolic syndrome, and atherogenic risk

Chávez-Pagola Jorge Teodoro [1], Hernández-Zavala Araceli [2], Valenzuela-Limón Olga [3], Sánchez-Gutiérrez Manuel [1], Izquierdo-Vega Jeannett Alejandra [1] *

[1] Institute of Health Sciences at the Autonomous University of the State of Hidalgo. Hidalgo, Mexico
[2] Research and Postgraduate Section, Higher School of Medicine of the National Polytechnic. Mexico City, Mexico
[3] Faculty of Chemical Sciences, Veracruzana University. Veracruz, Mexico
**Corresponding author E-mail: ivega@uaeh.edu.mx*

Abstract

Objective: Non-alcoholic fatty liver disease (NAFLD) represents the most common liver disease worldwide. The Latin American population has the highest obesity rates in the world. The aim was to research the factors associated with NAFLD in young adults. Methods: A cross-sectional study was performed on 171 participants with an average age of 21 years who underwent a physical and laboratory examination, anthropometric evaluation, and abdominal ultrasound. Results: Subjects with NAFLD were significantly overweight, with dyslipidemia, and with atherogenic risk. They had the presence of metabolic syndrome compared to those without NAFLD. Bivariate logistic regression showed that body mass index, atherogenic risk, Homeostatic Model Assessment (HOMA) value, and metabolic syndrome were associated with NAFLD development. Conclusions: The variables of HOMA, metabolic syndrome, and atherogenic risk were most associated as risk predictors of this pathology in young adults.

Keywords: *Atherogenic Risk; Dyslipidemia; HOMA; Metabolic Syndrome; Non-Alcoholic Fatty Liver Disease.*

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined by macrovesicular steatosis in ≥ 5% of hepatocytes without alcohol or drugs. It includes a spectrum of conditions from NAFLD to non-alcoholic steatohepatitis, fibrosis, and cirrhosis with complex pathophysiology [1]. As a result, metabolic diseases such as diabetes, abdominal obesity, hyperlipidemia, hypertension, and low HDL levels are often associated with it [2]. Therefore, it is frequently associated with metabolic disorders such as diabetes, abdominal obesity, hyperlipidemia, hypertension, and low HDL levels [3]. Although, there has been a considerable percentage of non-obese subjects have also presented NAFLD [4]. The evidence suggests that NAFLD development results from "three hits." The first one involves increased free fatty acids derived from insulin-resistant adipose tissue, increased hepatic lipogenesis, or an alteration in the export of lipids from hepatocytes. The second “hit” refers to stress and progressive damage events, and the final one is due to hepatocellular inflammation [5].
Hepatologists recently proposed a new definition of fatty liver: fatty liver disease linked to metabolic dysfunction, encompassing the concomitant causes of this liver illness [6]. Numerous epidemiological studies have revealed a link between metabolic syndrome (MetS) and NAFLD [7], [8]. Since it can worsen NAFLD or raise the likelihood of it developing in people without a prior diagnosis, this correlation is now thought to be bidirectional [3,9]. NAFLD's global prevalence is approximately 25%, with the highest prevalence in South America and the lowest prevalence in Africa [3], [10]. Studies in this regard in the Mexican population are limited. The prevalence of NAFLD in this country is higher than 60% [4], [7], [11], [12]. This value was due to the high prevalence of overweight and obesity in the Mexican population in 2018 [13]. This disease affects 70% of overweight people and 90% of the morbidly obese population [3]. As obesity rates rise worldwide, the ratio f NAFLD is projected to continue growing. The lack of knowledge about obesity in NAFLD development highlights the necessity to identify patients early to avoid complications of live diseases in their adult stage. Therefore, this work aims to know the risk factors associated with NAFLD in young adults.

2. Methodology

The selection of the population was carried out according to the following criteria; inclusion criteria, subjects who signed the written informed consent; exclusion criteria for all participants with a history of ethanol addiction; subjects with daily alcohol consumption ≥ 30 g for men or ≥ 20 g for women; subjects with a history of being carriers of hepatitis B or C. Subjects with a history of drug-induced liver disease or autoimmune liver disease and finally subjects with incomplete evaluations in the study.

This cross-sectional observational study was conducted on young university students from the Autonomous University of the State of Hidalgo. The Declaration of Helsinki was followed when completing the survey. All study participants gave their informed consent in writing. The Institutional Ethics Committee approved the protocol. Random sampling was performed to select study participants. A total of 171 participants with an average age ± SD was 21±1.6 years had an anthropometric evaluation. The body mass index (BMI), calculated as "the weight in kilograms divided by the height in square meters," was determined based on each individual's height, weight, and waist-hip ratio.

Subjects with BMI> 30 kg/m^2 are considered overweight [14]. To measure biochemical markers, venous blood samples were taken from each individual in the morning following a 12-hour fast. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and insulin were analyzed by a biochemical analyzer according to the manufacturer's instructions. Insulin resistance was evaluated by the Homeostatic Model Assessment (HOMA) using the formula [insulin x glucose]/22.5 [15].

The presence of MetS was defined based on the guidelines proposed by the third report of the Adult Treatment Panel of the National Cholesterol Program (ATP III) and by the International Diabetes Federation (IDF). The criteria included in ATP III definition requires the presence of three or more of the following five criteria: 1) waist circumference >102 cm (men) or >88 cm (women), 2) blood pressure >130/85 mmHg, 3) fasting triglyceride (TG) ≥150 mg/dl, 4) high lipoprotein cholesterol level fasting density (HDL) < 40 mg/dl (men) or < 50 mg/dl (women), and 5) fasting blood glucose ≥100 mg/dl [16]. Likewise, the criteria included in the definition of the IDF requires the presence of central obesity (defined as waist circumference, men ≥ 94 cm and woman ≥ 80 cm; when BMI> 30 kg/m^2) and the presence of two or more of the following criteria: 1) Triglycerides ≥150 mg/dl, 2) HDL< 40 mg/dl (men) or < 50 mg/dl (women), 3) blood pressure ≥130/85 mmHg, 4) Fasting plasma glucose >100 mg/dl [17], [18]. The atherogenic risk was estimated through the radio LDL/HDL [19].

NAFLD diagnosis in this research was based on abdominal ultrasound, determining hepatic steatosis (accumulation of triglycerides >5% in hepatocytes), accompanied by the exclusion of other etiology such as drug or alcohol-induced (<20 g/day in women and <30 g/day in men), and liver disease cholestatic using specific clinical criteria and biochemical parameters. According to the previously established international classification, the degree of severity was classified as mild, moderate, and severe [20]. A radiologist-physician performed an abdominal ultrasound to identify NAFLD, and subsequently, the ultrasound was independently reviewed by another radiologist without consulting the prior clinical diagnosis. Strict double-blindness was maintained during data collection, and the radiologists were unaware of the results of the biochemical parameters in the evaluated subjects.

Statistical Analysis. The database was analyzed using the Stata 14 program and descriptive statistics, presenting the continuous variables' arithmetic mean and standard deviation with a normal distribution (Shapiro-Wilks test: p> 0.05). Categorical variables were present in absolute and relative numbers. To determine the differences between the variables due to NAFLD's presence or absence, we used the t-Student test since all the study variables had a normal distribution. The Chi-square test and Fisher's exact test were used to determine differences in the proportion of qualitative variables. When comparing variables according to NAFLD's severity, the one-way analysis of variance (ANOVA) test was used for continuous variables and Fisher's exact test for categorical variables. NAFLD's potential risk factors were determined using bivariate logistic regression analysis by estimating the odds ratio (OR) and the 95% confidence interval (CI). A type I error of 0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

First, the characteristics of the study population were described. This study included a total of 171 young subjects. Sixty-two were men, and 109 women were, with a mean of 21.2 ± 1.6. There was no significant difference in the age and gender of the subjects identified with NAFLD. Of the individuals analyzed, 57 issues were identified with NAFLD, and there were no significant differences in the age and sex of the issues identified with NAFLD. In NAFLD subjects, we found significant differences in mean overweight, obesity, waist/hip ratio, and abdomen circumference. Concerning hereditary-antecedents, hypertriglyceridemia and hypertension were substantial in subjects with NAFLD (Table 1).

Table 1: Characteristics of the Population According to the Presence of Non-Alcoholic Fatty Liver

Variable	Total (n=171)	Without NAFLD (n=114)	With NAFLD (n=57)	P value
Gender				
Male	62 (36%)	37(59.7%)	25(40.3%)	
Female	109 (64%)	77(70.6%)	32 (29.4%)	0.14
Age (years)		21.1 ± 1.2	21.5 ± 2.2	0.12
BMI level		24.3 ± 2.9	31.3 ± 4.3	< 0.001 [b]
Normal weight	73 (43%)	70 (95.9%)	3 (4.1%)	<0.0001[c]
Overweight	59 (34%)	41 (69.5%)	18 (30.5%)	<0.0001[c]
Obesity	39 (23%)	3 (7.7%)	36 (92.3%)	<0.0001[c]
Waist /Hip Index		0.81 ± 0.06	0.88 ± 0.06	< 0.001 [b]
Abdomen circumference (cm)		80.7 ± 7.7	97.9 ± 9.9	< 0.001 [b]

[a] Chi-square, [b] Student t-test, [c] Fisher's exact test.
BMI= Body mass index

3.2. Differences between patients with and without NAFLD

The prevalence of NAFLD was 33% in young adults. Regarding the lipid parameters, the concentrations of cholesterol, LDL, and triglycerides were significantly higher (p <0.001), and the HDL concentrations were significantly lower (p = 0.001) compared with the ones without the disease. These data reflect the significant atherogenic risk in subjects with NAFLD than in subjects without the disease. MetS were determined based on both criteria proposed by ATP III and IDF with all the above parameters. The insulin resistance condition was present in subjects with NAFLD, whose HOMA value was significantly higher than in subjects who did not have the disease (p < 0.001). We identified more subjects (with NAFLD) with MetS in the group considering the IDF criteria. (Table 2).

Table 2: Comparison between Patients Due to the Presence of Non-Alcoholic Fatty Liver

Parameters	Without NAFLD (n=114)	With NAFLD (n=57)	P value
Cholesterol (mmol/L)	4.18 ±0.82	4.91 ± 1.02	< 0.001 [b]
LDL (mmol/L)	2.37 ± 0.66	3.36 ± 0.83	< 0.001 [b]
HDL (mmol/L)	1.22 ± 0.22	1.08 ± 0.23	0.001 [b]
Triglycerides (mmol/L)	1.62± 0.48	2.44 ± 1.33	< 0.001 [b]
Atherogenic risk	4 (3.51%)	24 (42.11%)	< 0.001 [b]
MetS-ATP III	2 (1.75%)	18 (31.58%)	< 0.001 [c]
MetS-IDF	10 (8.77%)	30 (52.63%)	< 0.001 [a]
Glucose (mmol/L)	4.7±0.19	4.93±0.22	< 0.001 [b]
Insulin (µU/mL)	10.1 ± 1.3	14.2 ± 3.1	< 0.001 [b]
HOMA	2.06 ± 0.34	3.07 ± 0.73	< 0.001 [b]

[a] Chi-square, [b] Student t-test, [c] Fisher´s exact test.
ATP III= Adult treatment panel of the national cholesterol program, HDL=High density lipoprotein, HOMA= Homeostatic model assessment, IDF= International diabetes federation, LDL= Low-density lipoprotein, MetS=Metabolic syndrome.

Table 3: Comparison between Patients by Severity of NAFLD

Variable	Without NAFLD (n=114)	Mild NAFLD (n=44)	Moderate and severe NAFLD (n=13)	P value
Cholesterol (mmol/L)	4.18 ± 0.82	4.85 ± 1.02	5.1 ± 1	< 0.001 [b]
LDL (mmol/L)	2.37 ± 0.66	3.35 ± 0.89	3.41 ± 0.63	< 0.001 [b]
HDL (mmol/L)	1.22± 0.22	1.08 ± 0.25	1.08 ± 0.17	0.001 [b]
Triglycerides (mmol/L)	1.62 ± 0.48	2.3 ± 1.29	2.92 ± 1.4	< 0.001 [b]
Atherogenic risk	4 (3.51%)	18 (40.91%)	6 (46.15%)	< 0.001 [a]
HOMA	2.06 ± 0.34	3.1 ± 0.7	2.9 ± 0.7	< 0.001 [b]
MetS-ATP III	2 (1.75%)	8 (18.18%)	10 (76.92%)	< 0.001 [a]
MetS-IDF	10 (8.77%)	18 (40.91%)	12 (92.3%)	< 0.001 [a]

[a] Fisher's exact test and [b] ANOVA
ATP III= Adult treatment panel of the national cholesterol program, BMI= Body mass index, HDL=High density lipoprotein, HOMA= Homeostatic model assessment, IDF= International diabetes federation, LDL= Low-density lipoprotein, MetS=Metabolic syndrome.

Table 4: Clinical Parameters Associated with the Risk of Non-Alcoholic Fatty Liver or NAFLD in Young Adults

Variable	OR	IC 95%	P value
BMI (Kg/m^2)	1.88	1.55 - 2.29	< 0.001
Waist (cm)	1.31	1.21 - 1.42	< 0.001
Hip (cm)	1.20	1.13 - 1.27	< 0.001
Waist/Hip index	1.29	1.19 - 1.40	< 0.001
Total colesterol (mmol/L)	1.02	1.01 - 1.03	< 0.001
LDL (mmol/L)	1.04	1.02 - 1.05	< 0.001
HDL(mmol/L)	0.92	0.88 - 0.96	< 0.001
Triglycerides (mmol/L)	1.01	1.01 - 1.01	< 0.001
Atherogenic risk presence	20	6.47 - 61.7	< 0.001
HOMA	19.14	8.41 - 43.54	< 0.001
MetS-ATP III	25.84	5.73 - 116.4	< 0.001
MetS-IDF	11.55	5.03 - 26.54	< 0.001

Bivariate logistic regression analysis estimates the odds ratio (OR) and the 95% confidence interval (CI). ATP III= Adult treatment panel of the national cholesterol program, BMI= body mass index, HOMA= Homeostatic model assessment, IDF= International diabetes federation, MetS=Metabolic syndrome.

3.3. Differences between patients by severity of NAFLD

Second, we evaluated the parameters of BMI, dyslipidemia, and MetS based on the severity of NAFLD. Therefore, the NAFLD group was subdivided into two subgroups; NAFLD-mild consisted of 44 subjects (21 women and 23 men), and NAFLD-moderate-severe consisted of 13 people (11 women and two men). As shown in Table 3, all the parameters evaluated to determine overweight and obesity were significantly higher ($p < 0.001$) in subjects with NAFLD-moderate-severe compared to individuals with mild and without NAFLD. According to the BMI value and the World Health Organization criteria, most patients with moderate and severe NAFLD had class II obesity, and only 3 had normal BMI. In contrast, the group with mild NAFLD remained in class I obesity. It was considered abdominal obesity in both subgroups because waist circumference values were higher than the cut-off point proposed by the World Health Organization [14].
In the NAFLD-moderate-severe group, mean LDL and triglyceride concentrations were higher than the reference values for the diagnosis of dyslipidemia and significantly higher than the subgroups with mild NAFLD and without the disease. Likewise, insulin resistance was present in subjects with both degrees of severity of NAFLD with HOMA values higher than 2.9. MetS determined that the percentage of people with the MetS was based on the ATP III and IDF criteria for both diagnoses. It was higher in the NAFLD-moderate and severe group ($p < 0.001$) than in people with mild and non-NAFLD. We identified more subjects with MetS in mild NAFLD with the IDF criteria considering the ATP III and IDF criteria.

3.4. Risk factors in young subjects with NAFLD

Finally, we performed the bivariate logistic regression analysis. Table 4 shows that the predictor variables with the highest risk of NAFLD are HOMA, which represents a 19 times higher risk of NAFLD due to the presence of insulin resistance; MetS, where the classification proposed by ATP III was associated with a 25 times higher risk for NAFLD; and the atherogenic risk with an OR = 20. Although cholesterol, LDL, and triglyceride levels were associated with a low risk of NAFLD (OR = 1.02, 1.04, 1.01, respectively). Likewise, the BMI (OR = 1.88 95% CI) and the waist, with each increase of one centimeter in the core, show a 31% risk of developing NAFLD in young adults.

4. Discussion

NAFLD has become the most prevalent chronic liver disease worldwide. In the present study, we found a 33.3% prevalence of NADLF in a group of 171 subjects, 77% with a mild state, and 23% with a moderate-severe form. In Mexico, a prevalence greater than 60% has been

reported in adults with a wide age range from 16 to 80 years [4], [7], [11]. Considering a majority 2.4 times higher than the world prevalence, early detection of this disease in young adults is necessary.

NAFLD is characterized by lipid disorders such as atherogenic dyslipidemia, postprandial lipemia, and HDL dysfunction [3]. Since NAFLD is a metabolic disease, it has recently been renamed Metabolism-Associated Fatty Liver Disease (MAFLD) [21]. In this study, most subjects with NAFLD presented obesity and overweight, with higher serum triglycerides, LDL, and lower HDL levels than those without NAFLD, as previously reported in selected obese patient populations [22–24]. The accumulation of lipids causes chronic inflammation in obese subjects. This excess is vital in developing NAFLD and is closely associated with dyslipidemia, insulin resistance, and central obesity [24], [25]. Also, dyslipidemia is considered a risk factor in developing progressive states of NAFLD [12]. The findings described were confirmed in our study. Also, we found that BMI, waist circumference, and atherogenic risk variables k factors for NAFLD in young overweight and obese subjects. These results agree with a meta-analysis study showing that obesity increases the risk of developing NAFLD. There is a dependent relationship between BMI and NAFLD, and waist circumference can contribute to insulin resistance and NAFLD development [26].

NAFLD is defined as a "disease characterized by excessive buildup of liver fat associated with insulin resistance" by the European Association for the Study of the Liver (EASL) [27]. Other authors have defined NAFLD as "hepatic steatosis associated with some metabolic factor" [28]. Another significant finding in this study was that subjects with both levels of severity of NAFLD had HOMA values greater than 2.9. This variable was also a predictor (OR = 19) for developing this disease. Several studies have also suggested considering the value of HOMA> 2 for diagnosing this disease [29], [30]. According to specific authors, BMI and waist circumference should be considered in clinical evaluations of individuals with a likelihood of having NAFLD, according to specific authors [31]. They were demonstrated in this study to be risk factors for young adults' development of NAFLD. Our findings support earlier research that NAFLD frequently occurs in the context of MetS. The NAFLD-positive par reveals additional FID classification problems with the FID classification. However, the ATP III classification was associated with a more significant increase (OR = 25 vs. OR = 11) in the risk than the FID classification in developing NAFLD. There is evidence that NAFLD can develop or worsen insulin resistance and MetS. Additionally, there is growing proof that insulin resistance may be a factor in developing liver injury [9,32]. Specifically, elevated levels of plasminogen activator inhibitor 1 (PAI-1), a serine protease that mediates the fibrinolytic system, are associated with obesity, insulin resistance, type 2 diabetes, and dyslipidemia [33]. Furthermore, tumor necrosis factor (TNF-α) can induce PAI-1 expression, leading to increased liver fibrosis and atherosclerosis in insulin-resistant individuals [34].

NAFLD is a multifactorial disorder with a vital genetic component, the inheritance of which ranges from 20-70% [35]. In this study, hypertension and dyslipidemia were significant in subjects with NAFLD for hereditary-antecedent. However, only the hereditary antecedent of hypertension was a risk factor for the disease. Hypertension is a multifactorial disease resulting from genetic predisposition and environmental factors. Because NAFLD is closely linked to hypertension and can be a risk factor for it on its own, insulin resistance may serve as a connection mechanism [36].

Our study has some limitations; ultrasound was first used to diagnose NAFLD; however, since liver biopsy is an invasive procedure, it was unnecessary and impossible to perform in all probable NAFLD patients. Furthermore, ultrasound is a non-invasive, risk-free procedure and a good option for clinical screening [37]. Likewise, it is essential to highlight that in this study, we identified three non-obese subjects with NADFL, as recently shown in meta-analyses and reviews highlighting that obesity should not be the only criteria for NAFLD detection [4,38].

5. Conclusion

In the asymptomatic young population, NAFLD should be avoided; we suggest that HOMA, MetS, and atherogenic risk are predictive variables for developing NAFLD in young adults.

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Conflict of interest statement

NONE

References

[1] Maurice, J.; Manousou, P. Non-Alcoholic Fatty Liver Disease. Clin Med (Lond) 2018, 18, 245–250, https://doi.org/10.7861/clinmedicine.18-3-245.
[2] Italian Association for the Study of the Liver (AISF) AISF Position Paper on Nonalcoholic Fatty Liver Disease (NAFLD): Updates and Future Directions. Dig Liver Dis 2017, 49, 471–483, https://doi.org/10.1016/j.dld.2017.01.147.
[3] Younossi, Z.M. Non-Alcoholic Fatty Liver Disease - A Global Public Health Perspective. J Hepatol 2019, 70, 531–544, https://doi.org/10.1016/j.jhep.2018.10.033.
[4] Ye, Q.; Zou, B.; Yeo, Y.H.; Li, J.; Huang, D.Q.; Wu, Y.; Yang, H.; Liu, C.; Kam, L.Y.; Tan, X.X.E.; et al. Global Prevalence, Incidence, and Outcomes of Non-Obese or Lean Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Lancet Gastroenterol Hepatol 2020, 5, 739–752, https://doi.org/10.1016/S2468-1253(20)30077-7.
[5] Day, CP; James, O.F.W. Steatohepatitis: A Tale of Two "Hits"? Gastroenterology 1998, 114, 842–845, https://doi.org/10.1016/S0016-5085(98)70599-2.
[6] Kawaguchi, T.; Tsutsumi, T.; Nakano, D.; Torimura, T. MAFLD: Renovation of Clinical Practice and Disease Awareness of Fatty Liver. Hepatol Res 2022, 52, 422–432, https://doi.org/10.1111/hepr.13706.
[7] Castro-Martínez, M.; Banderas-Lares, D.; Ramírez Martínez, J.; Escobedo de la Peña, J. Prevalencia de Hígado Graso No Alcohólico En Individuos Con Síndrome Metabólico. Cirujía y Cirujanos 2012, 80, 128–132.
[8] Tsai, C.-H.; Li, T.-C.; Lin, C.-C. Metabolic Syndrome as a Risk Factor for Nonalcoholic Fatty Liver Disease. South Med J 2008, 101, 900–905, https://doi.org/10.1097/SMJ.0b013e31817e8af9.

[9] Wainwright, P.; Byrne, C.D. Bidirectional Relationships and Disconnects between NAFLD and Features of the Metabolic Syndrome. Int J Mol Sci 2016, 17, 367, https://doi.org/10.3390/ijms17030367.

[10] Arshad, T.; Golabi, P.; Henry, L.; Younossi, Z.M. Epidemiology of Non-Alcoholic Fatty Liver Disease in North America. Curr Pharm Des 2020, 26, 993–997, https://doi.org/10.2174/1381612826666200303114934.

[11] Pimentel, J.G.; Chávez, V.J.S.; Alonso, C.G.; Lara, A.C.; Pastrana, I.R.M.; Valladares, P.C. Relación de obesidad con esteatosis hepática no alcohólica en una unidad de medicina familiar. Aten Fam 2018, 26, 8–12, https://doi.org/10.22201/facmed.14058871p.2019.1.67710.

[12] Méndez-Sánchez, N.; Cerda-Reyes, E.; Higuera-de-la-Tijera, F.; Salas-García, A.K.; Cabrera-Palma, S.; Cabrera-Álvarez, G.; Cortez-Hernández, C.; Pérez-Arredondo, L.A.; Purón-González, E.; Coronado-Alejandro, E.; et al. Dyslipidemia as a Risk Factor for Liver Fibrosis Progression in a Multicentric Population with Non-Alcoholic Steatohepatitis. F1000Res 2020, 9, 56, https://doi.org/10.12688/f1000research.21918.1.

[13] DiBonaventura, M.D.; Meincke, H.; Le Lay, A.; Fournier, J.; Bakker, E.; Ehrenreich, A. Obesity in Mexico: Prevalence, Comorbidities, Associations with Patient Outcomes, and Treatment Experiences. Diabetes Metab Syndr Obes 2017, 11, 1–10, https://doi.org/10.2147/DMSO.S129247.

[14] WHO Consultation on Obesity (1997: Geneva, S.; Diseases, WHOD of N.; World Health Organization. Programme of Nutrition, F. and RH Obesity : Preventing and Managing the Global Epidemic : Report of a WHO Consultation on Obesity, Geneva, 3-5 June 1997. 1998.

[15] Matthews, D.R.; Hosker, J.P.; Rudenski, A.S.; Naylor, B.A.; Treacher, DF; Turner, R.C. Homeostasis Model Assessment: Insulin Resistance and Beta-Cell Function from Fasting Plasma Glucose and Insulin Concentrations in Man. Diabetologia 1985, 28, 412–419, https://doi.org/10.1007/BF00280883.

[16] Alberti, KGMM; Zimmet, P.; Shaw, J. Metabolic Syndrome--a New World-Wide Definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006, 23, 469–480, https://doi.org/10.1111/j.1464-5491.2006.01858.x.

[17] Alberti, KGMM; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.-C.; James, W.P.T.; Loria, C.M.; Smith, S.C.; et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009, 120, 1640–1645, https://doi.org/10.1161/CIRCULATIONAHA.109.192644.

[18] Charatcharoenwitthaya, P.; Lindor, K.D. Role of Radiologic Modalities in the Management of Non-Alcoholic Steatohepatitis. Clinics in Liver Disease 2007, 11, 37–54, https://doi.org/10.1016/j.cld.2007.02.014.

[19] Kazemi, T.; Hajihosseini, M.; Moossavi, M.; Hemmati, M.; Ziaee, M. Cardiovascular Risk Factors and Atherogenic Indices in an Iranian Population: Birjand East of Iran. Clin Med Insights Cardiol 2018, 12, 1179546818759286, https://doi.org/10.1177/1179546818759286.

[20] Shannon, A.; Alkhouri, N.; Carter-Kent, C.; Monti, L.; Devito, R.; Lopez, R.; Feldstein, A.E.; Nobili, V. Ultrasonographic Quantitative Estimation of Hepatic Steatosis in Children With NAFLD. J Pediatr Gastroenterol Nutr 2011, 53, 190–195, https://doi.org/10.1097/MPG.0b013e31821b4b61.

[21] Eslam, M.; Sanyal, AJ; George, J.; International Consensus Panel MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology 2020, 158, 1999-2014.e1, https://doi.org/10.1053/j.gastro.2019.11.312.

[22] Martin-Rodriguez, J.L.; Gonzalez-Cantero, J.; Gonzalez-Cantero, A.; Arrebola, J.P.; Gonzalez-Calvin, J.L. Diagnostic Accuracy of Serum Alanine Aminotransferase as Biomarker for Nonalcoholic Fatty Liver Disease and Insulin Resistance in Healthy Subjects, Using 3T MR Spectroscopy. Medicine (Baltimore) 2017, 96, https://doi.org/10.1097/MD.0000000000006770.

[23] Maximos, M.; Bril, F.; Portillo Sanchez, P.; Lomonaco, R.; Orsak, B.; Biernacki, D.; Suman, A.; Weber, M.; Cusi, K. The Role of Liver Fat and Insulin Resistance as Determinants of Plasma Aminotransferase Elevation in Nonalcoholic Fatty Liver Disease. Hepatology 2015, 61, 153–160, https://doi.org/10.1002/hep.27395.

[24] Kim, D.; Touros, A.; Kim, W.R. Nonalcoholic Fatty Liver Disease and Metabolic Syndrome. Clin Liver Dis 2018, 22, 133–140, https://doi.org/10.1016/j.cld.2017.08.010.

[25] du Plessis, J.; van Pelt, J.; Korf, H.; Mathieu, C.; van der Schueren, B.; Lannoo, M.; Oyen, T.; Topal, B.; Fetter, G.; Nayler, S.; et al. Association of Adipose Tissue Inflammation With Histologic Severity of Nonalcoholic Fatty Liver Disease. Gastroenterology 2015, 149, 635-648.e14, https://doi.org/10.1053/j.gastro.2015.05.044.

[26] Li, L.; Liu, D.-W.; Yan, H.-Y.; Wang, Z.-Y.; Zhao, S.-H.; Wang, B. Obesity Is an Independent Risk Factor for Non-Alcoholic Fatty Liver Disease: Evidence from a Meta-Analysis of 21 Cohort Studies. Obes Rev 2016, 17, 510–519, https://doi.org/10.1111/obr.12407.

[27] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO) EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease. J Hepatol 2016, 64, 1388–1402, https://doi.org/10.1016/j.jhep.2015.11.004.

[28] Tokushige, K.; Ikejima, K.; Ono, M.; Eguchi, Y.; Kamada, Y.; Itoh, Y.; Akuta, N.; Yoneda, M.; Iwasa, M.; Yoneda, M.; et al. Evidence-Based Clinical Practice Guidelines for Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis 2020. J Gastroenterol 2021, 56, 951–963, https://doi.org/10.1007/s00535-021-01796-x.

[29] Salgado, A.L.F. de A.; Carvalho, L. de; Oliveira, A.C.; Santos, V.N. dos; Vieira, J.G.; Parise, E.R. Insulin Resistance Index (HOMA-IR) in the Differentiation of Patients with Non-Alcoholic Fatty Liver Disease and Healthy Individuals. Arq Gastroenterol 2010, 47, 165–169, https://doi.org/10.1590/S0004-28032010000200009.

[30] Isokuortti, E.; Zhou, Y.; Peltonen, M.; Bugianesi, E.; Clement, K.; Bonnefont-Rousselot, D.; Lacorte, J.-M.; Gastaldelli, A.; Schuppan, D.; Schattenberg, J.M.; et al. Use of HOMA-IR to Diagnose Non-Alcoholic Fatty Liver Disease: A Population-Based and Inter-Laboratory Study. Diabetologia 2017, 60, 1873–1882, https://doi.org/10.1007/s00125-017-4340-1.

[31] Chitturi, S.; Farrell, G.C.; Hashimoto, E.; Saibara, T.; Lau, G.K.K.; Sollano, J.D.; Asia-Pacific Working Party on NAFLD Non-Alcoholic Fatty Liver Disease in the Asia-Pacific Region: Definitions and Overview of Proposed Guidelines. J Gastroenterol Hepatol 2007, 22, 778–787, https://doi.org/10.1111/j.1440-1746.2007.05001.x.

[32] Adams, L.A.; Sanderson, S.; Lindor, K.D.; Angulo, P. The Histological Course of Nonalcoholic Fatty Liver Disease: A Longitudinal Study of 103 Patients with Sequential Liver Biopsies. J Hepatol 2005, 42, 132–138, https://doi.org/10.1016/j.jhep.2004.09.012.

[33] Bayomy, O.; Rao, A.D.; Garg, R.; Vaidya, A.; Kotin, A.R.; Reiber, B.; Nijmeijer, S.; Di Carli, M.F.; Jerosch-Herold, M.; Kwong, R.Y.; et al. Plasminogen Activator Inhibitor-1 and Pericardial Fat in Individuals with Type 2 Diabetes Mellitus. Metab Syndr Relat Disord 2017, 15, 269–275, https://doi.org/10.1089/met.2017.0031.

[34] Takeshita, Y.; Takamura, T.; Hamaguchi, E.; Shimizu, A.; Ota, T.; Sakurai, M.; Kaneko, S. Tumor Necrosis Factor-Alpha-Induced Production of Plasminogen Activator Inhibitor 1 and Its Regulation by Pioglitazone and Cerivastatin in a Nonmalignant Human Hepatocyte Cell Line. Metabolism 2006, 55, 1464–1472, https://doi.org/10.1016/j.metabol.2006.06.016.

[35] Sookoian, S.; Pirola, C.J. Genetic Predisposition in Nonalcoholic Fatty Liver Disease. Clin Mol Hepatol 2017, 23, 1–12, https://doi.org/10.3350/cmh.2016.0109.

[36] Zhao, Y.-C.; Zhao, G.-J.; Chen, Z.; She, Z.-G.; Cai, J. Nonalcoholic Fatty Liver Disease: An Emerging Driver of Hypertension - PubMed. Hypertension 2020, 2, 275–284, https://doi.org/10.1161/HYPERTENSIONAHA.119.13419.

[37] Isaksen, V.T.; Larsen, M.A.; Goll, R.; Florholmen, J.R.; Paulssen, E.J. Hepatic Steatosis, Detected by Hepatorenal Index in Ultrasonography, as a Predictor of Insulin Resistance in Obese Subjects. BMC Obes 2016, 3, https://doi.org/10.1186/s40608-016-0118-0.

[38] Hu, P.-F.; Zeng, X.; Zou, Z.-Y.; Tang, W.; Guo, Y.-B.; Yuan, Z.-L.; Shi, P.-M.; Tan, Y.; Song, Y.; Shi, Y.-Q.; et al. The Presence of NAFLD in Nonobese Subjects Increased the Risk of Metabolic Abnormalities than Obese Subjects without NAFLD: A Population-Based Cross-Sectional Study. Hepatobiliary Surg Nutr 2021, 10, 811–824, https://doi.org/10.21037/hbsn-20-263.