eISSN 2255-0569

ORIGINAL

Estimation of hepatic repercussion in obesity and cardiometabolic risk

Estimación de repercusión hepática en obesidad y riesgo cardiometabólico

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Received: 11 - VII - 2022
Accepted: 22 - VII - 2022

doi: 10.3306/AJHS.2022.37.05.93

Abstract

Introduction: Obesity is a global pandemic with cardiometabolic repercussions and increased risk in the development of non-alcoholic liver disease. The objective of this work is to relate the cardiometabolic risk in obesity with the risk of hepatic repercussion in the working population.
Method: Cross-sectional descriptive study in 815 workers between March 2020-June 2021. The FLI-fatty liver index and FIB-4 Index for liver fibrosis calculators and their relationship with body mass index and cardiometabolic risk are used.
Results: A greater presence of high FLI and FIB-4 values was found in groups with a higher level of cardiometabolic risk and with BMI at levels of overweight/obesity, with more unfavorable results in men.
Conclusions: In workers with obesity and cardiovascular risk or metabolic syndrome, a higher risk of hepatic repercussion quantified with FLI and FIB-4 is detected.

Key words: FLI index; FIB index 4; cardiometabolic risk, obesity; nonalcoholic liver disease, occupational health.

Resumen

Introducción: La obesidad es una pandemia mundial con repercusión cardiometabólica y riesgo aumentado en el desarrollo de enfermedad hepática no alcohólica. Es objetivo de este trabajo relacionar el riesgo cardiometabólico en obesidad con el riego de repercusión hepática en población trabajadora.
Método: Estudio descriptivo transversal en 815 trabajadores entre marzo de 2020- junio de 2021. Se utilizan las calculadoras FLI- fatty liver index y FIB-4 Index for liver fibrosis y su relación con el índice de masa corporal y el riesgo cardiometabólico.
Resultados: Se encontró una mayor presencia de valores altos de FLI y FIB-4 en los grupos con mayor nivel de riesgo cardiometabólico y con IMC en niveles de sobrepeso/obesidad, con resultados más desfavorables en hombres.
Conclusiones: En trabajadores con obesidad y riesgo cardiovascular o síndrome metabólico se detecta mayor riesgo de repercusión hepática cuantificada con FLI y FIB-4.

Palabras clave: índice FLI; índice FIB 4; riesgo cardiometabólico, obesidad; enfermedad hepatica no alcohólica, salud laboral.

Introduction

Obesity continues to be a public health problem throughout the world and has a demonstrated association with health behaviors and outcomes. Over the last 2 decades, obesity has increased worldwide, so it is essential to act in prevention and reduce its impact on health[1]. Programs such as Healthy people 2030 have encouraged interventions that make it easier for people to be more physically active, eat a balanced diet, and maintain a healthy weight[2].

BMI is typically used to define overweight and obesity in epidemiological studies. However, it has low sensitivity and there is a large interindividual variability in body fat percentage for any BMI value[3]. Some authors propose reviewing the prevalence and possible causes and comorbidities associated with obesity[4].

Current clinical and epidemiological evidence has linked obesity to a wide spectrum of cardiovascular diseases (CVD) and it is assumed that it can directly and indirectly increase CVD morbidity and mortality[5,6]. Similarly, the finding that obesity and metabolic disorders are accompanied by low-grade chronic inflammation has changed the view of underlying causes and their health consequences[7]. This concept has been useful as a screening approach to better identify subgroups of high-risk people who would benefit from clinical and population approaches aimed primarily at their lifestyle[8].

In obesity, adipose tissue and the liver play an important role in regulating whole-body energy homeostasis, and prolonged metabolic stress leads to adipose tissue dysfunction, inflammation, and adipokine release resulting in increased blood flow lipids to the liver[9]. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world and its presentation varies from simple steatosis to non-alcoholic steatohepatitis. It is a hepatic manifestation of the metabolic syndrome that includes central abdominal obesity along with other components[10].

The objective of this work is to estimate the relationship between the cardiometabolic risk associated with obesity and the risk of developing non-alcoholic liver disease using the FLI and FIB-4 questionnaires.

Method

Cross-sectional descriptive study in a sample of the Spanish working population of 815 workers (481 men and 334 women), aged between 18 and 66 years in a total population of 1028, of which 76 workers were excluded because they did not meet criteria and 137 refused to participate. Data collected by the occupational physician during the periodic health surveillance examinations of the participating companies in the service sector of the Balearic Islands from March 2020 to June 2021, with voluntary participation and informed consent for the epidemiological use of the results obtained. The inclusion criteria are: being active in the company and not being treated for previous cardiovascular disease or having uncontrolled or compensated cardiovascular risk factors.

The study was approved by the Clinical Research Ethics Committee of the Balearic Health Area (IB 4383/20).

BMI was calculated as weight in kg divided by the square of height in meters. The ranges for BMI considered by the WHO and included in this study are: normal weight <25; overweight >25-<30; grade 1 obesity >30-<40; grade 2 obesity >40[11].

To calculate the Cardiometabolic Risk Level (NR), the presence or absence of: Metabolic Syndrome (MetS), high cardiovascular risk (CVR) (Score or Regicor) and abnormal values in 2 or more of the adiposity indicators (AI) are assessed. These values were independently related to the BMI value classified by the WHO with the aforementioned parameters[12].

Cardiovascular risk has been calculated with the Score and Regicor calculators,[13,14,15] which are the two available in Spain, although the REGICOR function is the only one validated in our population. Score estimates the risk of death in 10 years and includes: sex, age, tobacco use, systolic blood pressure and total cholesterol. Regicor includes: age, gender, basal blood glucose, tobacco use, systolic and diastolic blood pressure, total and HDL cholesterol.

Metabolic syndrome has been calculated with the application available online based on the ATP-III definition and validated in Spanish patients, which includes: sex, abdominal circumference, triglycerides, maximum and minimum blood pressure, and basal glycaemia[16].

Body composition was determined with the TANITABC-420MA analyzer, estimating the percentage of body fat and visceral fat. The following have been calculated as adiposity indicators (AI):[17,18] Waist circumference (WCI): considering a value <94 cm normal in men and <80 cm in women waist/hip ratio (WHR): it is considered normal in men if it is <0.94 and in women if it is <0.84 waist-to-height ratio (WHR): it is considered normal if it is <0.5 for both men and women. Body fat percentage (BF): it is considered normal in men if it is <10 and in women if it is <20. Visceral fat (VF): considered normal if it is <10 for both men and women.

Four levels of Cardiometabolic Risk are established based on the presence of none, 1, 2 or 3 altered aspects: NR 0= none of the altered aspects assessed; NR1= 1 of the 3 aspects evaluated in non-normal limits; NR 2= 2 of the 3 aspects assessed within non-normal limits and NR 3= the 3 aspects assessed within non-normal limits[19].

To estimate Fatty Liver, the fatty liver index-FLI calculator was used, an algorithm based on waist circumference, BMI, and triglyceride and γ-glutamyltransferase levels, available at: https://www.mdapp.co/fatty-liver -index-fli-calculator-356/ and validated for the general population. A value <30 is considered low risk of fatty liver and rules out steatosis with a sensitivity of 87% and a negative predictive value of 0.2, while a score >60 is considered indicative of the presence of steatosis with a specificity of 86% and a positive predictive value of 4.3. Between 30-59 is considered an intermediate zone, ultrasound is required and for liver fibrosis estimation the FIB 4 Index for liver fibrosis calculator validated algorithm based on age, platelet count and glutamic oxaloacetic transaminase (GOT) or levels of γ-glutamyltransferase (GGT). In non-alcoholic steatohepatitis, using the lower cut-off value of 1.45, a FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4 to 6, which includes early bridging fibrosis to cirrhosis). In contrast, an FIB-4 >3.25 would have a specificity of 97% and a positive predictive value of 65% for advanced fibrosis[20,21].

The validated PREDIMED survey of adherence to the Mediterranean diet, available at: https://dietamediterranea.com/test-de-la-dieta-mediterranea/ qualifies adherence to the Mediterranean diet (MedDiet) with the score: < 9 low adherence >= 9 good adherence[22,23].

For the assessment of healthy lifestyle habits in physical activity, the IPAQ-reduced validated survey with self-registration from the last week was used. It collects the following score: moderate physical activity of at least 600 METs and high, at least 3000 METs7. In both cases, the self-administered survey was conducted through a face-to-face interview[24,25].

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of responses for each of them. For quantitative variables, the mean and standard deviation were calculated, and for qualitative variables, the percentage. A bivariate association analysis was performed using the 2 test (with a correction with Fisher's exact statistical test, when the conditions required it) and a Student's t-test for independent samples. To assess the concordance between the different scales, Cohen's Kappa test is applied. Statistical analysis was performed with the SPSS 27.0 program and a p value of <0.05 was considered statistically significant.

Results

The characteristics of the population sample show higher mean BMI values in men (27.49) than in women (26.33) and significant differences between both (p_0.001) (**Figure 1**). Greater adherence to the Mediterranean diet is observed in women and without significant differences in physical activity between men and women, both at moderate/high levels (**Table I**).

Figure 1: Percentage results of Prevalence. Overweight / Obesity according to BMI. Gender differences.

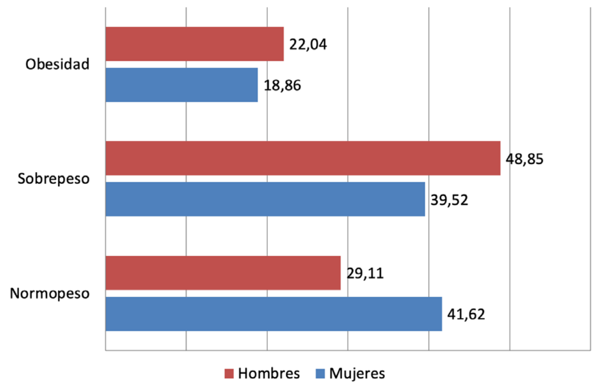


Table I: Population characteristics. Comparison between genders.

Variables analyzed		Male (N = 481)		Female (N = 334)		Value_p
		Mean	(SD)	Mean	(SD)	
Age		48.25	8.35	48.89	8.16	0.277
Anthropometric variables: mean (SD)	Weight	82.79	13.93	67.97	11.98	<0.0001
	Height	173.42	6.81	160.72	5.98	<0.0001
	BMI	27.49	4.01	26.33	4.47	<0.0001
Adiposity variables mean (SD	Waist	94.61	10.96	84.35	11.43	<0.0001
	Waist/height	0.55	0.06	0.53	0.07	<0.0001
	Hip	106.22	58.83	99.00	10.13	0.027
	Waist/Hip	0.92	0.07	0.85	(0.06	<0.0001
	Total body fat	24.70	6.58	36.08	7.78	<0.0001
	Visceral fat	11.35	4.53	7.53	2.65	<0.0001
BMI classification	Normal weight	29.11		41.62		
	Overweight	48.86		39.52		0.001
	Obesity	22.04		18.86		
Life habits: adherence to the Mediterranean Diet-PREDIMED	Hight Adherence MedD	43.87		56.89		<0.0001
Life habits: Physical Activity-IPAQ	Low physical activity	1.87		3.29		
	Moderate physical activity	40.33		47.31		0.041
	High physical activity	57.80		49.40		

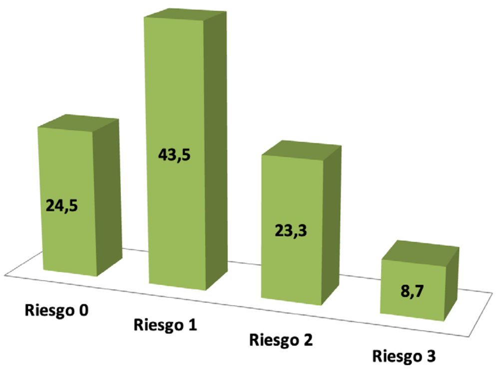
ST= standard deviation ; p value lower than 0.05 was considered statistically significant (p<0,05)

More than 75% of the population studied presented some degree of cardiometabolic risk, although the most prevalent level was NR-1 (**Figure 2**) (43.5% had at least 1 of the 3 factors studied altered). The estimated level of risk shows a statistically significant relationship between high BMI and the risk increases as obesity increases, the relationship being significant. The prevalence of NR 1 stands out in people with overweight or type 1 obesity.

In all the parameters included in the risk estimation, higher percentages of altered values are observed in men with statistical significance, this difference being especially wide in high CVR (41.85% in men versus 11.34% in women) (**Table II**).

The presence of hepatic steatosis estimated with FLI in medium and high values increases as the level of cardiometabolic risk increases, with statistically significant results (p<0.0001). It is especially significant that 47.62% of workers with NR 2 and 66.20% of those with NR 3 present high FLI.

Figure 2: Percentage distribution of Estimated Cardiometabolic Risk Level.



The risk of liver fibrosis, estimated with FIB-4, increases according to the level of cardiometabolic risk, although with little difference between the highest levels[2-3] (p<0.0001) (**Table III**).

Discussion

Monitoring the prevalence of obesity and overweight is important to assess interventions aimed at preventing or reducing the burden of obesity. According to a 2014 study in 20 European countries, more than half of the European population is overweight and obese (53.1%), more men than women are overweight (44.7% compared to 30.5%) (26) and this coincides with our results. In our study, the BMI values correspond to pre-obesity/overweight and are higher in men (27.49% vs. 26.33%).

The scientific literature is consistent on the risks associated with obesity. The metabolic syndrome, which includes abdominal obesity, dyslipidemia, hyperglycemia and hypertension, is a major challenge for public health and its average prevalence is 31% of the population and is associated with a double risk of coronary heart disease, cerebrovascular disease, and a 1.5-fold

Table II: Percentage distribution of the assessment included factors to estimated liver risk. Relationship with BMI and the risk factors included.

Percentage distribution of the factors included in the liver risk evaluation							
Gender differences		**Male %**		**Female %**			**Value_P**
MetS Presence		20.88		16,82			<0.0001
CVR Presence- Score/Regicor		41,85		11,34			<0.0001
Adiposity indicators (AI) ≥ 2 IA out of normal values		75,05		68.26			0.001
Relationship between the estimated cardiometabolic risk level and BMI.							
LR estimated	**Normal weight**		**Overweight**		**Obesity (I and II)**		**Value_P**
	n	%	n	%	n	%	
LR 0	173	62.0	26	7.1	0	0	<0.0001
LR 1	89	31.9	207	56.9	57	33.9	<0.0001
LR 2	16	5.7	100	27.5	72	42.9	<0.0001
LR 3	1	0,4	31	8,5	39	23.2	<0.0001

Table III: FLI fatty liver and FIB-4 fibrosis liver. Relationship with the estimated cardiometabolic risk level.

FLI	**Cardiometabolic risk level classification**								**Value_P**
	RL0		**RL1**		**RL2**		**RL3**		
	n	%	n	%	n	%	n	%	
FLI- low	188	94,47	189	53,54	34	17,99	1	1,41	<0.0001
FLI - medium	11	5,53	105	29,75	65	34,39	23	32,39	<0.0001
FLI high	0	0	59	16,71	90	47,62	47	66,20	<0.0001
FIB-4	**Cardiometabolic risk level classification**								**Value_P**
	RL0		**RL1**		**RL2**		**RL3**		
	n	%	n	%	n	%	n	%	
Normal	175	87,94	292	82,72	138	71,88	52	73,24	<0.0001
Intermediate	24	12,06	61	17,28	54	28,12	19	26,76	<0.0001

Fatty liver estimate =fatty liver index-FLI; Liver fibrosis estimate = FIB 4 Index for liver fibrosis; p value lower than 0.05 was considered statistically significant (p<0,05) increased risk of all-cause mortality[27]. In our work, risk levels are established by combining both the presence of metabolic syndrome and CVR calculated by Score or Regicor, and it shows that more than 75% of the population studied has some degree of cardiometabolic risk, with the results, in all cases, being more unfavorable in men (20.88% vs. 16.82% in MetS and 41.85% vs. 11.34% in CVR), although it must be considered as a bias in the calculation of CVR in workers under the age of 40 years.

Currently, it is still a matter of discussion that individuals with a similar body mass index may have different metabolic and cardiovascular risk profiles. It is recognized that susceptibility to obesity-related cardiometabolic complications is not mediated solely by total body fat, but is largely dependent on individual differences in the regional distribution of body fat and the expandability of subcutaneous adipose tissue, which is considered one of the key clinical variables that explain the metabolic heterogeneity of obesity and the associated cardiovascular risk[28]. In our work, both men and women present at least two indicators of adiposity outside the normal ranges, this being the most outstanding aspect of the three included in the estimation of the level of risk (body fat, visceral fat, waist/height ratio, waist-hip ratio or waist circumference) is the most prominent aspect of the three included in the estimation of the level of risk and is more prevalent in men than in women (75.05% vs. 68.26%) and with statistical significance.

An outstanding aspect in our study is the estimation of hepatic repercussion both in estimated risk of steatosis (with the FLI calculator) and fibrosis (with the FIB-4 calculator).

Non-alcoholic fatty liver disease (NAFLD) is a disorder of excessive accumulation of fat in the liver, it can manifest as simple steatosis or as steatohepatitis, known as non-alcoholic steatohepatitis (NASH), which is accompanied by inflammation and possibly fibrosis. The pathophysiology of NAFLD and NASH is not fully elucidated, but it is known that it involves the complex interaction between different metabolic, environmental, and genetic factors, among which obesity is one of the most prominent. Despite its growing prevalence throughout the world, to date there is no treatment approved by the FDA, so its prevention and early action on modifiable risk factors is of special importance[29].

Although the gold standard for the diagnosis of NASH is liver biopsy, other non-invasive methods have been developed: FibroTest, ELF, Hepascore, FIB-4, NFS, FLI and ION (biochemical panels), but they lack specificity to detect the mild fibrosis[30]. However, these estimation calculation methods are easily accessible at basic levels such as occupational medicine and allow preventive action to be taken, anticipating liver damage or delaying its evolution.
In our work we have used FLI as a method of estimating the risk of hepatic steatosis and FIB-4 for the case of hepatic fibrosis, in both related to obesity and its cardiometabolic repercussion, and concluded with both methods that the highest values of hepatic repercussion (steatosis or fibrosis) are significantly associated with high cardiometabolic risk (NR2 and NR3) and increase as these risk levels rise.

Assuming the high rate of unreliable results with these predictive tools and, given their easy use and accessibility and the high prevalence of NAFLD in the general population, these non-invasive methods could be used in clinical practice as first-line tools for early detection in patients with NAFLD, in order to help determine who might need a liver biopsy or other interventional or expensive methods not accessible in occupational medicine[31].

Conclusion

The cardiometabolic risk is significantly related to the estimation of hepatic repercussion obtained with the FLI indicators of steatosis and FIB-4 of fibrosis in patients with obesity or overweight. The results obtained with the FLI and FIB-4 indicators increase with the level of cardiometabolic risk obtained.

This research has not received any specific grants from agencies in the public, commercial, or for-profit sectors.

Conflict of interest

The authors declare that they have no conflict of interest.

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