eISSN 2255-0569

ORIGINAL

Relationship between atherogenic dyslipidemia and lipid triad with scales that assess non alcoholic liver disease in 418,343 spanish workers

Relación entre la dislipemia aterogínca y la tríada lipídica con el hígado graso no alcohólico en 418.343 Trabajadores españoles

José Ignacio Ramírez-Manent[1,2,3,4], Pilar Tomás-Gil[4], Josep Lluis Coll Villalonga[4], Pau Marti-Lliteras[4], Ángel Arturo López-González[2,4,5], Hernán Paublini[4]

1. Faculty of Medicine, University of the Balearic Islands, 07009 Palma, Balearic Islands, Spain
2. IDISBA, Balearic Islands Health Research Institute Foundation, 07004 Palma, Balearic Islands, Spain
3. General Practitioner Department, Balearic Islands Health Service, 07003 Palma, Balearic Islands, Spain
4. Investigation Group ADEMA SALUD IUNICS, 07003 Palma, Balearic Islands, Spain
5. Faculty of Dentistry, University School ADEMA, 07009 Palma, Balearic Islands, Spain

Corresponding author
Ángel Arturo López González
E-mail: angarturo@gmail.com

Received: 28 - VI - 2023
Accepted: 31 - VII - 2023

doi: 10.3306/AJHS.2023.38.06.66

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent hepatic pathology in the world today. Different biochemical processes are involved in NAFLD thus, in steatosis there is an accumulation of triglycerides in the hepatocytes. NAFLD is associated with alterations in lipoprotein metabolism similar to the atherogenic dyslipidemia (AD) observed in conditions with insulin resistance, such as obesity and diabetes. The aim of this study was to determine the relationship between AD and lipid triad (LT) and different risk scales for NAFLD in a group of Spanish workers.

Methods: A descriptive, cross-sectional study in 418,343 Spanish workers, in which different anthropometric parameters, different risk scales for NAFLD, AD and LT were evaluated. And we have proceeded to relate these last two parameters with the different NAFLD formulas. In the univariate analysis, the t-student test was used, when the variables were quantitative, calculating the mean and the standard deviation. When the variables were qualitative, the chi-square test was applied and the prevalences were calculated. The possible usefulness of the NAFLD risk scales to be able to predict the appearance of AD and LT was assessed using ROC curves, obtaining the area under the curve (AUC) and the cut-off points.

Results: The mean values of all the NAFLD risk scales used show higher values in persons with AD and LT, both in men and in women. In the analysis of the ROC curves, we found that all the formulas used to assess the risk of fatty liver present a good AUC in both sexes, both for predicting AD and for the LT, with the exception of the HSI, which presents an AUC that would be evaluated as regular.

Conclusions: There are higher mean values and prevalence of elevated values for all different NAFLD risk scales in persons with AD and LT.

Key words: Non-alcoholic Fatty Liver Disease, Atherogenic dyslipidemia, Lipid triad.

Resumen

Antecedentes: La enfermedad del hígado graso no alcohólico (NAFLD) es la patología hepática más prevalente en el mundo actual. En la NAFLD intervienen distintos procesos bioquímicos, así, en la esteatosis se produce una acumulación de triglicéridos en los hepatocitos. La NAFLD se asocia a alteraciones en el metabolismo de las lipoproteínas similares a la dislipidemia aterogénica (DA) observada en condiciones de resistencia a la insulina, como la obesidad y la diabetes. El objetivo de este estudio fue determinar la relación entre la DA y la tríada lipídica (LT) y diferentes escalas de riesgo de NAFLD en un grupo de trabajadores españoles.

Métodos: Estudio descriptivo, transversal, en 418.343 trabajadores españoles, en el que se han evaluado diferentes parámetros antropométricos, diferentes escalas de riesgo para NAFLD, DA y TL y se ha procedido a relacionar estos dos últimos parámetros con las diferentes fórmulas de NAFLD. En el análisis univariante se utilizó la prueba t-student, cuando las variables eran cuantitativas, calculando la media y la desviación típica. Cuando las variables eran cualitativas, se aplicó el test de chi-cuadrado y se calcularon las prevalencias. La posible utilidad de las escalas de riesgo de NAFLD para poder predecir la aparición de DA y TL se valoró mediante curvas ROC, obteniendo el área bajo la curva (AUC) y los puntos de corte.

Resultados: Los valores medios de todas las escalas de riesgo de NAFLD utilizadas muestran valores más elevados en las personas con DA y TL, tanto en hombres como en mujeres. En el análisis de las curvas ROC, encontramos que todas las fórmulas utilizadas para valorar el riesgo de hígado graso presentan un buen AUC en ambos sexos, tanto para predecir la DA como para el TL, a excepción del HSI, que presenta un AUC que sería valorado como regular.

Conclusiones: Existen mayores valores medios y prevalencia de valores elevados para las diferentes escalas de riesgo de NAFLD en personas con DA y TL.

Palabras clave: Enfermedad de Hígado Graso no Alcohólica, Dislipemia aterogénica, Tríada lipídica.

Cite as: Ramírez-Manent JI, Tomás-Gil P , Coll-Villalonga JL , Marti-Lliteras P, López-González AA, Paublini H. Relationship between atherogenic dyslipidemia and lipid triad with scales that assess non alcoholic liver disease in 418,343 spanish workers. *Academic Journal of Health Sciences 2023*; 38 (6):66-73 doi: 10.3306/AJHS.2023.38.06.66

Introduction

Atherosclerosis is an anatomopathological alteration characterized by the accumulation of lipids in the walls of medium and large calibre arteries[1]. In its genesis we find a prolonged inflammation of the arterial wall due to an increased susceptibility to oxidation by free radicals of low density lipoproteins (LDL cholesterol)[2]. This oxidized LDL binds to monocytes and both adhere to the arterial intimal layer causing an important inflammatory response that is responsible for the transformation of these monocytes into macrophages. When LDL levels are elevated, these macrophages will not be able to eliminate it and will be transformed into cells highly loaded with cholesterol, which will be responsible for the formation of atheromatous plaque[3]. At present, lipoproteins rich in triglycerides (TRLs) have also been included in this process, which also cause endothelial dysfunction and inflammation in the vessel wall, and favour atherogenic changes in LDL lipoproteins[4] This whole process develops silently and slowly and will only manifest itself clinically when it is at a very advanced stage[5]. For this reason, it is essential to make a diagnosis as early as possible, mainly in the so-called subclinical atheromatosis phase[6] in which the process can still be controlled and thus reduce cardiovascular risk.

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent hepatic pathology in the world today[7] and encompasses a series of pathological entities ranging from the simple and generally asymptomatic accumulation of fat in the hepatocytes (steatosis)[8] through an inflammatory condition (steatohepatitis)[9] to a process of fibrosis of variable intensity that can lead to liver cirrhosis[10] and even hepatocarcinoma[11]. Different biochemical processes are involved in NAFLD[12]; thus, in steatosis there is an accumulation of triglycerides in the hepatocytes. This accumulation may be due to a decrease in the synthesis of very low density lipoproteins (VLDL) and an increase in the synthesis of triglycerides in the liver, possibly caused by a decrease in the oxidation of fatty acids or by an increase in the transport of free fatty acids to the liver. Steatohepatitis seems to be due to lipoperoxidative damage of hepatocyte membranes which, if prolonged over time, can stimulate hepatic stellate cells causing a fibrotic picture (cirrhosis) that could become malignant (hepatocarcinoma)[13].

At present we do not know whether NAFLD is associated with atherosclerosis due to common risk factors or whether NAFLD independently increases the occurrence of atherosclerosis[14]. Inflammation of visceral fat, especially in NAFLD, causes a release of inflammatory cytokines and adipokines[15-17] and further increases insulin resistance (IR)[17-19]. This inflammatory picture, in addition to worsening liver disease, will increase the secretion of procoagulant and antifibrinolytic agents that play a fundamental role in the genesis and development of atherosclerosis[20,21].

NAFLD is associated with alterations in lipoprotein metabolism similar to the atherogenic dyslipidemia observed in conditions with insulin resistance, such as obesity and diabetes[22-24], and cardiovascular disease[17], which is the leading cause of death in patients with NAFLD[25,26].

In recent years, several studies have found a relationship between the plasma atherogenic index and NAFLD regardless of obesity[27-29].

Based on the above, we can propose that NAFLD would be a marker of cardiovascular risk that could be expressed by elements of subclinical atherosclerosis: early atheroma plaques, flow-mediated vasodilatation, and increased carotid intima media thickness.

The aim of this study was to determine the relationship between dyslipidemia and lipid triad and different risk scales for NAFLD in a group of Spanish workers.

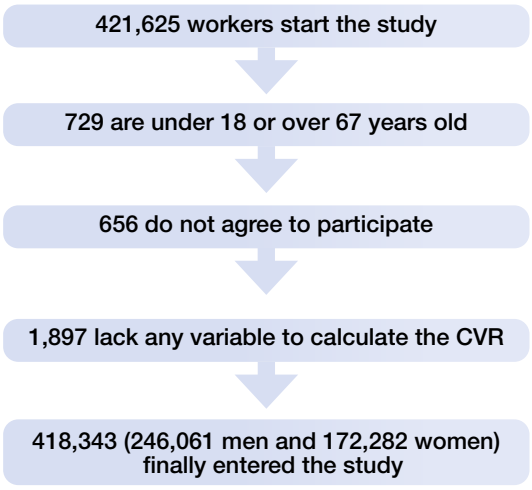
Methods

A descriptive, cross-sectional study was conducted between January 2019 and June 2020 in 418,343 Spanish workers (172,282 women and 246,061 men), from different areas of Spain and belonging to various employment sectors, essentially hospitality, construction, commerce, health, public administration, transport, education, industry and cleaning. The workers were selected from those who attended occupational medical examinations.

The inclusion criteria were:
- To be between 18 and 69 years old.
- Belonging to one of the companies included in the study.
- Agreeing to participate in the study.

The flow diagram is shown in **figure 1**.

Figure 1: flow chart.



Determination of variables

All the variables (anthropometric, clinical and analytical) were determined by the different health professionals of the different companies. In an attempt to reduce interobserver bias, all the measurement processes were standardized.

With the person standing and the abdomen relaxed, waist circumference was measured by placing the tape measure at the level of the last rib and parallel to the floor.

Blood pressure was obtained after a rest period of at least 10 minutes while the person was seated and three determinations were made. The mean result pressure was obtained with the person seated and after a rest period of at least 10 minutes. Three determinations were made and the mean of the three was obtained. An OMRON M3 sphygmomanometer was used for this determination.

The analytical parameters were obtained by venipuncture after prolonged fasting (at least 12 hours) and applying different techniques: enzymatic for cholesterol, triglycerides and glycemia and precipitation with dextran sulfate Cl2Mg for HDL. LDL values were obtained by indirect methods applying the Friedewald formula. All parameters were expressed in mg/dL.

Different NAFLD and risk scales were calculated:

- Fatty liver index (FLI)[30]

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) \times 100$$

Low risk <30, moderate 30-59 high risk ≥ 60

- Hepatic steatosis index (HSI)[31]
8 × AST/ALT + BMI + 2 if diabetes + 2 if woman. Low risk <30, moderate 30-59, high risk ≥ 36.

- Zhejiang University index (ZJU index)[32]
BMI + Glycaemia (mmol L) + Triglycerides (mmol L) +3 AST/ALT +2 if woman.
Low risk < 32, moderate 32-37,9 high ≥ 38.

- Fatty liver disease index (FLD)[33]
BMI+ Triglycerides + 3 × (AST/ALT) +2 × Hyperglycaemia (present=1; absent=0).
Low risk < 28, moderate 28-36,9 high ≥ 37.

- Framingham steatosis index (FSI)[34]
FSI = -7,981 + 0,011 x age – 0,146 x sex (woman =1, man =0) + 0,173 x BMI + 0,007 x triglycerides + 0,593 x hypertensión (yes = 1, no = 0) + 0,789 x diabetes (yes = 1, no = 0) + 1,1 x AST/ALT ratio ≥ 1,33 (yes = 1, no = 0)

- Korean steatosis index (KSI)[35]
- Lipid accumulation product (LAP)[36]
Men: (waist (cm) - 65) x (triglycerides (mMol)). Women: (waist (cm) - 58) x (triglycerides (mMol)). High risk ≥ 42.7

Atherogenic dyslipidemia was defined as the coexistence of triglyceride values above 150mg/dL with low HDL values (less than 40mg/dL in men and less than 50 mg/dL in women) and normal LDL values. If LDL values higher than 160 mg/dL were also added, a lipid triad was considered[37].

If the person had consumed at least one cigarette daily (or its equivalent in other forms of consumption) in the last 30 days or had quit smoking less than one year ago, the person was considered to be a smoker.

Based on the 2011 National Classification of Occupations (CNO-11) and taking into account the criteria of the Spanish Society of Epidemiology38, three social classes were determined: I. Managers, university professionals, athletes and artists; II. Intermediate occupations; III. Manual workers.

Ethical considerations and aspects

The ethical standards of the institutional research committee and the 2013 Declaration of Helsinki were respected throughout the study. Anonymity and confidentiality of the data collected could be guaranteed at all times. The study had the approval of the Research Ethics Committee of the Balearic Islands (CEI-IB): IB 4383/20. The data of each of the workers included in the study were coded and only the person responsible for the study could know the identity of each person. The research team undertook to comply strictly with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study the exercise of the rights of access, rectification, cancellation and opposition of the data collected.

Statistical analysis

In the univariate analysis, the t-student test was used, when the variables were quantitative, calculating the mean and the standard deviation. When the variables were qualitative, the chi-square test was applied and the prevalences were calculated. The possible usefulness of the non-alcoholic fatty liver risk scales to be able to predict the appearance of atherogenic dyslipidemia and lipid triad was assessed using ROC curves, obtaining the area under the curve (AUC) and the cut-off points with their sensitivity, specificity and Youden's index. Multivariate analysis was performed using multinomial logistic regression. Statistical analysis was performed using the SPSS 28.0 program, with $p<0.05$ being the accepted level of statistical significance.

Results

Table I shows that slightly more than 58% of the people included in the study were men. The average age is 40 years, with the majority grouped between 30 and 49 years of age. Slightly more than 75% of the people belong to social class III and slightly more than 33% are smokers. The clinical and analytical variables show more favourable values in women.

Table II shows that the mean values of all the non-alcoholic fatty liver disease risk scales used show higher values in persons with atherogenic dyslipidemia and lipid triad, both in men and in women.

Table III shows the same trend regarding the prevalence of high-risk values for non-alcoholic fatty liver disease with all the scales used.

Table IV shows the results of the multinomial logistic regression according to which the risk of developing atherogenic dyslipidemia and lipid triad taking into account the values of the different non-alcoholic fatty liver disease risk scales is considerably higher in persons at high risk. The highest ORs correspond to LAP.

Figure 2 and **table V** show the results of the ROC curves. The highest areas under the curve were found for the triglyceride/HDL scale with values very close to 1.

Table I: Characteristics of the population.

	Women n=172,282 Mean (SD)	Men n=246,061 Mean (SD)	Total n=418,343 Mean (SD)	p-value
Age (years)	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height (cm)	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight (kg)	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
Waist circumference (cm)	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP (mmHg)	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP (mmHg)	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Total colesterol (mg/dL)	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c (mg/dL)	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c (mg/dL)	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides (mg/dL)	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycaemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
ALT (U/L)	20.2 (13.6)	31.0 (20.2)	26.6 (18.6)	<0.0001
AST (U/L)	18.2 (7.9)	24.4 (13.3)	21.7 (11.7)	<0.0001
GGT (U/L)	20.4 (19.7)	35.8 (39.3)	29.6 (33.6)	<0.0001
	%	%	%	p
18-29 years	20.7	18.8	19.6	
30-39 years	29.7	27.6	28.4	
40-49 years	29.6	30.1	29.9	
50-70 years	20.0	23.6	22.2	
Social class I	6.9	4.9	5.7	
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
Non-smokers	67.2	66.6	66.9	
Smokers	32.8	33.4	33.2	

SBP systolic blood pressure. DBP diastolic blood pressure. HDL-c high density lipoprotein-cholesterol. LDL-c low density lipoprotein-cholesterol. ALT aspartate transaminase. ALT alanine transaminase GGT gammaglutamyl transferase.

Table II: Mean values of NAFLD and liver fibrosis risk scales according presence or absence of atherogenic dyslipidemia and lipid triad by sex.

	Women			Men		
	Non AD n=165,431	Yes AD n=6,851		Non AD n=227,030	Yes AD n=19,031	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
FLI	16.7 (20.1)	56.4 (27.7)	<0.0001	34.6 (25.6)	76.0 (20.0)	<0.0001
HSI	36.0 (6.7)	42.0 (7.4)	<0.0001	36.4 (6.6)	41.8 (7.0)	<0.0001
ZJU	36.6 (5.9)	43.8 (6.9)	<0.0001	36.7 (5.4)	43.0 (6.0)	<0.0001
FLD	29.8 (5.7)	36.4 (6.5)	<0.0001	31.7 (5.2)	37.4 (5.5)	<0.0001
FSI	0.1 (0.1)	0.4 (0.2)	<0.0001	0.2 (0.2)	0.5 (0.2)	<0.0001
KSI	1.9 (1.5)	2.1 (1.1)	<0.0001	2.8 (1.5)	4.4 (1.01)	<0.0001
LAP	16.3 (14.4)	60.8 (39.3)	<0.0001	27.5 (26.5)	82.8 (54.9)	<0.0001
	Non LT n=170,566	Yes LT n=1,716	p-value	Non LT n=240,669	Yes LT n=5,392	p-value
FLI	17.9 (21.4)	55.1 (27.6)	<0.0001	37.0 (27.0)	78.5 (19.1)	<0.0001
HSI	36.2 (6.9)	41.1 (6.9)	<0.0001	36.7 (6.7)	41.5 (6.8)	<0.0001
ZJU	36.8 (6.1)	43.5 (6.6)	<0.0001	37.0 (5.6)	43.8 (6.3)	<0.0001
FLD	30.0 (5.9)	35.9 (6.1)	<0.0001	31.9 (5.3)	38.0 (5.7)	<0.0001
FSI	0.1 (0.2)	0.4 (0.3)	<0.0001	0.2 (0.2)	0.5 (0.3)	<0.0001
KSI	2.0 (1.5)	3.9 (1.0)	<0.0001	2.8 (1.5)	4.5 (1.0)	<0.0001
LAP	17.6 (17.0)	64.0 (51.1)	<0.0001	30.3 (29.5)	99.5 (82.0)	<0.0001

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham steatosis index. KSI Korean steatosis index LAP Lipid accumulation product. AD atherogenic dyslipidemia. LT lipid triad.

Table III: Prevalence of high values of NAFLD and liver fibrosis risk scales according presence or absence of atherogenic dyslipidemia and lipid triad by sex.

	Women			Men		
	Non AD n=165,431	Yes AD n=6,851		Non AD n=227,030	Yes AD n=19,031	
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
FLI high	6.1	49.2	<0.0001	19.6	80.2	<0.0001
HSI high	43.2	78.9	<0.0001	47.4	80.0	<0.0001
ZJU high	33.5	79.7	<0.0001	35.3	80.5	<0.0001
FLD high	42.9	48.5	<0.0001	44.3	47.3	<0.0001
KSI high	48.9	88.1	<0.0001	67.6	96.1	<0.0001
LAP high	21.9	86.9	<0.0001	31.7	92.8	<0.0001
	Non LT n=170,566	**Yes LT n=1,716**	**p-value**	**Non LT n=240,669**	**Yes LT n=5,392**	**p-value**
FLI high	23.0	83.6	<0.0001	7.4	46.3	<0.0001
HSI high	44.4	77.8	<0.0001	49.1	79.0	<0.0001
ZJU high	35.0	79.0	<0.0001	37.6	83.3	<0.0001
FLD high	44.4	55.3	<0.0001	45.6	57.4	<0.0001
KSI high	50.3	92.3	<0.0001	69.1	96.8	<0.0001
LAP high	23.9	85.7	<0.0001	35.2	92.4	<0.0001

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. KSI Korean steatosis index. LAP Lipid accumulation product AD atherogenic dyslipidemia. LT lipid triad.

Table IV: Multinomial logistic regression.

	Atherogenic dyslipidemia	Lipid triad
	OR (95% CI)	OR (95% CI)
FLI low	1	1
FLI moderate	1.81 (1.65-1.99)	1.97 (1.64-2.36)
FLI high	2.09 (1.81-2.41)	2.09 (1.57-2.77)
HSI low	1	1
HSI moderate	1.45 (1.37-1.52)	1.53 (1.46-1.60)
HSI high	1.63 (1.52-1.71)	1.70 (1.62-1.79)
ZJU normal	1	1
ZJU high	1.88 (1.64-2.17)	2.46 (1.87-3.25)
FLD normal	1	1
FLD high	1.27 (1.20-1.33)	1.23 (1.10-1.35)
KSI normal	1	1
KSI high	2.81 (2.26-3.48)	2.97 (1.91-4.60)
LAP normal	1	1
LAP high	7.64 (6.65-8.78)	6.28 (4.73-8.33)

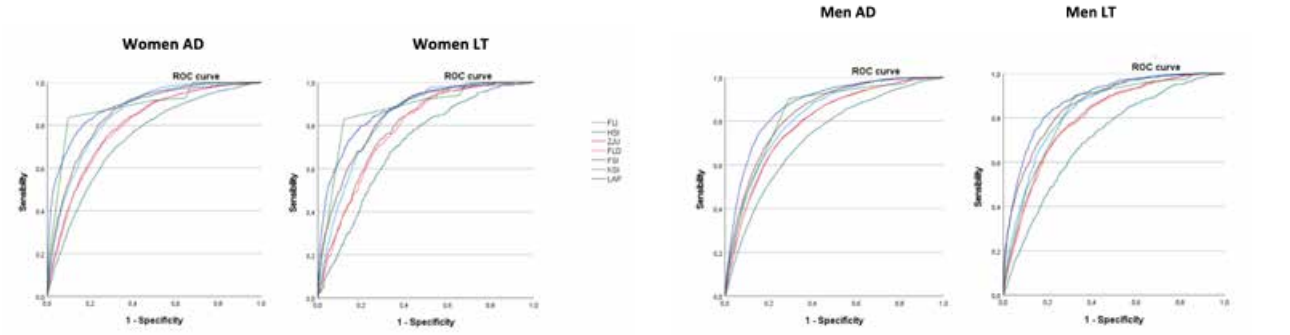
FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index.
FLD Fatty liver disease. KSI Korean steatosis index. LAP Lipid accumulation product.
AD atherogenic dyslipidemia. LT lipid triad.

Table V: Areas under the curve and cutoff points of the different NAFLD risk scales for predicting atherogenic dyslipidemia and lipid triad.

	Women AD	Women LT
	AUC-cutoff-sensib-specif-Youden index	AUC-cutoff-sensib-specif-Youden index
FLI	0.850 (0.842-0.859)-24-77.7-76.2-0.539	0.834 (0.818-0.851)-24-77.5-74.5-0.520
HSI	0.739 (0.726-0.752)-38.1-69.3-68.3-0.376	0.709 (0.685-0.733)-38.1-67.3-67.3-0.346
ZJU	0.800 (0.789-0.811)-39.2-73.8-72.8-0.466	0.788 (0.768-0.807)-39.2-73.1-71.3-0.444
FLD	0.794 (0.783-0.805)-32.2-72.8-72.4-0.452	0.778 (0.758-0.798)-32.2-71.0-71.0-0.420
FSI	0.856 (0.847-0.865)-0.17-80.8-80.5-0.613	0.846 (0.829-0.864)-0.17-78.7-74.2-0.529
KSI	0.885 (0.875-0.895)-3-87.5-71.7-0.592	0.874 (0.855-0.893)-3-87.7-68.8-0.565
LAP	0.888 (0.878-0.898)-27.9-81.7-81.7-0.634	0.875 (0.855-0.894)-27.9-79.9-79.6-0.595
	Men AD	**Men LT**
FLI	0.824 (0.817-0.831)-55.9-74.9-74.5-0.494	0.840 (0.827-0.853)-61-76.6-76.3-0.529
HSI	0.729 (0.719-0.738)-38.1-69.0-66.2-0.352	0.707 (0.688-0.726)-38.4-66.4-66.0-0.324
ZJU	0.794 (0.786-0.803)-39.2-73.5-72.6-0.461	0.802 (0.787-0.818)-39.7-74.0-73.9-0.479
FLD	0.792 (0.783-0.800)-34.0-73.2-72.4-0.456	0.796 (0.781-0.812)-34.5-74.0-73.2-0.472
FSI	0.838 (0.831-0.845)-0.25-76.5-75.9-0.524	0.861 (0.848-0.874)-0.25-83.2-73.4-0.566
KSI	0.835 (0.828-0.842)-3-93.2-51.5-0.447	0.827 (0.812-0.841)-3-93.5-52.5-0.460
LAP	0.871 (0.865-0.877)-44-79.9-79.9-0.598	0.880-(0.867-0.892)-47-81.7-81.7-0.634

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. KSI Korean steatosis index. LAP Lipid accumulation product AD atherogenic dyslipidemia. LT lipid triad. AUC área under the curve. Sensib sensibility. Specif specificity.

Figure 2: ROC curve.



FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. KSI Korean steatosis index. LAP Lipid accumulation producto AD atherogenic dyslipidemia. LT lipid triad.

Discussion

The present study was performed in 418,343 workers from different autonomous communities of Spain (Balearic Islands, Canary Islands, Andalusia Valencian Community, Madrid, Catalonia, Castilla y León, Castilla La Mancha, and Basque Country) belonging mainly to labour sectors of public administration, health, construction, and commerce. The participants were selected from labour medical examinations between the months of January 2019 and June 2020 of the different companies that participated in the study.

In the sample (**Table I**) it stands out that a third of the population were smokers, with an equal distribution between men and women. More than half of the sample is between 30 and 49 years of age, and 80% of the men correspond to social class III. And the average of the clinical and analytical variables presents more favourable results in women.

When evaluating the mean values of NAFLD and liver fibrosis according to different risk scales (FLI, HSI, ZJU, FLD, FSI, KSI, LAP) and their correlation with the presence or absence of atherogenic dyslipidemia, we found a close relationship between the population with atherogenic dyslipidemia and all formulas evaluated for the risk of NAFLD and liver fibrosis. With highly significant differences between the group of women with atherogenic dyslipidemia compared to the group that did not present it (all values p<0.0001). The same results can be observed in the sample that corresponds to the male population. Other authors found a relationship between NAFLD and atherogenic dyslipidemia assessed by other means, however not in such large samples nor in statistical significance as in our study[39-41].

In that same table (**Table II**) we have reflected the results obtained between the relationship of presenting Lipid triad and the risk of NAFLD and liver fibrosis evaluated with the same formulas. The results are identical to those obtained for atherogenic dyslipidemia. With a link between the Lipid triad and the risk of NAFLD and liver fibrosis with high statistical significance, values p<0.0001 in all formulas and for both sexes. This association between NAFLD and liver fibrosis with elevated lipid levels has also been described by other autors[40-42].

At present, some studies have found a difference between the sexes in the relationship between atherogenic dyslipidemia and NAFLD[43,45]. Given the results obtained, we wanted to assess the prevalence of high values of NAFLD and liver fibrosis risk scales according to the presence or absence of atherogenic dyslipidemia and lipid triad by sex (Table 3). We have been able to verify that shows the same trend regarding the prevalence of high-risk values for non-alcoholic fatty liver disease with all the scales used. This coincides with the study carried out by Li et al28.

In the multinomial logistic regression for the low, moderate and high risks of the different formulas studied, we have obtained that both the presence of atherogenic dyslipidemia and the Lipid triad are related to a higher risk in all the evaluated formulas. With an OR ranging between 1.27 (FLD High) and 7.64 (LAP High) for atherogenic dyslipidemia, and between 1.23 (FLD High) and 6.28 (LAP High) for the Lipid triad, all with a narrow 95% confidence interval.

In the analysis of the ROC curves, we found that all the formulas used to assess the risk of fatty liver present a good AUC (range between 0.794 and 0.888) in women to predict atherogenic dyslipidemia, with the exception of the HSI, which presents an AUC of 0.739. and therefore it would be valued as regular. It presents the same behaviour in its male partners, where the AUC oscillates between 0.792 and 0.871, with also regular results for the HSI, which obtains an AUC value of 0.729.

In the assessment of the AUC of the ROC curves for the predictive value of the Lipid triad, the results are

very similar with AUC values ranging between 0.778 and 0.875 for women, and between 0.796 and 0.880 for men. Except for the HSI formula which again offers regular results in both sexes.

If we examine the results, we find that the highest AUC for atherogenic dyslipidemia occurs with LAP in both men and women, and that it is these results that are also accompanied by a better Younden index. This indicates a lower probability of error in the test. When evaluating the different formulas to estimate the predictive value of the Lipid triad, the one that offers the best results in both sexes is again LAP with the highest AUC results and a Younden index of 0.634 for men and 0.595 in women.

Although the relationship between NAFLD and the atherogenic dyslipidemia and Lipid triad is known, the Gold Standard for the diagnosis of NAFLD continues to be liver biopsy. We wanted to demonstrate the validity of 7 formulas for the indirect assessment of NAFLD with the prediction of atherogenic dyslipidemia and Lipid triad. This allows us to have a non-aggressive method to predict these events and to be able to establish the appropriate preventive treatment.

Strengths and limitations

The main strengths of our research are the large sample size, which exceeds 418,000 workers, and seven different NAFLD risk scales analysed.

The main limitation is that NAFLD was not determined by objective tests but by risk scales.

Conclusions

There are higher mean values and prevalence of elevated values for all different NAFLD risk scales in persons with atherogenic dyslipidemia and lipid triad.
In the ROC curves, we observed that all scales NAFLD risk scales allow us to adequately classify the presence of atherogenic dyslipidemia and lipid triad, with the highest areas under the curve for the LAP scale.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Libby P. The changing landscape of atherosclerosis. Nature. 2021 Apr;592(7855):524-533. doi: 10.1038/s41586-021-03392-8.

2. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X,et al. Research Progress on the Relationship between Atherosclerosis and Inflammation. Biomolecules. 2018 Aug 23;8(3):80. doi: 10.3390/biom8030080.

3. Mitra S, Deshmukh A, Sachdeva R, Lu J, Mehta JL. Oxidized low-density lipoprotein and atherosclerosis implications in antioxidant therapy. Am J Med Sci. 2011 Aug;342(2):135-42. doi: 10.1097/MAJ.0b013e318224a147.

4. Castillo-Núñez Y, Morales-Villegas E, Aguilar-Salinas CA. Triglyceride-Rich Lipoproteins: Their Role in Atherosclerosis. Rev Invest Clin. 2022 Mar 15;74(2):061-070. doi: 10.24875/RIC.21000416. PMID: 34759386.

5. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019 Aug 16;5(1):56. doi: 10.1038/s41572-019-0106-z.

6. Ahmadi A, Argulian E, Leipsic J, Newby DE, Narula J. From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Sep 24;74(12):1608-1617. doi: 10.1016/j.jacc.2019.08.012.

7. 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 Sep;7(9):851-861. doi: 10.1016/S2468-1253(22)00165-0.

8. Idilman IS, Ozdeniz I, Karcaaltincaba M. Hepatic Steatosis: Etiology, Patterns, and Quantification. Semin Ultrasound CT MR. 2016 Dec;37(6):501-510. doi: 10.1053/j.sult.2016.08.003.

9. Romero-Gómez M. Non-alcoholic steatohepatitis. Med Clin (Barc). 2022 Oct 28;159(8):388-395. English, Spanish. doi: 10.1016/j.medcli.2022.06.017.

10. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. Lancet. 2021 Oct 9;398(10308):1359-1376. doi: 10.1016/S0140-6736(21)01374-X.

11. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021 Jan 21;7(1):6. doi: 10.1038/s41572-020-00240-3.

12. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021 Jun 5;397(10290):2212-2224. doi: 10.1016/S0140-6736(20)32511-3.

13. Scavo MP, Depalo N, Rizzi F, Carrieri L, Serino G, Franco I, et al. Exosomal FZD-7 Expression Is Modulated by Different Lifestyle Interventions in Patients with NAFLD. Nutrients. 2022 Mar 8;14(6):1133. doi: 10.3390/nu14061133.

14. Tsai TY, Hsu PF, Wu CH, Huang SS, Chan WL, Lin SJ, et al. Association between Coronary Artery Plaque Progression and Liver Fibrosis Biomarkers in Population with Low Calcium Scores. Nutrients. 2022 Jul 30;14(15):3163. doi: 10.3390/nu14153163.

15. Sookoian S, Pirola CJ. Nonalcoholic Fatty Liver Disease Progresses into Severe NASH when Physiological Mechanisms of Tissue Homeostasis Collapse. Ann Hepatol. 2018 Mar 1;17(2):182-186. doi: 10.5604/01.3001.0010.8631. PMID: 29469051.

16. Nier A, Huber Y, Labenz C, Michel M, Bergheim I, Schattenberg JM. Adipokines and Endotoxemia Correlate with Hepatic Steatosis in Non-Alcoholic Fatty Liver Disease (NAFLD). Nutrients. 2020 Mar 5;12(3):699. doi: 10.3390/nu12030699. PMID: 32151020; PMCID: PMC7146245.

17. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: An update. Metabolism. 2016 Aug;65(8):1109-23. doi: 10.1016/j.metabol.2016.05.003. Epub 2016 May 13. PMID: 27237577.

18. Tanase DM, Gosav EM, Costea CF, Ciocoiu M, Lacatusu CM, Maranduca MA, et al. The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD). J Diabetes Res. 2020 Jul 31;2020:3920196. doi: 10.1155/2020/3920196.

19. George ES, Georgousopoulou EN, Mellor DD, Chrysohoou C, Pitsavos C, Panagiotakos DB. Exploring the Path of Mediterranean Diet, Non-Alcoholic Fatty Liver Disease (NAFLD) and Inflammation towards 10-Year Cardiovascular Disease (CVD) Risk: The ATTICA Study 10-Year Follow-Up (2002-2012). Nutrients. 2022 Jun 7;14(12):2367. doi: 10.3390/nu14122367. PMID: 35745097; PMCID: PMC9229573.

20. Parise ER. Nonalcoholic fatty liver disease (NAFLD), more than a liver disease. Arq Gastroenterol. 2019 Sep 30;56(3):243-245. doi: 10.1590/S0004-2803.201900000-45.

21. Tripodi A, Fracanzani AL, Primignani M, Chantarangkul V, Clerici M. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. J Hepatol. 2014 Jul;61(1):148-54. doi: 10.1016/j.jhep.2014.03.013.

22. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. Gut. 2020 Sep;69(9):1691-1705. doi: 10.1136/gutjnl-2020-320622.

23. Vural H, Armutcu F, Akyol O, Weiskirchen R. The potential pathophysiological role of altered lipid metabolism and electronegative low-density lipoprotein (LDL) in non-alcoholic fatty liver disease and cardiovascular diseases. Clin Chim Acta. 2021 Dec;523:374-379. doi: 10.1016/j.cca.2021.10.018.

24. Babu AF, Csader S, Lok J, Gómez-Gallego C, Hanhineva K, El-Nezami H, et al. Positive Effects of Exercise Intervention without Weight Loss and Dietary Changes in NAFLD-Related Clinical Parameters: A Systematic Review and Meta-Analysis. Nutrients. 2021 Sep 8;13(9):3135. doi: 10.3390/nu13093135.

25. Fan H, Xu C, Li W, Huang Y, Hua R, Xiong Y, et al. Ideal Cardiovascular Health Metrics Are Associated with Reduced Severity of Hepatic Steatosis and Liver Fibrosis Detected by Transient Elastography. Nutrients. 2022 Dec 16;14(24):5344. doi: 10.3390/nu14245344.

26. Akhtar DH, Iqbal U, Vazquez-Montesino LM, Dennis BB, Ahmed A. Pathogenesis of Insulin Resistance and Atherogenic Dyslipidemia in Nonalcoholic Fatty Liver Disease. J Clin Transl Hepatol. 2019 Dec 28;7(4):362-370. doi: 10.14218/JCTH.2019.00028.

27. Dong BY, Mao YQ, Li ZY, Yu FJ. The value of the atherogenic index of plasma in non-obese people with non-alcoholic fatty liver disease: a secondary analysis based on a cross-sectional study. Lipids Health Dis. 2020 Jun 23;19(1):148. doi: 10.1186/s12944-020-01319-2.

28. Li K, Li J, Cheng X, Wang J, Li J. Association between the atherogenic index of plasma and new-onset non-alcoholic fatty liver disease in non-obese participants. Front Endocrinol (Lausanne). 2022 Aug 18;13:969783. doi: 10.3389/fendo.2022.969783

29. Chen Z, Qin H, Qiu S, Chen G, Chen Y. Correlation of triglyceride to high-density lipoprotein cholesterol ratio with nonalcoholic fatty liver disease among the non-obese Chinese population with normal blood lipid levels: a retrospective cohort research. Lipids Health Dis. 2019 Aug 9;18(1):162. doi: 10.1186/s12944-019-1104-6.

30. Koralegedara IS, Warnasekara JN, Rathnayake A, Dayaratne KG, Agampodi SB. Fatty Liver Index is a valid predictor of non-alcoholic fatty liver disease (NAFLD) in pregnancy. BMJ Open Gastroenterol. 2022 Jun;9(1):e000913. doi: 10.1136/bmjgast-2022-000913.

31. Preveden T, Veres B, Ruzic M, Pete M, Bogic S, Kovacevic N, et al. Triglyceride-Glucose Index and Hepatic Steatosis Index for the assessment of liver steatosis in HCV patients. Minerva Gastroenterol (Torino). 2023 Jun;69(2):254-260. doi: 10.23736/S2724-5985.22.03168-0.

32. Fu CP, Ali H, Rachakonda VP, Oczypok EA, DeLany JP, Kershaw EE. The ZJU index is a powerful surrogate marker for NAFLD in severely obese North American women. PLoS One. 2019 Nov 26;14(11):e0224942. doi: 10.1371/journal.pone.0224942.

33. Lee I, Cho J, Park J, Kang H. Association of hand-grip strength and non-alcoholic fatty liver disease index in older adults. J. Exerc. Nutr. Biochem. 2018, 22, 62–68. https://doi.org/10.20463/jenb.2018.0031.

34. Motamed N, Nikkhah M, Karbalaie Niya MH, Khoonsari M, Perumal D, Ashrafi GH, et al. The Ability of the Framingham Steatosis Index (FSI) to Predict Non-alcoholic Fatty Liver Disease (NAFLD): A Cohort Study. Clin Res Hepatol Gastroenterol. 2021 Nov;45(6):101567. doi: 10.1016/j.clinre.2020.10.011.

35. Park YJ, Lim JH, Kwon ER, Kim HK, Jung MC, Seol KH, et al. Development and validation of a simple index system to predict nonalcoholic fatty liver disease. Korean J Hepatol. 2011 Mar;17(1):19-26. doi: 10.3350/kjhep.2011.17.1.19.

36. Bullen AL, Katz R, Kumar U, Gutierrez OM, Sarnak MJ, Kramer HJ, et al. Lipid accumulation product, visceral adiposity index and risk of chronic kidney disease. BMC Nephrol. 2022 Dec 15;23(1):401. doi: 10.1186/s12882-022-03026-9.

37. Busquets-Cortés C, López C, Paublini H, Arroyo Bote S, López-González ÁA, Ramírez-Manent JI. Relationship between Atherogenic Dyslipidaemia and Lipid Triad with Different Scales of Overweight and Obesity in 418,343 Spanish Workers. J Nutr Metab. 2022 Aug 9;2022:9946255. doi: 10.1155/2022/9946255.

38. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C; del Grupo de Determinantes Sociales de Sociedad Española de Epidemiología. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72. doi: 10.1016/j.gaceta.2012.12.009.

39. Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. Mol Metab. 2020 Dec;42:101092. doi: 10.1016/j.molmet.2020.101092. Epub 2020 Oct 1. PMID: 33010471; PMCID: PMC7600388.

40. Heeren J, Scheja L. Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol Metab. 2021 Aug;50:101238. doi: 10.1016/j.molmet.2021.101238. Epub 2021 Apr 20. PMID: 33892169; PMCID: PMC8324684.

41. Julián MT, Pera G, Soldevila B, Caballería L, Julve J, Puig-Jové C, et al Atherogenic dyslipidemia, but not hyperglycemia, is an independent factor associated with liver fibrosis in subjects with type 2 diabetes and NAFLD: a population-based study. Eur J Endocrinol. 2021 Apr;184(4):587-596. doi: 10.1530/EJE-20-1240.

42. Hassen G, Singh A, Belete G, Jain N, De la Hoz I, Camacho-Leon GP, et al. Nonalcoholic Fatty Liver Disease: An Emerging Modern-Day Risk Factor for Cardiovascular Disease. Cureus. 2022 May 30;14(5):e25495. doi: 10.7759/cureus.25495.

43. Martin A, Lang S, Goeser T, Demir M, Steffen HM, Kasper P. Management of Dyslipidemia in Patients with Non-Alcoholic Fatty Liver Disease. Curr Atheroscler Rep. 2022 Jul;24(7):533-546. doi: 10.1007/s11883-022-01028-4. Epub 2022 May 4. PMID: 35507279; PMCID: PMC9236990.

44. Lonardo A, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, et al. Sex Differences in Nonalcoholic Fatty Liver Disease: State of the Art and Identification of Research Gaps. Hepatology. 2019 Oct;70(4):1457-1469. doi: 10.1002/hep.30626. Epub 2019 Sep 23. PMID: 30924946; PMCID: PMC6766425.

45. Ciardullo S, Oltolini A, Cannistraci R, Muraca E, Perseghin G. Sex-related association of nonalcoholic fatty liver disease and liver fibrosis with body fat distribution in the general US population. Am J Clin Nutr. 2022 Jun 7;115(6):1528-1534. doi: 10.1093/ajcn/nqac059. PMID: 35244676.