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CONSUÊLO PADILHA VILAR

DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA

TESE DE DOUTORADO

Salvador
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Tese apresentada ao Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito para a obtenção do grau de Doutor em Medicina e Saúde.

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DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA

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“*A mente que se abre a uma nova ideia jamais voltará ao seu tamanho original*”

Albert Einstein

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LISTA DE SIGLAS E ABREVIATURAS

ALB	albumina
ALT	Alanina aminotransferase
AMI	Acute myocardial infarction
AST	Aspartato aminotransferase
AUS	Abdominal Ultrasound
BIOMOL	Laboratório de Biologia Molecular
BD	Bilirrubina direta
BMI	Body mass index
BT	Bilirrubina total
CAC	Coronary artery calcium
CAD	Coronary artery disease
CAG	Coronary angiography
CCS	Coronary calcium score
CEP	Comitê de Ética em Pesquisa
CI	Confidence interval
cm	Centímetro
CVD	Cardiovascular disease
CT	Computed tomography
DCV	Doenças cardiovasculares
DHGNA	Doença hepática gordurosa não alcoólica
DAC	Doença arterial coronariana
DM	Diabetes Mellitus
DM2	Diabetes Mellitus tipo 2
DP	Desvio padrão
ECG	Eletrocardiograma
EHNA	esteatohepatite não alcoólica
FA	Fosfatase Alcalina
FAN	Fator Anti-Núcleo
FCM	Faculdade de Ciências Médicas
FMB	Faculdade de Medicina da Bahia
FPG	Fasting plasma glucose
GGT	Gamma-glutamyltransferase

GNASH	Grupo de Estudo em Nonalcoholic steatohepatitis.
HAS	Hipertensão Arterial Sistêmica
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Vírus
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
HOMA	Homeostasis model assessment
HOMA-IR	Homeostasis model assessment insulin resistance
HU	Hounsfield Units
HUAC	Hospital Universitário Alcides Carneiro
IAM	Infarto agudo do miocárdio
IBECS	Índice Bibliográfico Espanhol em Ciências da Saúde
IHD	Ischemic heart disease
IMC	Índice de massa corpórea
INR	International Normalized Ratio
IR	Insulin resistance
JNC VII	Seventh report of the Joint Committee
kg	Quilograma
Kg/m^2	Quilograma por metro quadrado
LDL	Low Density Lipoprotein
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
m^2	Metro quadrado
MI	Myocardial infarction
mg	Miligrama
mmHg	Milímetro de mercúrio
MS	Metabolic syndrome
MSCT	Multislice computed tomography
µUI/mL	Micro unidades internacionais por mililitro
NAFLD	Nonalcoholic fatty liver disease
NCEP/ATPIII	National Cholesterol Education Program Adult Treatament Panel III
ng/mL	Nanograma por mililitro
NMR	Nuclear magnetic resonance
OR	Odds ratio
PA	Pressão arterial

PPgMS	Programa de Pós-graduação em Medicina e Saúde
PT	Proteína total
RI	Remodeling index
ROI	Region of interest
SD	Standard deviations
SM	Síndrome metabólica
SPSS	Statistical Package for Social Sciences
SUS	Sistema Único de Saúde
TC	Total cholesterol
TP	Tempo de protrombina
TG	Triglycerides
UFBA	Universidade Federal da Bahia
UFCG	Universidade Federal de Campina Grande
U/L	Unidade por litro
UI/dl	Unidade Internacional por decilitro
US	Ultrasound
USG	Ultrassonografia
USAB	Ultrassonografia Abdominal
χ^2	Chi-square
WHO	World Health Organization

1 RESUMO

DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA EM PACIENTES COM DOENÇA ARTERIAL CORONARIANA

A Doença Hepática Gordurosa Não Alcoólica (DHGNA) representa a causa mais comum de doença do fígado na atualidade. Está associada com síndrome metabólica e, mais recentemente, às doenças cardiovasculares. **Objetivo**: avaliar a associação entre DHGNA e doença arterial coronariana (DAC) e os fatores preditivos desta associação em indivíduos submetidos à cineangiocoronariografia (CAG). **Metodologia:** Foi realizado estudo transversal, que avaliou indivíduos submetidos à CAG com suspeita de DAC. Os pacientes realizaram avaliação clínico–laboratorial e ultrassonografia abdominal (USAB). Critérios para DAC: presença de lesão obstrutiva em artérias coronárias epicárdicas ou seus principais ramos. Critérios para DHGNA: presença de esteatose na USAB; ingestão alcoólica ≤20 g/dia; ausência de outras doenças hepáticas. As variáveis contínuas foram avaliadas pelos testes t de Student ou teste de Mann-Whitney e as categóricas pelo teste do qui-quadrado com nível de significância (p) < 0,05. Análise de regressão mediu a força da relação entre os fatores de risco e a presença concomitante de DAC e DHGNA. **Resultados:** Foram estudados 244 pacientes com média de idade de 61,5±9,3 anos. A DAC foi observada em 63,5%, e a DHGNA, em 42,2% dos pacientes. Aqueles com DAC eram, predominantemente, do gênero masculino (p<0,01); diabéticos (p<0,05) e tabagistas (p=0,045), e 43,9% deles tinham DHGNA. A DHGNA esteve associada à $DM_{2,}$ resistência insulínica, síndrome metabólica, obesidade central, índice de massa corpórea, triglicérides e alanina aminotransferase (p<0,05). A ocorrência concomitante de DAC e DHGNA foi positivamente correlacionada a sobrepeso/obesidade e HOMA-IR ≥3,0. **Conclusões:** A amostra teve elevada frequência de ambas, DAC e DHGNA; DHGNA foi mais elevada em pacientes com DAC, porém não houve associação estatisticamente significante entre as duas doenças; pacientes com associação DAC e DHGNA apresentavam sobrepeso/obesidade, e resistência insulínica. Os resultados sugerem a relevância clínica de investigar a DHGNA em pacientes com DAC, no sentido de diminuir a morbimortalidade desses pacientes.

Palavras-chave: DHGNA; Doença coronariana; DAC; Esteatose hepática.

ABSTRACT

NONALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH CORONARY ARTERY DISEASE

Nonalcoholic Fatty Liver Disease (NAFLD) is the most common cause for liver disease at present. The disease is associated with metabolic syndrome and, more recently, cardiovascular diseases. **Objective**: To evaluate the association between NAFLD and coronary artery disease (CAD) and the predictive factors of this association in subjects undergoing coronary angiography (CAG). **Methodology:** a cross-sectional study was carried out to evaluate the individuals submitted to CAG for suspected CAD. The patients were submitted to clinical and laboratory evaluation and abdominal ultrasound (AUS). Criterion for CAD: presence of obstructive lesion in the epicardial coronary arteries or their major branches. Criteria for NAFLD: presence of steatosis in the AUS; individuals that drink alcohol ≤20g/day; absence of other liver diseases. The continuous variables were evaluated either by the t test or Mann-Whitney test; the categories variables were evaluated by Pearson's chi-square test with level of significance (p) < 0.05. Multivariate regression analysis was used to measure the strength of the relationship between risk factors and the concomitant presence of CAD and NAFLD **Results:** 244 patients were investigated with average age of 61.5±9.3. CAD was observed in 63.5% and NAFLD in 42.2% of individuals. Patients with CAD were predominantly men (p<0.01), had diabetic and were smokers (p=0.045); 43.9% of them had NAFLD. The presence of NAFLD was related to DM_2, insulin resistance, metabolic syndrome, central obesity, body mass index, neck circumference, triglycerides, and alanine aminotransferase (p<0.05). The possibility of simultaneous occurrence of NAFLD and CAD was positively correlated with overweight / obesity and HOMA-IR ≥ 3.0. **Conclusion:** The sample had high frequency both of CAD and NAFLD; the presence of NAFLD was also high among patients with CAD, however there was no significant statistical association between the two diseases; patients with CAD and NAFLD were overweight/obesity and had insulin resistance. Results suggest that NAFLD should be investigated in patients with CAD in order to decrease morbidity and mortality among these patients.

Keywords: NAFLD; Coronary disease; CAD; Hepatic steatosis.

2 INTRODUÇÃO

Doença hepática gordurosa não alcoólica (DHGNA) é uma condição clínica com características histológicas semelhantes àquelas encontradas nas hepatopatias induzidas pelo álcool, porém acometendo pacientes não consumidores de bebida alcoólica ou que ingerem quantidade igual ou inferior a 140 g de etanol por semana. Caracteriza-se pelo acúmulo focal ou difuso de gordura no parênquima hepático.

A DHGNA compreende um espectro de condições que varia de pura esteatose (fígado gorduroso) a esteatohepatite não alcoólica (EHNA), que pode evoluir para cirrose e carcinoma hepatocelular.

A doença tem alcançado proporções epidêmicas, representando a causa mais comum de doença hepática crônica na atualidade. Sua prevalência está estimada em cerca de 20 a 30% na população geral[*]. No entanto, estes valores podem chegar a aproximadamente 70 a 80% nos obesos e diabéticos tipo 2[**], os quais tem um maior risco de desenvolver fibrose e cirrose. EHNA é mais rara, acometendo 2 a 3% da população geral, porém estes valores se elevam para 25 a 55 % nos pacientes obesos submetidos à cirurgia bariátrica[***].

Uma série de fatores tem sido associada à presença, à progressão e à gravidade da DHGNA. Os mais importantes são: resistência à insulina, hiperglicemia/diabetes tipo 2 (DM_2), obesidade, idade, hipertensão arterial sistêmica (HAS) e dislipidemia. A influência da etnia também tem sido discutida. Estudos demonstram que a DHGNA é mais frequente em hispânicos do que em brancos e os afro-americanos são considerados o grupo étnico com a menor prevalência.

A associação entre EHNA e resistência à insulina indica ser esta uma forma de doença hepática metabólica, na qual a resistência à insulina e a esteatose hepática são complicadas por alterações necroinflamatórias crônicas, com potencial progressão para fibrose.

Evidências atuais apontam uma forte relação entre a gravidade das alterações histológicas da DHGNA e aterosclerose, a qual permanece associada com o

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[*] Neuschwander-Tetri & Caldwell. Nonalcoholic Steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; 37: 1202-19.

[**] Williams KH, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and Nonalcoholic Fatty Disease: A Pathogenic Duo. *Endocrine Reviews* 2013; 34: 84-129.

[***] Clark JM. The Epidemiology of nonalcoholic Fatty Liver Disease in Adults. *Clin Gastroenterol* 2006; 40, sup 1: S5-10

aumento do risco cardiovascular mesmo após ajustamento para os fatores de risco que compõem a síndrome metabólica. E alguns estudos demostram a relevância da associação entre DHGNA e doença arterial coronariana (DAC). DHGNA seria um fator de risco independente para a presença de DAC e esta, por sua vez, seria uma das principais causas de morbidade e mortalidade nesses pacientes.

No entanto, a maioria dos indivíduos portadores de DHGNA/EHNA é assintomática e não apresenta sinais clínicos de doença hepática à época do diagnostico, embora alguns relatem fadiga, sensação de plenitude ou desconforto abdominal. A hepatomegalia pode ser o único achado na maioria dos pacientes e a discreta elevação das enzimas hepáticas pode ser a única anormalidade laboratorial encontrada, o que dificulta o diagnóstico precoce. E embora DHGNA/EHNA esteja associada a fatores de risco comuns as doenças cardiovasculares (DCV) e possa representar *per si* um fator de risco independente para essas doenças, uma vez que tem evolução geralmente silenciosa, seu diagnóstico e tratamento são tardios, o que pode influenciar no surgimento e progressão de DCV.

Por isso, mas também pela escassez de estudos relacionados à associação de DHGNA e DCV no Brasil e em especial em nossa região, este trabalho tem como objetivos avaliar a associação entre DHGNA e DAC, os fatores de risco relacionados com a presença de DAC e DHGNA isoladamente, bem como os fatores preditivos da associação de DHGNA e DAC em pacientes submetidos à angiografia coronariana.

3 OBJETIVOS

3.1 Principal

- Avaliar a associação entre Doença Hepática Gordurosa Não Alcoólica (DHGNA) e Doença Arterial Coronariana (DAC) em pacientes submetidos a Cineangiocoronariografia (CAG).

3.2 Secundários

- Descrever as características clínicas dos pacientes estudados;
- Avaliar os fatores de risco associados a DAC e DHGNA isoladamente;
- Determinar os fatores preditivos para a associação DAC e DHGNA.

4 METODOLOGIA

4.1 Delineamento do estudo

Trata-se de um estudo de corte transversal no qual foram avaliados indivíduos de ambos os gêneros, submetidos à CAG eletiva, com suspeita clínica de DAC, entre abril de 2009 a setembro de 2010.

4.2 População

4.2.1 População de referência

Pacientes atendidos nos serviços de Hemodinâmica do Hospital Universitário Alcides Carneiro e do Centro Hospitalar João XXIII, os quais são referenciados pelo Sistema Único de Saúde (SUS) para atendimento em Cardiologia intervencionista na Cidade de Campina Grande-PB.

4.2.2 População do estudo

A amostra estudada foi constituída de 244 indivíduos com suspeita clínica de DAC por angina estável, dor precordial ou avaliação prognóstica após infarto agudo do miocárdio (IAM), com solicitação de CAG, feita por seus respectivos médicos assistentes, na qual constava a hipótese diagnóstica de DAC.

4.3 Seleção amostral

4.3.1 Critério de Inclusão

- Hipótese diagnóstica de DAC em pacientes submetidos à CAG.

4.3.2 Critérios de exclusão

- Ingestão alcoólica > 20g/dia para os homens e mulheres;
- Uso de drogas que induzem doença hepática gordurosa tais como amiodarona, glicocorticóides, estrogênios, carbamazepina, tamoxifeno ou outros agentes nos últimos três meses;
- Sorologia positiva para hepatite B e C;
- Diagnóstico de hepatite auto-imune, hemocromatose ou outras doenças

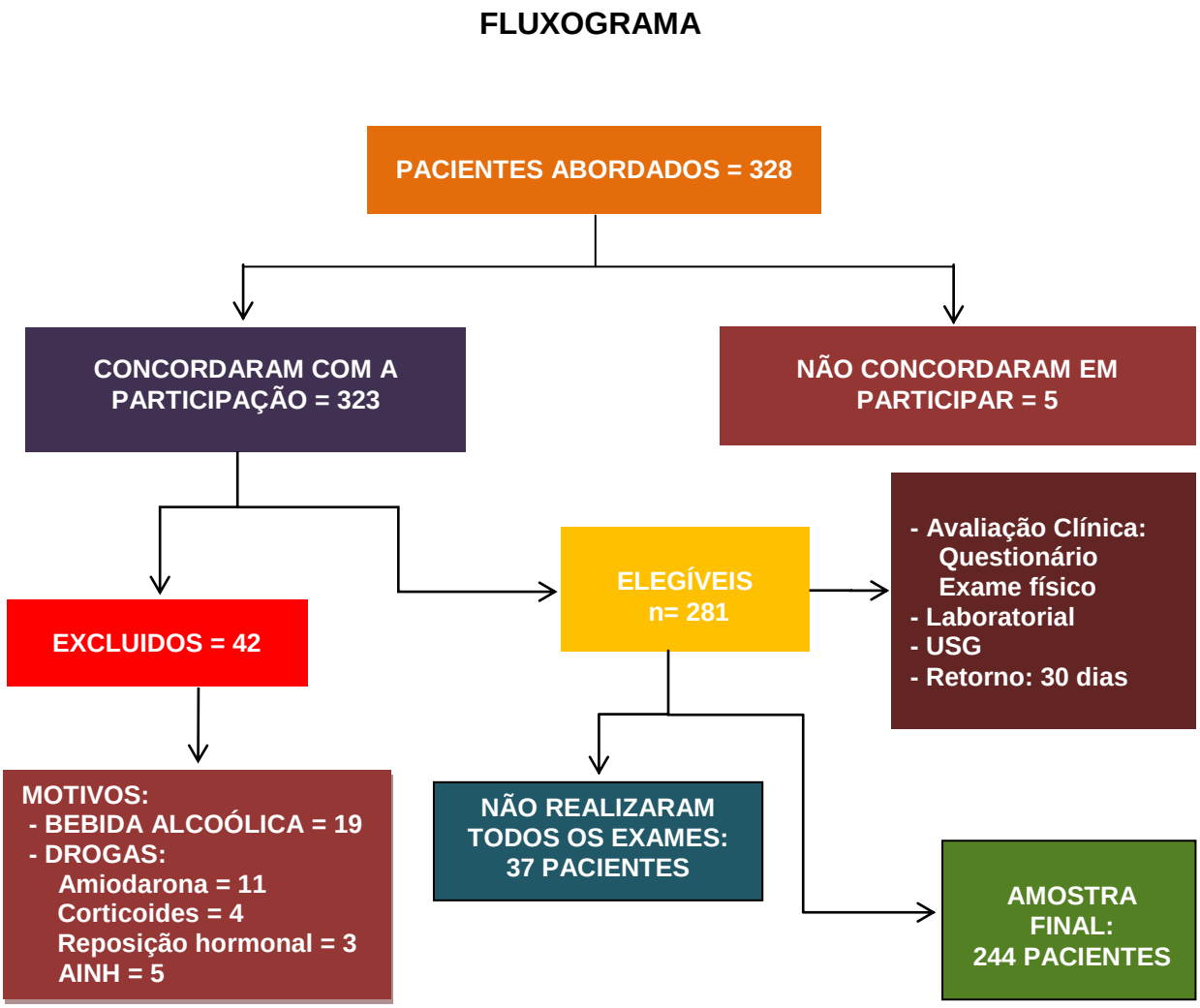
hepáticas;

- Pacientes com CAG realizada por outras razões que não DAC.

4.4 Tamanho da amostra

A amostra, estimada (IC=99,99%) pelo Epi-Info®, levando em consideração uma prevalência antecipada de 20% de DHGNA, foi calculada como sendo de 245 pacientes. Foram entrevistados 323 pacientes e após aplicar os critérios de exclusão foram alocados 244 pacientes no estudo.

4.5 Fluxograma de captação e segmento dos pacientes



4.6 Variáveis estudadas

4.6.1 Avaliação clínica

Na avaliação clínica, realizada através de aplicação de questionário e exame físico, foram estudadas ou descritas as seguintes variáveis: gênero, idade, indicação da CAG, antecedentes pessoais de diabetes tipo 2 (DM_2), de hipertensão arterial sistêmica (HAS), de dislipidemia e de infarto agudo do miocárdio (IAM), prática de atividade física, consumo diário de bebida alcoólica, tabagismo, exposição a petroquímicos, uso de medicações (incluindo anti-diabéticos, hipolipemiantes, anti-hipertensivos, e medicações hepatotóxicas) e drogas ilícitas, bem como antecedentes de doenças hepáticas.

- **Medidas de peso e altura**

O peso foi determinado em quilogramas (kg) e a altura em metros (m), utilizando-se balança antropométrica, aferida previamente à realização de cada medida (Marfell-Jones *et al*., 2006).

- **Índice de Massa Corpórea (IMC)**

O IMC foi calculado pela fórmula: IMC = peso (kg) / altura^2 (m) (Gray, 1989), adotando-se a classificação de obesidade da Organização Mundial de Saúde (WHO, 1995).

- **Circunferência abdominal**

A circunferência abdominal foi medida com fita métrica metálica, com escala em centímetros (cm), na linha média entre a borda inferior do gradil costal e a borda superior da crista ilíaca. Foi considerada obesidade central valor > 102 cm para homens e > 88 cm para mulheres (NCEP-ATP III, 2002).

- **Tabagismo**

O tabagismo foi considerado como consumo de pelo menos um cigarro diário por um período não inferior a seis meses e ex-tabagismo o abandono do cigarro há pelo menos seis meses (WHO, 1984)

- **Alcoolismo**

O alcoolismo foi definido como ingestão alcoólica > 20g/dia para os homens e mulheres (Ahlström *et al*., 2001).

- **Hipertensão Arterial**

A medida da pressão arterial foi obtida com esfigmomanômetro aneróide tipo padrão, previamente calibrado, na posição sentada, seguindo as recomendações do VII JOINT. Hipertensão arterial foi definida como pressão arterial sistólica (PAS) ≥ 140 milímetros de mercúrio (mmHg) e/ou pressão arterial diastólica ≥ 90 mmHg ou uso de medicação anti-hipertensiva (Chobanian *et al*., 2003).

- **Diabetes Mellitus**

O critério de diabetes foi glicemia de jejum > 125 miligramas por decilitro (mg/dL) ou uso de medicação anti-diabética, enquanto intolerância a glicose foi definida como glicemia em jejum ≥ 110 mg/dL sem uso de medicação (Alberti *et al*.,1998).

- **Resistência à Insulina**

A resistência insulínica foi estimada indiretamente pelo índice de resistência à insulina, obtido através do modelo de avaliação da homeostase (Homeostasis Model Assessment-HOMA) descrito por Matthews *at al.* (1985): HOMA-IR = [insulina sérica de jejum (mU/mL) x glicemia de jejum (mmol/L)]. Os valores de glicemia em mg/dL foram convertidos em mmol/L multiplicando-se os valores encontrados pelo fator 0,056. Os valores de HOMA aumentam com o aumento da resistência à insulina. Os pacientes foram caracterizados como resistentes à insulina quando o valor de HOMA foi igual ou superior a 3,0 (Guidorizzi *et al*., 2005).

- **Síndrome Metabólica (SM)**

Como critério de síndrome metabólica (SM) foi considerada a presença de três dos seguintes parâmetros de acordo com o *National Cholesterol Education Program Adult Treatament Panel III* (NCEP/ATPIII) (NCEP/ATPIII, 2002):

Circunferência abdominal > 102 cm em homens e > 88 cm em mulheres;

Triglicerídeos em jejum > 150mg/dL;

HDL < 40mg/dL em homens e < 50mg/dl em mulheres;

Pressão arterial sistólica ≥ 130 mmHg ou pressão arterial diastólica ≥ 85 mmHg ou uso de medicação anti-hipertensiva;

Glicemia em jejum ≥ 110 mg/dL ou diabetes tipo 2 previamente diagnosticado.

4.6.2 Avaliação laboratorial

Para realização de exames laboratoriais foi coletado sangue venoso pela manhã, antes da realização da CAG, após jejum noturno de 12 horas. As provas de função hepática e outros e exames bioquímicos foram realizados por procedimentos laboratoriais padrão e incluíram dosagens séricas de alanina aminotransferase (ALT), aspartato aminotransferase (AST), fosfatase alcalina (FA), gama glutamiltransferase (GGT), proteínas, ferritina e índice de saturação de transferrina. O colesterol total, HDL-colesterol e triglicérides foram dosados por método enzimático. O LDL-colesterol foi calculado pela fórmula de Friedwald [LDL-c = CT-(HDL-c + TG/5)], para níveis de triglicérides < 400 mg/dL. A glicemia foi determinada por método enzimático da glicose-oxidase e os resultados foram expressos em mg/dL. A insulina foi dosada por ensaio imunométrico quimioluminescente. Também foram realizados sorologia para hepatites B e C (ELISA), fator anti-núcleo (FAN), anticorpos anti-músculo liso e anti-mitocôndria (Imunofluorescência indireta).

4.6.3 Angiografia Coronariana

Todos os pacientes incluídos no estudo tinham angiografia coronária seletiva esquerda e direita realizada pela técnica de Judkins, utilizando um dispositivo PólluX 100KW (XPRO Sistemas Ltda., Belo Horizonte, Minas Gerais, Brazil).. As CAG foram avaliadas e registradas por pelo menos dois cardiologistas experientes, que não tinham informações sobre o estudo.

- **Critério para DAC**

A DAC foi diagnosticada pela detecção angiográfica de estenose em artérias coronárias epicárdicas ou seus principais ramos.

4.6.4 Ultrassonografia (USG) Abdominal

A USG abdominal foi realizada em seguida à CAG, utilizando o aparelho de ultrassom Nemio 17 (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japão), com um transdutor convexo de 3,5 MHz de freqüência, por um mesmo e experiente ultrassonografista que desconhecia a historia clínica e o resultado da CAG.

- **Critério para DHGNA**

Como critério diagnóstico para DHGNA foram utilizados os seguintes parâmetros:

- História de ingestão de etanol ≤ 20 gramas/dia (Ahlström et al., 2001; Angulo, 2002.)
- Exclusão de outras doenças hepáticas;
- Presença de esteatose hepática na ultrassonografia abdominal (USG).

- **Critério para esteatose à ultrassonografia**

A esteatose hepática foi diagnosticada pelas características ecográficas padrão, de acordo com os critérios convencionais: aumento da ecogenicidade do parênquima hepático que podia vir associada à atenuação do feixe sonoro em planos posteriores ou ainda à perda da definição das estruturas vasculares hepáticas e do diafragma. À medida que se somam as alterações, aumenta a gravidade da doença (Pacífico *at al*., 2007; Mehta *et al*., 2008).

4.7 Aspectos Éticos

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa com Seres Humanos (CEP-HUAC) da Universidade Federal de Campina Grande (UFCG), Brasil. Os participantes assinaram termo de consentimento, livre e esclarecido (Anexo I), de acordo com a resolução CONEP nº 196 de 10 de outubro de 1996.

4.8 Análise estatística

Os dados foram processados e analisados através do SPSS (SPSS Inc., Chicago, IL, EUA, versão 17.0.1, 2008). Inicialmente à estatística descritiva foram aplicados ao teste de Kolmogorov-Smirnov e os critérios de Bartlett. As variáveis categóricas foram descritas em freqüências e porcentagens e as variáveis contínuas foram sumarizadas como médias e desvios-padrão (SD). Os dados contínuos foram analisados usando teste t de Student ou teste U de Mann-Whitney, quando apropriado. Para comparação de dados de frequência foi utilizado o teste do qui-quadrado (χ^2). Foi realizada a análise de regressão multivariada para medir a força da relação entre os fatores de risco e a presença concomitante de DAC e DHGNA. Variáveis com valor de $p \leq 0,15$ na análise univariada foram selecionadas como

variáveis independentes no modelo multivariado. Um processo de seleção “passo a passo” foi aplicado para obter o modelo reduzido. A presença concomitante de DAC e DHGNA foi selecionada como variável dependente. Todos os métodos estatísticos foram bicaudais, os valores de *p* foram calculados e o nível de significância foi definido como menor que 0,05.

5. RESULTADOS

5.1 Artigo de Revisão

Situação: Publicado

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Review article

Association between nonalcoholic fatty liver disease and coronary artery disease☆

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ABSTRACT

Objective: Although some investigations have shown a relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases, there are few studies analyzing the relationship between NAFLD and coronary artery disease (CAD). The aim of this article was to review the relationship between NAFLD and CAD and the methods of diagnosis used to assess such relationship.

Methods: A review was performed using search engines of indexed scientific material, including MEDLINE (by PubMed), Web of Science, IBECS, and LILACS, to identify articles published in Portuguese, English, and Spanish until August, 2012. The studies were eligible if they included the following data: place and year of publication, prevalence and methods used to diagnose NAFLD (ultrasound, computed tomography, nuclear magnetic resonance, or biopsy) and CAD (coronary angiography, or computed tomography), and the exclusion of patients due to alcohol consumption greater than 20 g/day.

Results: Ten articles were selected, most of which were cross-sectional studies. The studies mostly observed the association between NAFLD and the presence and severity of CAD.

Conclusion: The analysis of the review showed that evaluating the existence of NAFLD in patients with CAD from its subclinical form up to the symptomatic clinical form is important due to the higher risk of acute myocardial infarction and consequent increase of mortality.

☆ Study conducted at Universidade Federal de Campina Grande, Campina Grande, PB, Brazil.

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Associação entre doença hepática gordurosa não-alcoólica e doença arterial coronariana

Palavras-chave:
Doença hepática gordurosa
Doenças cardiovasculares
Doença hepática gordurosa não alcoólica
Doença arterial coronariana

RESUMO

Objetivo: Embora algumas investigações demonstrem uma associação entre a doença hepática gordurosa não-alcoólica (DHGNA) e doenças cardiovasculares, existem poucos estudos analisando a relação entre DHGNA e doença arterial coronariana (DAC). O objetivo deste artigo foi realizar uma revisão sobre a associação entre DHGNA e CAD e os métodos diagnósticos usados para avaliar esta associação.

Métodos: Foi realizada uma revisão da literatura utilizando métodos de busca de material científico indexado, incluindo MEDLINE (através do PubMed), Web of Science, IBECS e LILACS para identificar artigos publicados em português, inglês e espanhol até agosto de 2012. Os estudos eram elegíveis se incluíam os seguintes dados: local e ano de publicação, prevalência e os métodos utilizados para o diagnóstico da DHGNA (ultrassonografia, tomografia computadorizada, ressonância nuclear magnética ou biópsia) e DAC (angiografia coronária ou tomografia computadorizada), e a exclusão de pacientes com consumo de álcool maior do que 20 g/dia.

Resultados: Dez artigos foram selecionados, predominando os estudos de corte transversal. Na maioria dos estudos foi observada a associação entre DHGNA e a presença e gravidade da DAC.

Conclusão: A análise da revisão mostra que é importante avaliar a existência de DHGNA em pacientes com DAC desde sua forma subclínica até a forma clínica sintomática, devido ao maior risco de infarto agudo do miocárdio e consequente aumento da mortalidade.

Introduction

Some investigations have shown a relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVDs),[1–3] with the latter being one of the main causes of morbidity and mortality in these patients. Although fatty liver is related to factors (such as dyslipidemia, central obesity, diabetes, and metabolic syndrome [MS]) that may cause CVDs including coronary artery disease (CAD), there are few studies analyzing the relationship between NAFLD and CAD, and they present controversial results.

Different methods can be applied to diagnose NAFLD and CAD. NAFLD can be diagnosed by ultrasound (US), computed tomography (CT), nuclear magnetic resonance (NMR), and liver biopsy. A recent meta-analysis showed that US has a sensitivity from 73.3% to 90.5% and a specificity from 69.6% to 85.2%. CT has a sensitivity from 46.1% to 72% and a specificity from 88.1% to 94.6%, but its cost is higher. NMR has a sensitivity from 82.0% to 97.4% and a specificity from 76.1% to 95.3%, and as a noninvasive technique, NMR is good at diagnosing, especially cases of steatosis < 25%.[4] However, due to its high cost, NMR is not available to most patients. Liver biopsy is considered the gold standard for diagnosing steatosis, but it is an invasive method that may cause bleeding. US is relatively precise for the diagnosis of NAFLD; and since it is low-cost, risk-free, and widely available, it has been the most used method.

Although angiography is the gold standard exam for CAD diagnosis, the coronary calcification score identified by multislice computed tomography (MSCT) has been proposed as a potential method to improve the risk discrimination without invasive intervention, because it visualizes not only the coronary artery stenosis but also the characteristics of the plaque.[5] Thus, this method can be used to diagnose subclinical CAD.

The aim of this article was to review the relationship between NAFLD and CAD and the methods of diagnosis used to assess their relationship.

Methods

A review was performed using bibliographic databases MEDLINE (by PubMed), Web of Science, IBECS and LILACS, to identify articles published in Portuguese, English, and Spanish until August, 2012. The references of the articles were also surveyed and retrieved manually to find additional published investigations. During the search, the following strategy were used in PubMed: (Fatty Liver [MeSH] OR "Non-alcoholic Fatty Liver Disease"[Supplementary Concept] OR "Non-alcoholic Fatty Liver Disease"[All Fields] OR "nonalcoholic fatty liver disease"[All Fields] OR Steatohepatitis OR steatosis OR NASH OR NAFLD OR (fatty liver AND (non-alcoholic OR non-alcoholic))AND "coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields] OR "coronary artery disease"[MeSH Terms]). Similar terms were used in other databases. From each investigation, the specified protocols were observed, including the place and year of publication, CAD diagnosis at the beginning of the investigation, inclusion and exclusion criteria, criteria for the diagnosis of NAFLD and CAD, maximum alcohol consumption, NAFLD and CAD prevalence, and the risk factors involved in the association between NAFLD

and CAD. The studies were eligible if they had included the following data: place and year of publication, prevalence and methods used to diagnose NAFLD (US, CT, NMR, or biopsy) and CAD (angiography or tomography), exclusion of patients due to alcohol consumption higher than 20 g/day, and other causes of fatty liver.

Results

Nineteen articles involving the relationship of CAD and NAFLD or steatosis were identified, and nine were excluded: three[6–8] for not fulfilling the NAFLD criteria, five for using other methods to diagnose CAD,[9–13] and one for not citing the diagnostic method for CAD.[14]

However, a global interpretation of the investigations selected (Table 1) was not allowed because they differ with respect to the design of the study, the size and selected samples, inclusion and exclusion criteria of patient in each study (Table 2), methods used to diagnose NAFLD and CAD, and the confounding factors included in the analysis. Thus, to evaluate the association of NAFLD and CAD, the studies were grouped according to the method used for CAD diagnosis.

Analysis of the selected articles

Type of study

The articles selected had different methods. The majority were characterized as prospective cross-sectional studies[15,19,22] there was also one case-control study,[20] two retrospective cross-sectional studies,[21,24] and a prospective cohort study.[23]

Locale of the studies and sample size

Nine of the selected studies involved research with Asian patients. The samples varied from 61[20] to 4,023 patients.[24] In the investigations using the prospective cross-sectional model,[15–19,22] a total of 2,585 patients were evaluated (Table 1).

Inclusion criteria used for the selection of samples

The studies used the following inclusion criteria: clinical suspicion of CAD;[15,16,18] clinical suspicion of CAD in hospitalized patients;[22] MS;[17] evaluation of risk factors for CVD and cancer;[19] low-intermediate risk for CAD and the presence of NAFLD without any other hepatobiliary disease;[20] the first coronary angiography (CAG);[15] check-up for hepatobiliary disease and CAD in asymptomatic individuals;[21] adults who received health evaluation[24] and age ≥ 18 years[21,23] who underwent CAG.[23]

Exclusion criteria

There were varied criteria (Table 2) and most investigations listed only alcohol consumption > 20 g/day and the presence of other liver diseases as common exclusion criteria.

Studies with CAD diagnosis by MSCT

Five investigations assessed CAD by MSCT,[16,19–21,24] but the CAD criteria varied among the investigations. Most of these studies[19,21,24] evaluated the coronary artery calcium (CAC) score. Two of these investigations[21,24] quantified the total calcium score according to a scoring system proposed by Agatston et al.[25] In two articles,[19,21] a CAC score > 100 was considered to indicate a moderate-high risk of CAD. In another,[24] CAC presence (CAC > 0) was considered as evidence of calcification. Two studies analyzed the characteristics of coronary lesions in MSCT: Akabame et al.[16] classified the lesions of coronary arteries as calcified plaques, non-calcified plaques, low-density plaques, and positive remodeling vessels, and they observed that all major arteries had a diameter > 2.0 mm using enhanced images. The lipid pool was defined as having a plaque density of < 60 Hounsfield units (HU), and positive remodeling as having a remodeling index (RI) > 1.1. A calcified plaque was considered severe if > 180 HU, and as mild if < 180 HU. Assy et al.[20] used the degree of stenosis of the coronary artery (> 50%) as the CAD criterion. The plaques were classified as calcified or non-calcified on a segmental basis according to plaque features, including volume, attenuation, and calcification pattern. A calcified lesion was defined as a minimum of two pixels (area, 0.52 mm^2) with a minimum attenuation of 130 HU.

Methods and diagnostic criteria of NAFLD: In two of these studies, steatosis was diagnosed by CT[16,20]. In the study by Akabame et al.,[16] hepatic and splenic attenuation values were measured on non-contrast CT scans using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. The calculation of the relationship between the liver and spleen was made by the division between the average value of the liver attenuation (16 points) and the average value of the splenic attenuation (4 points). The cut-off value for the liver to spleen ratio to diagnose NAFLD was defined as < 1.1. Assy et al.[20] defined hepatic steatosis as the result of an attenuation of ≥ -10 HU (calculated as the liver attenuation minus the spleen attenuation).

Two studies used US for diagnosis of steatosis. In the study by Jung et al.,[19] subjects were diagnosed with steatosis if at least two of the following three findings were present: increased liver echogenicity, deep attenuation, and vascular blurring. In Kim et al.[24] steatosis diagnosis was made based on ultrasound feature characteristics consisting of "bright liver" and evident contrast between hepatic and renal parenchyma, vessel blurring, focal sparing, and narrowing of the lumen of the hepatic veins.

One study[21] diagnosed steatosis using US (218 patients) or CT (77 patients). In CT the following parameters were used: a liver attenuation lower than the spleen attenuation, pronounced contrast attenuation between the liver and spleen with blurred intrahepatic vessels, or markedly reduced attenuation of the liver with evident contrast between the liver and the intrahepatic vessels. In patients that had the US exam, the following parameters were considered: a diffuse increase in liver echogenicity with clear contrast between the liver and kidney, liver echogenicity diffusely increased with undefined intrahepatic vessels or diaphragm, or bright liver echogenicity with little penetration in the posterior

Table 1 – Selected studies about the association of CAD and NAFLD.

Author	Locale	year	N	Population	CAD prevalence	NAFLD prevalence	CAD and NAFLD association
Arslan et al.[15]	Turkey	2007	92	Suspicion of CAD	43 (46.7%)	65 (70.7%)	NAFLD is predictor of CAD (OR: 6.73; 95% CI: 1.14-39.61; p= 0.035)
Akabame et al.[16]	Japan	2008	298	Suspicion of CAD	Remodeling lesions: 56 (18.8%); lipid core plaques: 50 (16.8%); calcified plaque: 165 (55.4%); coronary lumen narrowing: 165 (55.4%)	60 (20.1%)	In NAFLD patients: Remodeling lesions: 19/60 (31.7%), p = 0.01; lipid core plaques: 17/60 (28.3%), p= 0.01; calcified plaque: 36/60 (60.0%), p = 0.47; coronary lumen narrowing: 47/60 (78.3%), p = 0.47
Alper et al.[17]	Turkey	2008	80	MS (ATP III) + suspected CAD	63 (78.8%)	43 (53.8%)	NAFLD patients had higher vessel (2.5 ± 0.9 vs. 1.1 ± 1.0) and CAD severity scores (90.0 ± 40.0 vs 36.4 ± 28.9), than patients without NAFLD (p < 0.0001)
Açikel et al.[18]	Turkey	2009	355	Suspicion of CAD	250 (70.4%); Gensini score: ≤ 36: 178 (50.1%); >36: 177 (49.9%)	Fatty liver: 215 (60.5%); fatty liver grades 2-3: 115 (32.4%)	Fatty liver grades 2-3 and CAD: 93/115 (80.9%), p = 0.003; fatty liver grades 2-3 and Gensini score > 36: 67/115 (58.3%), p = 0.041
Jung et al.[19]	Korea	2010	1,218	Subject submitted to evaluation of risk factors for CVD and cancer	CCS >100: 110 (9.0%)	514 (42.2%)	Steatosis and ALT > 30 U/L predict CCS > 100 (OR: 2.12; 95% CI: 1.08-4.20; p<0.05), but not steatosis alone (OR: 1.24; 95% CI: 0.68-2.26)
Assy et al.[20]	Israel	2010	61	Low or intermediate risk of CAD + fatty liver or healthy	Cases: 11 (38%) Controls: 4 (14%)	Cases: 29	NAFLD vs. controls: non-obstructive lesions: 38% vs. 14%; Obstructive lesions: 10% vs. 14%. Fatty liver is predictor of coronary atherosclerosis (OR: 2.0; 95% CI: 1-4; p < 0.04)
Chen et al.[21]	Taiwan	2010	295	Asymptomatic adults who received a check-up	CAC score: 0: 179 (60.7%); >100: 38 (12.9%)	121 (41%)	NAFLD was an independent factor that increased the risk of CAC >100: 23/38 (60.5%); (OR: 2.462; 95% CI: 1.065-5.691; p = 0.035)
Sun and Lu[22]	China	2011	542	High suspicion of CAD in hospitalized patients	Significant stenosis (≥ 70%): 382 (70.5%); mild or moderate injury: 136 (25.1%)	248 (45.7%)	Prevalence of NAFLD was associated with significant CAD: 222/382 (58.1%); (OR: 7.585; 95% CI: 4.617-12.461; p < 0.0001)
Wong et al.[23]	China	2011	612	Aged ≥ 18 years who underwent CAG	465 (76%)	356 (58.2%)	Fatty liver was associated with CAD: 301/465 (64.7%); (OR: 2.31; 95% CI: 1.46-3.64; p < 0.001); the association was independent of other metabolic factors
Kim et al.[24]	Korea	2012	4,023	Adults who visited health screening centers for a health evaluation (including CAC)	CAC score > 0: 1,286 (32%)	1,617 (40.2%)	NAFLD was associated with CAC > 0: 649/1,617 (40.1%); (OR: 1.35; 95% CI: 1.15-1.59; p < 0.001)

ALT, alanine aminotransferase; ATP, Adult Treatment Panel; CAC, coronary artery calcium; CAD, coronary artery disease; CAG, coronary angiography; CCS, coronary calcium score; CI, confidence interval, CVD, cardiovascular disease; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

Table 2 – Exclusion criteria used in the selected studies.

Exclusion criteria	Arslan et al.[15]	Akabam et al.[16]	Alper et al.[17]	Açikel et al.[18]	Jung et al.[19]	Assy et al.[20]	Chen et al.[21]	Sun and Lu[22]	Wong et al.[23]	Kim et al.[24]
CAD documented in CAG	●									
Previous CAD						●				●
AMI	●							●		●
History of CVD					●					
Coronary bypass grafting						●				
Prior percutaneous revascularization	●					●			●	
Acute coronary syndrome	●		●				●	●		●
Alcohol consumption(>20g/day)	●	●	●	●	●	●	●	●	●	●
Use of drugs that induce steatosis		●		●		●	●	●	●	●
Hepatitis B and/or C	●	●	●	●		●	●		●	●
History of liver diseases known		●		●		●	●	●	●	●
Systemic diseases that cause steatosis	●						●			
Pregnancy				●						
Congestive heart failure			●	●				●		●
Severe pulmonary disease				●		●				
Cor pulmonale				●						
Renal insufficiency				●		●	●	●		
Active infection(chronic or acute)				●						
Surgery for weight reduction							●			
Cancer				●	●	●				
Positive serology for HIV and syphilis				●						
Severe obesity(BMI>35)						●				
DM2			●							
Drugs that improve NAFLD	●									
History of recent acute disease						●				
History of Cerebrovascular or IHD					●	●				
Typical chest pain						●				
Specific exclusion criteria for cardiac CT						●				
Incomplete test				●			●			
Contraindications to coronary angiogram									●	
Antinuclear antibody title >1/160									●	
History of heart attack										●

NOTE: AMI, acute myocardial infarction, BMI, body mass index; DM_2, diabetes mellitus type 2; CAD, coronary artery disease; CAG, coronary angiography; CVD, cardiovascular disease; CT, computed tomography; HIV, Human immunodeficiency virus; IHD, Ischemic heart disease; NAFLD, nonalcoholic fatty liver disease.

egment and the intrahepatic vessels or invisibility of the iaphragm.

Regarding the prevalences of CAD and NAFLD, in the investigation that evaluated the total calcium score (CAC), 9% to 2.9% of the individuals had a moderate-high risk of CAD (CAC 100), while the NAFLD prevalence ranged from 20.1% to 42.2% Table 1).

Regarding the relationship between CAD and NAFLD, in ıose investigations that used MSCT to diagnose CAD, Chen t al.[21] observed a prevalence of NAFLD of 41% (121/295), while moderate-high risk of CAD (CAC > 100) was observed in 2.9% (38/295). The prevalence of NAFLD increased as the CAC :ore increased (p = 0.003). The results indicated that NAFLD is :lated to a moderate-high risk of coronary artery disease (CAC 100), but NAFLD is not guaranteed to be an independent risk ıctor or an epiphenomenon of CAD. In Jung et al.,[19] hepatic :eatosis was found in 42.2% (514/1,218), and coronary calcium :ore (CCS) > 100 with moderate-high risk of CVD was found in % (110/1,218) of subjects. An association was observed among ıe simultaneous presence of steatosis and elevated alanine minotransferase (odds ratio [OR] = 2.12; 95% CI: 1.08-4.20; p 0.05) and CSS >100, but not with steatosis alone (OR = 1.24; 5% CI: 0.68-2.26). In the study by Kim et al.,[24] the presence of NAFLD was 40.2% (1,617/4,023) and that of CAC > 0 was 32% (1,286/4,023). In the univariate analysis, the presence of CAC (score > 0) was significantly associated with NAFLD. Increasing CAC scores (0, < 10, 10-100, ≥ 100) were associated with higher prevalence of NAFLD (OR, 1.84; 95% CI: 1.61-2.10; p < 0.001).

Akabame et al.[16] observed the existence of a relationship between NAFLD and the presence of remodeling lesions (OR = 2.41; 95% CI: 1.24-4.67; p = 0.0009) and lesions with a lipid core (OR = 2.29; 95% CI: 1.15-4.56; p = 0.0018), but they did not observe a correlation with calcified plaques or luminal stenosis. Assy et al.[20] found relationship of NAFLD with a higher prevalence of calcified and non-calcified plaques and nonstenotic lesions (38% *vs.* 14%). Although the presence of obstructive lesions was more frequent in the controls than in the patients with NAFLD (14% *vs.* 10%), the multivariate analysis showed the association of NAFLD with more severe coronary atherosclerosis.

Studies with CAD diagnosis by CAG

Five studies assessed CAD through angiography. Once again, the CAD criteria were different. Three studies defined CAD as the presence of at least 50% stenosis in at least one major

coronary artery.[15,22,23] Two studies[17,22] assessed CAD severity by the number of vessels affected (vessel score), the degree of coronary artery stenosis, and by use of the Gensini severity score.[26] The vessel scores ranged from 0 to 3, depending on the vessels involved. Significant stenosis was defined as a reduction of 70% or greater in the luminal diameter in any view compared with the nearest normal segment. The Gensini score considers the number of vessels affected, the importance

of these vessels, the degree of stenosis, and its localization in the artery. The cut-off was set as the average value of Gensini score = 36. The patients were divided into two groups, those with a Gensini score ≤ 36 points (absent or mild coronary atherosclerosis) and those with a Gensini score >36 points (medium to severe coronary atherosclerosis). One study[18] considered CAD if the stenosis was ≥ 50% in the epicardial coronary arteries or their major branches. In this investigation, to assess the severity of the coronary atherosclerosis, a modified Gensini score and the number of vessels affected (one, two, or three vessels) were used.

Regarding the methods and diagnostic criteria of NAFLD, four studies used US for NAFLD[15,17,18,23] diagnosis. Arslan et al.[15] defined the presence of hepatic steatosis as the diffuse increase in the echogenicity of the liver compared with the kidney according to the conventional criteria. In Açikel et al.,[18] the right kidney echogenicity was used to determine the echogenicity of the hepatic parenchyma, and the liver was considered normal if it presented echogenicity equal to that of the kidney (degree 0). Fatty infiltration of the liver was described in three levels: mild (degree 1), when there was a minimum diffuse increase in the hepatic echogenicity, contours of the diaphragm and intrahepatic vessels with normal appearance; average (degree 2), when there was a moderate diffuse increase in the hepatic echogenicity and a slight deterioration in the image of the vessels of the liver and diaphragm; and severe (degree 3), when there was an apparent increase in the echogenicity. The posterior segment of the right lobe of the liver was difficult to visualize, and the structure of the intrahepatic vessels and contours of the diaphragm were smeared or not viewed.

Alper et al.[17] described the US criteria to diagnose steatosis, including the hyperechoic appearance of the liver parenchyma with fine, tightly packed echoes and posterior beam attenuation. Steatosis was classified as mild, moderate, or severe when using the following parameters: normal liver – a normal hepatic echotexture and normal beam attenuation; mild hepatic steatosis –presence of a minimum increase in the echogenicity of the liver parenchyma, with a slight decrease in the definition of the portal vein walls, and minimal or no posterior beam attenuation; severe steatosis – a grossly increased hepatic parenchyma echotexture, allowing only for the visualization of the main portal vein walls and a strikingly increased posterior beam attenuation; moderate steatosis – the characteristics of these parameters (hepatic echogenicity, portal venous definition, and beam attenuation) fall between mild and severe. In the case of a confounding coexistence, the grade was assigned according to the most predominantly abnormal finding. The study by Wong et al.[23] was based on ultrasonographic features of diffusely increased liver echogenicity greater than that of the kidney or spleen, vascular blurring, and deep attenuation of the ultrasound signal. In the study by Sun and Lu,[22] NAFLD was investigated by CT. They used the same criteria as Chen et al.[21]

CAD and NAFLD prevalence: CAD prevalence by CAG varied from 46.7% to 95.6%. In these patients, NAFLD prevalence varied from 32.4% to 70.7% (Table 1)

Regarding the relationship between CAD and NAFLD, Arslan et al.[15] found a prevalence of NAFLD of 70.7% (65/92), while significant CAD was observed in 46.7% (43/92) of the patients. The probability of detecting the presence of CAD was 6.73 times higher in patients with NAFLD than in patients without it (p = 0.035). The presence of NAFLD was independently related to the presence and extent of CAD. Alper et al.[17] observed NAFLD and CAD in 53.8% (43/80) and 78.8% (63/80), respectively, of the patients with MS. Patients with NAFLD had significantly higher scores for affected vessels (2.5 ± 0.9 *vs.* 1.0 ± 1.0) and for the severity of CAD as evaluated by the Gensini score (90.2 ± 40.0 *vs.* 36.4 ± 28.9) than patients without NAFLD (p < 0.001). The presence of NAFLD, the degree of NAFLD, and the patient's age were significantly correlated with the severity score of CAD. Açikel et al.[18] found a prevalence of NAFLD of 32.4% (115/355), while CAD was present in 70.4% (250/355) of the patients. They concluded that the presence of steatosis in the US and its severity may represent an independent effect in both the presence and severity of CAD. Sun and Lu[22] showed that the prevalence of CAD was 95.6% (518/542) and significant CAD was 70.5% (382/542), while that of NAFLD was 45.7% (248/542). Patients with NAFLD had significantly higher vessel scores (1.5 ± 0.6 *vs.* 1.4 ± 08, p = 0.001) and more severe CAD scores. Wong et al.[23] found fatty liver prevalence of 58.2% (356/612) while significant CAD was observed in 76.0% (465/612) of subjects. Their study concluded that fatty liver is associated with CAD independently of other metabolic factors. However, fatty liver cannot predict cardiovascular mortality and morbidity in patients with established CAD.

Evaluation of other risk factors

Two studies[15,21] evaluated the relationship between CAD and risk factors, three[16,17,20] made a similar evaluation concerning NAFLD, and five evaluated the risk factors associated with these two conditions.[18,19,22–24]

The researchers observed relationships between CAD and increased age,[15,18,19,21–24] male gender,[18,21–24] previous myocardial infarction (MI),[18,22] hypertension,[19,21,24] body mass index (BMI),[24] waist circumference,[24] diabetes mellitus (DM),[18,21,24] smoking,[18,19,24] dyslipidemia,[18] lower levels of high-density lipoprotein (HDL) cholesterol,[18,23,24] high levels of low-density lipoprotein (LDL) cholesterol,[22] triglycerides[24] fasting plasma glucose (FPG),[19,21,24] total cholesterol (TC),[22] aspartate aminotransferase (AST),[18,21,22,24] alanine aminotransferase (ALT),[19,22–24] gamma-glutamyltranspeptidase (GGT),[18,24] and the use of lipid-lowering drugs[24] (p < 0.05, respectively). However, other investigations did not relate CAD to male gender,[15] hypertension,[15,18,22] DM,[22] smoking history[15,21-23] high levels of LDL cholesterol,[15,23] lower levels of HDL cholesterol,[15] TC,[18,21] triglycerides,[15,18,21,22] ALT,[18,21] obesity,[18,22] waist circumference,[15] MS,[18,22] or BMI.[15,18,22]

NAFLD was related to age in three studies,[19,22,24] but this relationship was not observed in four others.[16,17,20,23] NAFLD was also related to DM,[22-24] male gender,[23,24] waist circumference,[17,20,22-24] smoking,[24] obesity,[22] hypertension,[23,24] MS,[22] higher levels of triglycerides,[17,20,22-24] ALT,[20,24] AST,[24] GGT,[24] TC[24] homeostasis model assessment (HOMA),[20] lower HDL-cholesterol levels,[17,22-24] and Gensini score.[17,22] There was a relationship with BMI in five studies[16,17,22-24] but not in a different investigation.[20] NAFLD severity(grades 2-3) was associated with the male gender, dyslipidemia, BMI, obesity, MS, triglycerides, and Gensini score ($p < 0.05$).[18]

There were no relevant differences between patients with and without NAFLD regarding male gender[16,17,22] smoking[16,17,22,23] hypertension,[16,17,22] DM,[16,20] dyslipidemia[16] family history of CAD[17,22] biochemical parameters of glucose during fasting,[16,17] TC,[17,22,23] HDL-cholesterol,[20] LDL-cholesterol,[17,20,22] AST,[22] and ALT.[17,22]

Discussion

Due to differences concerning the selection criteria of the samples, methods, and parameters for CAD and steatosis in most of the investigations, it is difficult to compare the results. In investigations that used MSCT to diagnose CAD, two studies analyzed the characteristics of coronary plaques and their association with NAFLD and found different results. While Assy et al., in a small study, found an association of NAFLD with coronary stenosis of at least 50%, the results of Akabame et al. indicate that patients with NAFLD might have a risk factor for vulnerable plaque rather than coronary stenosis. This result, therefore, suggested that NAFLD was related to the initial phase of CAD, but not with CAD severity. These observations highlighted the importance of evaluating NAFLD in individuals with subclinical CAD to establish strategies to prevent the evolution of the disease. The study by Chen et al.[21] identified a correlation between NAFLD and CAC > 100. However, in the selection of the 295 participants, 1,391 individuals were excluded. In this study, individuals aged ≥ 18 were included, and the exams, which are expensive, were paid by the patients. This may have caused the selection of individuals with fewer risk factors and higher socioeconomic class. Jung et al.[19] considered CCS > 100 as moderate to severe risk of CAD, and identified a correlation among steatosis and elevated alanine aminotransferase and CAD. However, their sample only excluded patients with alcohol intake > 20 g/day and positive virus B and C. They did not exclude other secondary causes of steatosis such as autoimmune diseases and use of hepatotoxic drugs, which may constitute an important bias. Kim et al. considered CAC values > zero as positive, but most of the patients have positive values between 0 and 100 and therefore, low or very low risk for CAD. It was a retrospective study involving a large number of subjects conducted in two health screening centers. Due to the study design, information about patients may have been affected.

Regarding the studies involving angiography to evaluate the relationship between NAFLD and CAD, such relationship may be a consequence of the selection. The studies considered CAD to be the presence of stenosis ≥ 50%, representing the existence of moderate to severe obstruction of the coronary arteries. Nevertheless, these studies do not consider the initial phases of the disease when obstructions < 50% are observed, confirming the presence of mild CAD. Taking into account that coronary occlusion and myocardial ischemia may frequently be due to mild or moderate stenosis, the identification of such levels of obstruction in patients with NAFLD might be important for the risk stratification and therapeutic orientation, in addition to demonstrating such relationship more reliably. In the study by Arslan et al., NAFLD was observed in 70.7% of the patients, while coronary disease was present in only 46.7%, since only patients submitted to the first angiography could take part, and those individuals with previously diagnosed CAD were excluded. Wong et al.[23] also evaluated the effects of the presence of NAFLD for outcomes, and found no association of NAFLD and cardiovascular mortality in patients with confirmed CAD. These researchers concluded that NAFLD correlates with incident CAD, but cannot be used as a prognostic marker in patients with established CAD. In the latter case, the prognosis may be governed by other factors. Their study included patients referred for CAG by causes other than CAD.

Some comments can be made concerning the investigations that used the Gensini score,[17,18,22] which was used to establish the severity criterion because it evaluates lesions from mild to 100% obstruction. The score is determined according to the importance of the vessel affected, and has a cut-off value of 36 (Gensini score ≤ 36 points: absent or mild coronary atherosclerosis; > 36 points: moderate to severe coronary atherosclerosis). Acikel et al.,[18] used the Gensini score in a different form, and no justification for such a modification was presented, although the results were similar to other studies[17,22]. In the study by Sun and Lu,[22] the prevalence of CAD was 95.6%, with 70.5% (382/542) of the individuals presenting significant stenosis, taking into account the hospitalization of the patients. In their study, a Gensini score > 36 was established, indicating moderate to severe coronary atherosclerosis. However, even in the comparison between patients with significant and non-significant CAD, the average Gensini score (23.2 ± 12.1 *vs.* 10.1 ± 7.0, $p < 0.001$) was lower than the cut-off point. When the relationship of NAFLD with the CAD severity score was evaluated, the average value was again lower than the cut-off point, although the average score was higher in patients with NAFLD compared with patients without NAFLD (24.5 ± 12.6 *vs.* 14.9 ± 10.4, $p < 0.001$).

Finally, all selected studies involved Asian patients, and this should be noted because they have different epidemiological characteristics, lifestyles, and eating habits compared with Western individuals. The contribution of these characteristics to the association between CAD and NAFLD should not be neglected.

Conclusion

The studies reviewed in the present article point to the relevance of evaluating CAD in patients with NAFLD, since it may prevent higher risk of acute myocardial infarction and consequent increase in mortality. However, there are limitations in this review: the majority of the studies evaluated were cross-sectional and have a low level of scientific evidence. Most of

the studies were performed in Asian patients, and further trials using other study designs are needed, especially involving Western patients.

Conflicts of interest

The authors declare no conflicts of interest.

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PREDICTIVE FACTORS OF NONALCOHOLIC FATTY LIVER IN PATIENTS WITH CORONARY DISEASE FROM NORTHEAST OF BRAZIL

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common type of chronic liver injury around the world, and it is associated to metabolic syndrome and cardiovascular diseases. **Aim:** to evaluate the predictive factors of NAFLD in patients with coronary artery disease (CAD). **Methods:** the study included patients who underwent elective coronary angiography (CAG) from April 2009 to September 2010. The patients came from Northeast to Brazil, which population is composed of a variety of ethnic groups. All of them had clinical suspicion of CAD. Criteria to CAD included presence of obstructive lesions in the epicardial coronary arteries, or in their major branches. NAFLD criteria were presence of hepatic steatosis on ultrasound; exclusion of other liver diseases; ethanol intake ≤20 g/ day. Statistics analysis included Independent *t*-test, Mann-Whitney and Pearson's chi-squared test. Multivariate regression analysis measured the relationship strength between risk factors and the concomitant presence of CAD and NAFLD. **Results:** 244 patients who underwent CAG were included: 63.5% had CAD and 42.2% presented NAFLD; 43.9% of the patients with CAD had NAFLD association. The regression analysis showed that the possibility of concomitant occurrence of CAD and NAFLD was positively correlated with HOMA-IR ≥3.0, overweight and obesity. **Conclusion:** NAFLD was frequent among CAD patients; insulin resistance, overweight and obesity were predictive factors of NAFLD in patients with CAD.

Keywords: fatty liver; coronary disease; cardiovascular diseases; coronary angiography; steatosis.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common type of chronic liver injury. In general, it is an asymptomatic and under-diagnosed condition in patients with cardiovascular disease (CVD). Some parameters such as the presence of diabetes mellitus (DM), overweight, obesity, insulin resistance (IR), and liver enzyme abnormalities may suggest the existence of NAFLD. Coronary artery disease (CAD) and they have been associated with the severity, progression and mortality in patients with NAFLD. Some studies have shown histological changes of NAFLD in association with CVD (1, 2) and the relevance of the relationship between NAFLD and CAD (3-5). NAFLD also likely represents an independent risk factor for CAD and this is one of the most important causes of morbidity and mortality among these patients (6, 7).

The influence of ethnicity has been discussed in patients with NAFLD (8). The prevalence of NAFLD is more elevated in Hispanics than in whites, and African Americans ranking as the ethnic group with the least prevalence of NAFLD (9).

The present study evaluated the predictive factors of NAFLD in patients with CAD from a region of Northeast of Brazil.

PATIENTS AND METHODS

Study Design and Population Selection

From April 2009 to September 2010, patients who underwent elective coronary angiography (CAG) were included on this study. All of them came from a region of Northeast of Brazil. This population is composed of descends of Amerindians, Africans and Europeans.

Coronary angiography was performed in individuals under clinical investigation of CAD for stable angina pectoris, chest pain management or prognostic evaluation after acute myocardial infarction. All of them were previous evaluated at a public Cardiology Clinic, a reference center in Campina Grande, city of Northeast of Brazil.

The exclusion criteria were patients, who presented B and C virus infection; hemochromatosis; autoimmune hepatitis; alcohol intake more than 20 grams per day; CAG' performed for other reasons than CAD; drugs use such as glucocorticoids, estrogens, amiodarone, carbamazepine, tamoxifen or other agents considered risk factor to NAFLD.

The Ethics Committee on Human Research of Hospital Universitário Alcides Carneiro from Universidade Federal de Campina Grande, Brazil, approved the study. It was conducted according to the principles outlined in the Declaration of Helsinki (1964, revised 2008).

Patients' evaluation

All patients answered a questionnaire, underwent physical examination and performed laboratory analysis and abdominal ultrasound (AUS).

The study parameters included gender, age, anthropometric measures, blood pressure levels, CAG indications, history of type 2 diabetes, arterial hypertension, dyslipidemia, acute myocardial infarction, alcohol intake, smoking habits and use of medications (including anti-diabetic, lipid-lowering, antihypertensive and hepatotoxic drugs: glucocorticoids, estrogens, amiodarone, carbamazepine, tamoxifen, and nonsteroidal anti-inflammatory).

Laboratory exams included HBsAg, anti-HCV, auto-antibodies (antinuclear, anti-smooth muscle, anti-mitochondria), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), glucose, insulin, proteins, ferritin, transferrin saturation index, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and alkaline phosphatase.

NAFLD criteria: presence of hepatic steatosis on ultrasound; exclusion of other liver diseases; ethanol intake ≤ 20 g/day.

CAD criteria on coronary angiography: stenosis in the epicardial coronary arteries or their major branches.

Measurements

Anthropometric measurements were evaluated according to the World Health Organization guidelines (10, 11). Hypertension was diagnosed based on the Seventh report of the Joint Committee on Prevention, Detection, and Treatment of High Blood Pressure Guidelines (12). DM was defined in accordance with the World Health Organization guidelines (13). Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III report (14). HOMA-IR ≥ 3.0 was considered insulin resistance (15, 16).

Consumption of at least one cigarette a day in a period not less than 6 months defined regular smoking and former smokers, were those who smoked regularly up to six months before the examination (17). A practitioner conducted face-to-face interviews to determine daily alcohol intake, smoking habits and medication consumption.

The criterion for CAD on coronary angiography included stenosis in the epicardial coronary arteries or their major branches.

The diagnosis of fatty liver was based on abdominal ultrasonography with a 3.5 MHz transducer using a Nemio 17 ultrasound machine (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan). The same experienced sonographer, who was not informed of the clinical history and CAG results, performed the abdominal ultrasound. Hepatic steatosis was diagnosed according to previous criteria (18, 19)

Statistical analysis

Statistical analysis included the independent t test and Mann-Whitney test for analysis of continuous variables, as appropriate. Categorical data were analyzed using Pearson's chi-square test. Multivariate regression analysis has measured the strength of the relationship between risk factors and the concomitant presence of CAD and NAFLD. Variables with *P*-value ≤ 0.15 in the univariate analysis were selected as the independent variables for the multivariate study. A selection process "stepwise" was applied to obtain a reduced model. All continuous variables were entered into the logistic regression model as continuous variables; they weren´t converted into categorical data. Concomitant CAD and NAFLD was selected as

dependent variable. All statistical methods were two-tailed, *P* values were calculated and the significance level was set to less than 0.05.

RESULTS

Two hundred forty four patients were included. The clinical characteristics of the sample are in Table 1. CAG found 155 patients (63.5%) with CAD ([95%CI]: 57.1–69.6%). The prevalence of risk factors, such as male gender, type 2 diabetes and smoking, were significantly higher (*P*<0.05) than in the group without a CAD diagnosis (Table 2).

One hundred three patients (42.2%) had NAFLD (95%CI: 35.9–48.7%), and it was strongly associated with central obesity, diabetes and insulin resistance (IR), and significantly related to higher body mass index values, neck and waist circumferences (Table 3). The association of NAFLD with metabolic syndrome (*P*=0.024), lower levels of HDL-cholesterol (P=0.043), higher levels of TG (*P*=0.005), high levels of ALT (*P*=0.003), and ferritin (*P*=0.032) were significant.

The frequency of NAFLD in patients with a CAD was 43.9% (68/155). In univariate analysis (Table 4) several factors were statistically significant for the association between NAFLD and CAD including central obesity, neck circumference, ferritin, overweight / obesity, and HOMA-IR ≥ 3.0 (p <0.001) Multivariate regression analysis was performed to measure the strength of the relationship between risk factors and the concomitant presence of CAD and NAFLD compared to DAC presence only. For the multivariate study, it was selected variables with p < 0.15 in the univarieate analysis (Table 4). The variables age, DM, neck circumference, central obesity, overweight/obesity, fasting insulin, HOMA≥ 3.0, TG, HDL-cholesterol, and ferritin entered in the initial model. With these variables it was adjusted a multivariate logistic regression model. The model selected age, diabetes, central obesity, neck circumference, obesity, fasting insulin, HOMA≥ 3.0, HDL-cholesterol, TG, and ferritin. A selection process "stepwise" was applied to obtain a reduced model. The adjusted model was given by HOMA ≥ 3.0 and overweight or obesity. The result of regression analysis showed that the possibility of concomitant occurrence of CAD and NAFLD was positively correlated with these variables (Table 5). The positive predictive value found for HOMA≥ 3.0 was 67.3%, while the negative

predictive value was 67%. In relation to overweight or obesity, these values were 55.2% and 87.8%, respectively.

DISCUSSION

Some studies have evaluated the association between NAFLD and CAD diagnosed by coronary angiography (3-5, 20, 21) a gold standard method for diagnosis of coronary disease. However, most of them have evaluated the risk factors, and its relationship with the presence of CAD or NAFLD alone and the majority of the studies come from Asia.

The present study included a large series of patients submitted to coronary angiography, who come from an area of Northeast of Brazil which population has a low economic status and several ethnic descended, like Amerindians, Africans and Europeans.

These factors are relevant. Race and ethnicity can be predictive factors of liver diseases complications and response to treatment in patients with chronic liver disease. These ethnic differences should influence the prevalence and profile of NAFLD in South America and studies from some countries have shown the relevance of this liver disease in this continent (22, 23).

The risk factors related to the presence of CAD in these Brazilian patients were male gender, smoking, type 2 diabetes, lower levels of HDL-cholesterol and a higher frequency of use of lipid-lowering drugs. NAFLD was associated with DM, insulin resistance, BMI, higher levels of triglycerides and waist circumference, lower HDL-cholesterol, obesity, and metabolic syndrome. Similar results were found in other studies regarding DAC and gender (3, 20, 21), smoking, DM (3), lower levels of HDL-cholesterol, (3, 21) and a higher frequency of use of lipid-lowering drugs (3) and NAFLD association with DM (20, 21), BMI, higher levels of triglycerides and waist circumference, lower HDL-cholesterol levels (5, 20, 21), obesity, and metabolic syndrome (20).

This investigation did not observe association between NAFLD and age, arterial hypertension, gender, and CAD. These results are distinct from other studies especially regarding the absence of association between NAFLD and CAD (3-5, 20, 21). The hypothesis for these findings are the different population, who was

evaluated; the criteria of CAD diagnose; and the patients' precedence. The majority of these individuals came from out clinics to perform elective coronary angiography with suspicion of CAD. The similar studies included patients with metabolic syndrome (5), admitted with acute coronary syndrome and AMI (3, 21) and hospitalized patients (20). These cases, in general, have more severe CAD disease.

The criteria for DAC used here was different from other studies, because any obstructive lesion in the epicardial coronary arteries or in their major branches were considered. This approach can help early diagnosis of CAD in patients with NAFLD. Taking into account that coronary occlusion and myocardial ischemia may frequently be due to mild or moderate lesion, the identification of such levels of obstruction in patients with NAFLD might be important for the risk stratification and therapeutic orientation. It could also help to reduce morbidity and mortality of these patients. However, others considered the stenosis of at least 50% in at least one major coronary artery to CAD diagnosis (4, 20, 21), or stenosis of at least 50% in epicardial arteries or their major branches (3), and one study evaluated the association between NAFLD and CAD severity (5). In this sense, significant stenosis was defined as 70% or greater reduction in luminal diameter in any view compared with the nearest normal segment.

The patients' background and ethnicity should also be considered in the discussion. This study included patients with several ethnic descended who come from South America and the majority of others studies came from Asia. There they have others epidemiologic factors, ethnicity and behaviors, that could have influenced the results. Asians, even those living in the West, seem to be more at risk for NAFLD than their Caucasian and African American counterparts. In addition, they develop NAFLD at a younger age, and NAFLD patients are more likely to be male (24). These characteristics could contribute to the NAFLD and CAD association.

Therefore, this study made possible to inform the scientific community, results observed in our population which has socioeconomic, ethnic and behavioral characteristics different from other populations previously studied. On the other hand, our results agree with the study published by Feitosa *et al.* (25), which evaluated 2,756 European-American. In their study, no association was observed between fatty liver diagnosed by computed tomography and coronary heart disease.

In conclusion, the regression analysis showed that the possibility of concomitant occurrence of CAD and NAFLD had correlation with insulin resistance, overweight and obesity in patients who come from Northeast of Brazil. NAFLD was frequent among CAD; insulin resistance, overweight and obesity were predictive factors of NAFLD in patients with CAD.

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CONFLICTS OF INTEREST

All authors have none to declare

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Table 1. Clinical and laboratory characteristics of patients undergoing coronary angiography

Variables	**All patients** (n=244)
Age (years)	61.5 ± 9.3
Male, n (%)	126 (51.6)
Hypertension, n (%)	203 (83.2)
Diabetes Mellitus, n (%)	66 (27.0)
Fasting insulin (µUI/mL)	9.1 ± 8.5
HOMA-IR	2.8 ± 3.1
HOMA ≥ 3.0, n (%)	68 (27.9)
BMI (kg/m²)	28.0 ± 4.5
Waist circumference (cm)	99.3 ± 11.4
Central obesity, n (%)	147 (60.2)
Overweight/obesity, n (%)	182 (74.6)
Neck circumference (cm)	38.2 ± 3.6
Metabolic syndrome, n (%)	168 (68.9)
Smoking, n (%)	141 (57.8)
Use of statin therapy, n (%)	112 (45.9)
TC (mg/dL)	192.9 ± 54.2
HDL-cholesterol (mg/dL)	41.2 ± 9.7
LDL-cholesterol (mg/dL)	112.6 ± 42.5
Triglycerides (mg/dL)	200.3 ± 14.3
AST (U/L)	24.4 ± 13.5
ALT (U/L)	30.8 ± 20.0
Ferritin (ng/mL)	178.4 ± 169.3
GGT (U/L)	45.1 ± 53.2
CAD, n (%)	155 (63.5)
NAFLD, n (%)	103 (42.2)

Continuous variables: mean ± SD; categorical variables: n (%).
HOMA-IR - homeostasis model assessment-insulin resistance index; BMI - Body mass index; TC - Total cholesterol; HDL - high-density lipoprotein; LDL - low-density lipoprotein; AST - aspartate aminotransferase; ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase; CAD - coronary artery disease; NAFLD - nonalcoholic fatty liver disease

Table 2. Clinical and laboratory data of patients undergoing coronary angiography, according to the diagnosis of coronary artery disease

Variables	Total (n=244)	Coronary artery disease		*P* value
		Present (155)	Absent (89)	
Age (years)	61.5 ± 9.3	62.3 ± 9.3	60.0 ± 9.0	0.067
Male, n (%)	126 (51.6)	99 (63.9)	27 (30.3)	<0.001
Hypertension, n (%)	203 (83.2)	126 (81.3)	77 (86.5)	0.293
Diabetes Mellitus, n (%)	66 (27.0)	51 (32.9)	15 (16.9)	0.007
Smoking, n (%)	141 (57.8)	97 (62.6)	44 (49.4)	0.045
Waist circumference (cm)	99 ± 11	99 ± 10	100 ± 13	0.567
Central obesity, n (%)	147 (60.2)	85 (54.8)	62 (69.7)	0.023
Neck circumference (cm)	38 ± 4	39 ± 3	37 ± 3	0.015
Body mass index (kg/m²)	28.0 ± 4.5	27.6 ± 4.2	28.7 ± 5.0	0.084
Overweight/obesity, n (%)	182 (74.6)	114 (73.5)	68 (76.4)	0.622
Metabolic syndrome, n (%)	168 (68.9)	104 (67.1)	64 (71.9)	0.434
Fasting insulin (µUI/mL)	9.1 ± 8.6	10.0 ± 10.0	7.5 ± 4.5	0.008*
HOMA-IR index	2.8 ± 3.1	3.0 ± 3.5	2.3 ± 2.4	0.098*
HOMA-IR ≥ 3.0, n (%)	68 (27.9)	49 (32.9)	19 (22.6)	0.098
Total cholesterol (mg/dL)	192.9 ± 54.2	185.1 ± 54.5	206.4 ± 51.2	0.003
HDL cholesterol (mg/dL)	41.2 ± 9.7	38.9 ± 8.4	45.3 ± 10.5	<0.001
LDL cholesterol (mg/dL)	112.6 ± 42.5	107.7 ± 42.4	120.6 ± 41.6	0.026
Triglycerides (mg/dL)	200.2 ± 143.2	203.9 ± 159.6	193.8 ± 109.4	0.596
AST (U/L)	24.4 ± 13.5	24.3 ± 12.8	24.7 ± 14.8	0.847
ALT (U/L)	30.8 ± 20.0	31.8 ± 19.7	29.2 ± 20.4	0.326
Ferritin (ng/mL)	178.4 ± 169.3	205.6 ± 194.2	131.1 ± 98.7	<0.001*
GGT (U/L)	45.0 ± 53.2	49.6 ± 61.6	37.0 ± 32.2	0.074*
Use of statin therapy, n (%)	112 (45.9)	89 (57.4)	23 (25.8)	<0.001
NAFLD, n (%)	103 (42.2)	68 (43.9)	35 (39.3)	0.489

Continuous variables: mean ± SD; categorical variables: n (%).
* Mann-Whitney test.
HOMA-IR - homeostasis model assessment-insulin resistance index; HDL - high-density lipoprotein; LDL - low-density lipoprotein; AST - aspartate aminotransferase; ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase; NAFLD - nonalcoholic fatty liver disease.

Table 3. Clinical and laboratory data of patients undergoing coronary angiography, according to the diagnosis of nonalcoholic liver disease

Variables	Total (n=244)	Nonalcoholic liver disease		*P* value
		Present (n=103)	Absent (n=141)	
Age (years)	61.5 ± 9.3	60.7 ± 9.0	62.0 ± 9.5	0.259
Male, n (%)	126 (51.6)	52 (50.5)	74 (52.5)	0.758
Hypertension, n (%)	203 (83.2)	84 (81.6)	119 (84.4)	0.557
Diabetes Mellitus, n (%)	66 (27.0)	38 (36.9)	28 (19.9)	0.003
Smoking, n (%)	141 (57.8)	54 (52.4)	87 (61.7)	0.147
Waist circumference (cm)	99 ± 11	104 ± 9	95 ± 11	<0.001
Central obesity, n (%)	147 (60.2)	75 (72.8)	72 (51.1)	0.001
Neck circumference (cm)	38 ± 4	39 ± 3	37 ± 3	<0.001
Body mass index (kg/m²)	28.0 ± 4.5	30.2 ± 4.1	26.4 ± 4.2	<0.001
Overweight/obesity, n (%)	182 (74.6)	95 (92.2)	87 (47.8)	<0.001
Metabolic syndrome, n (%)	168 (68.9)	79 (76.7)	89 (63.1)	0.024
Fasting insulin (µUI/ml)	9.1 ± 8.6	11.4 ± 8.9	7.4 ± 7.9	<0.001*
HOMA-IR index	2.8 ± 3.1	3.6 ± 3.0	2.2 ± 3.1	0.001*
HOMA-IR ≥ 3.0, n (%)	68 (27.9)	45 (45.5)	23 (17.2)	<0.001
Total Cholesterol (mg/dL)	192.9 ± 54.2	193.6 ± 52.7	192.4 ± 55.4	0.864
HDL cholesterol (mg/dL)	41.2 ± 9.7	39.8 ± 9.1	42.3 ± 10.0	0.043
LDL cholesterol (mg/dL)	112.6 ± 42.5	108.8 ± 39.3	115.1 ± 44.5	0.268
Triglycerides (mg/dL)	200.2 ± 142.2	232.3 ± 172.4	176.8 ± 112.4	0.005
AST (U/L)	24.5 ± 13.6	25.7 ± 13.9	23.5 ± 13.2	0.224
ALT (U/L)	30.8 ± 20.0	35.3 ± 21.9	27.6 ± 17.9	0.003
Ferritin (ng/mL)	178.4 ± 169.3	205.4 ± 191.0	158.4 ± 149.0	0.032*
GGT (U/L)	45.0 ± 53.2	47.2 ± 36.1	43.5 ± 62.8	0.586*
Use of statin therapy, n (%)	112 (45.9)	44 (42.7)	68 (48.2)	0.394
CAD, n (%)	155 (63.5)	68 (66.0)	87 (61.7)	0.489

Continuous variables: mean ± SD; categorical variables: n (%).
*Mann-Whitney test.
HOMA-IR - homeostasis model assessment-insulin resistance index; HDL - high-density lipoprotein; LDL - low-density lipoprotein; AST - aspartate aminotransferase; ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase; CAD - coronary artery disease.

Table 4. Risk factors related to NAFLD in patients with CAD.

Variables	Total (n=155)	NAFLD		*P* Value
		Present (n=68)	Absent (n=87)	
Age (years)	62.3 ± 9.3	60.7 ± 9.3	63.6 ± 9.2	0.053
Gerder: Male, n (%)	99 (63.9)	41 (60.3)	58 (66.7)	0.412
Female, n (%)	56 (36.1)	27 (39.7)	29 (33.3)	
Hypertension, n (%)	126 (81.3)	53 (77.9)	73 (83.9)	0.344
Diabetes Mellitus, n (%)	51 (32.9)	27 (39.7)	24 (27.6)	0.111
Smoking, n (%)	97 (62.6)	40 (58.8)	57 (65.5)	0.393
Central obesity, n (%)	85 (54.8)	45 (66.2)	40 (46.0)	0.012
Neck circumference (cm)	38.6 ± 3.5	39.8 ± 3.2	37.7 ± 3.5	<0.001
Overweight/obesity, n (%)	114 (73.5)	63 (92.6)	51 (58.6)	<0.001
Metabolic syndrome, n (%)	104 (67.1)	49 (72.1)	55 (63.2)	0.245
Use of statin therapy, n (%)	89 (57.4)	36 (52.9)	53 (60.9)	0.319
Fasting insulin (µUI/mL)	10.0 ± 10.0	12.3 ± 10.1	8.2 ± 9.7	0.014*
HOMA-IR ≥ 3.0, n (%)	49 (32.9)	34 (50.0)	16 (19.3)	<0.001*
TC (mg/dL)	185.1 ± 54.5	186.2 ± 46.8	184.3 ± 60.1	0.882
HDL-cholesterol (mg/dL)	39.8 ± 8.4	37.7 ± 7.6	39.9 ± 8.9	0.110
LDL-cholesterol (mg/dL)	107.7 ± 42.4	106.5 ± 36.8	108.5 ± 46.4	0.770
Triglycerides (mg/dL)	203.9 ± 159.6	233.6 ± 187.3	180.7 ± 130.7	0.040
AST (U/L)	24.3 ± 12.8	24.6 ± 10.3	24.1 ± 14.6	0.800
ALT (U/L)	31.8 ± 19.7	34.2 ± 20.3	29.9 ± 19.2	0.173
Ferritin (ng/mL)	205.6 ± 194.2	231.5 ± 214.9	185.2 ± 174.7	0,041*
GGT (U/L)	49.5 ± 61.6	47.2 ± 3 2.8	51.4 ± 77.1	0.668*

Continuous variables: mean ± SD; categorical variables: n (%).
* Mann-Whitney test.
NAFLD - nonalcoholic fatty liver disease; CAD - coronary artery disease; HOMA-IR - homeostasis model assessment-insulin resistance index; TC - Total cholesterol; HDL - high-density lipoprotein; LDL - low-density lipoprotein; AST - aspartate aminotransferase; ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase.

Table 5. Multivariate regression analysis for predictors of NAFLD and CAD association.

Variables*	**Odds ratio**	**95%CI**	***P* value**
overweight / obesity	6.46	(2.29; 18.17)	< 0.001
HOMA-IR ≥ 3.0	3.00	(1.40; 6.47)	0.005

*Variables entered in the analysis: age, diabetes, central obesity, neck circumference, overweight / obesity, fasting insulin, HOMA ≥ 3.0, HDL-cholesterol, Triglycerides, and ferritin.
NAFLD - nonalcoholic fatty liver disease; CAD - coronary artery disease; CI - confidence interval; HOMA-IR - homeostasis model assessment-insulin resistance index.

5.2.1 Carta do editor da revista acusando a submissão do artigo

LIVint-13-00323

11-Apr-2013

PREDICTIVE FACTORS OF NONALCOHOLIC FATTY LIVER IN PATIENTS WITH CORONARY DISEASE FROM NORTHEAST OF BRAZIL

Dear Prof. Cotrim,

The editorial office of Liver International has received your recently submitted manuscript,entitled "PREDICTIVE FACTORS OF NONALCOHOLIC FATTY LIVER IN PATIENTS WITH CORONARY DISEASE FROM NORTHEAST OF BRAZIL" .

You will be informed of the decision within 60-90 days. Your manuscript should not be submitted to another journal while under review at Liver International.

Please take note of the assigned number above for the purpose of all future correspondence pertaining to this manuscript.

please add conflict of interest and fund source in between acknowledgments and references when you revise the manuscript.

Thank you for your interest in Liver International.

Yours Sincerely

Philippa Ekin
Editorial Assistant Liver International

5.3 Artigo em elaboração

Título do artigo: DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA E USO DE ESTATINAS: FATOR DE RISCO OU BENEFÍCIO?

Objetivo:

Avaliar a correlação entre uso de estatinas e alterações hepáticas em pacientes com DHGNA

Evidências observadas:

a) as estatinas foram eficazes para controlar a dislipidemia nos pacientes estudados;

b) uso ou tempo de uso da droga não se associou à maior frequência da DHGNA;

c) não foi observada elevação significativa de aminotransferases, GGT, ferritina e bilirrubinas nos pacientes em uso de estatinas;

d) não houve elevação significativa de aminotransferases, GGT e bilirrubinas nos pacientes em uso de estatinas e com DHGNA;

Os resultados sugerem que a utilização de estatinas parece trazer mais benefícios do que riscos para pacientes com DAC e DHGNA**.**

6 CONCLUSÕES

- Foi elevada a frequência de DAC (63,5%) e DHGNA (42,2%) na população estudada;
- DHGNA foi mais frequente em pacientes com DAC (43,9%/68/155), porém não houve associação estatisticamente significante entre as duas doenças;
- Resistência insulínica e índice de massa corpórea acima do normal (sobrepeso/obesidade) foram fatores preditivos da associação DAC e DHGNA.

7 CONSIDERAÇÕES FINAIS

A observação de que a DHGNA está assumindo proporções epidêmicas, sendo considerada a doença hepática mais frequente da atualidade, aliada ao fato de que esta doença está relacionada a fatores de risco comuns às DCV, tem despertado crescente interesse da comunidade científica.

No entanto, após uma ampla revisão da literatura, com utilização de várias bases de dados, foi observado que existem, de fato, poucos artigos publicados sobre a associação DAC e DAGNA, principalmente quando se leva em consideração os estudos que utilizaram a CAG para diagnóstico de DAC, por se tratar de método considerado padrão-ouro para este fim. Chama a atenção também a constatação de que a maioria desses estudos é procedente do continente asiático.

Estas observações despertaram interesse no desenvolvimento deste estudo, principalmente pela ausência de pesquisa sobre o tema nesta região. Participaram desta pesquisa não apenas pacientes procedentes de Campina Grande, mas principalmente de outras regiões da Paraíba e do nordeste, uma vez que o estudo foi realizado em serviços de cardiologia que são referenciados para atendimento aos usuários do Sistema Único de Saúde (SUS) na região. Este trabalho possibilitou, portanto, informar à comunidade científica, resultados observados em relação a nossa população, a qual tem características socioeconômicas e étnicas diferentes daquelas já estudadas.

Na amostra aqui avaliada observou-se elevada prevalência de DAC e DHGNA assim como maior frequência de DHGNA nos pacientes com DAC, porém não foi encontrada associação estatisticamente significante entre estas doenças. Observou-se também que os principais fatores de risco para a presença da associação DAC e DHGNA são a resistência insulínica e IMC acima do normal. Este fato assume relevância clinica e torna necessária a abordagem multidisciplinar dos pacientes com risco cardiovascular no sentido de incluir a avaliação diagnóstica de DHGNA, orientação e condutas visando à redução de risco de morbimortalidade relacionadas não apenas às doenças cardiocirculatórias, mas também às doenças hepáticas.

Entretanto, fica evidente a necessidade de realização de novos estudos dentro desta linha de pesquisa, envolvendo outros modelos tais como estudos de coorte, caso-controle e ensaios clínicos, para responder outros questionamentos

relacionados à associação de DHGNA e DCV. È importante também que se utilizem outros métodos diagnósticos para DHGNA uma vez que a ultrassonografia, embora seja um método seguro e de relativo baixo-custo, é pouco sensível para diagnóstico de DHGNA naqueles pacientes com infiltração gordurosa do fígado inferior a 30%.

O resultado desta pesquisa juntamente com o resultado de outro estudo relacionado à DHGNA em pacientes menopausadas, desenvolvido no HUAC da UFCG em parceria com a UFBA, tornou fundamental a implantação de ambulatório de DHGNA neste hospital, por se tratar de um hospital de referência. Este ambulatório, que já está em funcionamento, é direcionado a pacientes adultos de ambos os sexos que tenham DHGNA como diagnóstico inicial, uma vez que até então não contavam com atendimento direcionado a esta condição. Proporcionou ainda o desenvolvimento d uma nova linha de pesquisa na UFCG em parceria com a UFBA através do Grupo de Estudo em Nonalcoholic steatohepatitis (GNASH).

A implantação desse ambulatório está possibilitando a maior atuação deste grupo de pesquisadores, no sentido de implementar a realização de novos estudos, inclusive contando com a participação de médicos residentes, graduandos de medicina assim como de outros profissionais e estudantes de outras áreas da saúde. Neste sentido, entramos em contato com a direção do HUAC, solicitando a disponibilização do espaço físico para que possa ser ampliado o atendimento com a participação de outros profissionais, ensejando o desenvolvimento de um trabalho multidisciplinar, a exemplo do atendimento já prestado pelo GNASH na UFBA.

Esse fato teve adicionalmente, como reflexo, uma maior adesão dos pacientes, com acompanhamento por longo prazo, e possibilidade de realização de novas pesquisas com aplicação modelos de estudo longitudinais. Tornará possível também, em um futuro próximo, a realização de projetos de extensão direcionados aos profissionais e pacientes das Unidades básicas de Saúde e dos Programas de Saúde da Família desta e de outras localidades, objetivando esclarecer melhor sobre os fatores de risco e condutas a serem adotadas para redução de DHGNA e DCV, entre elas a DAC.

Do ponto de vista acadêmico, esta pesquisa possibilitou a apresentação de trabalhos científicos em congressos nacionais, mas principalmente internacionais, gerando publicações em anais, assim como artigo de revisão e artigo original, além de outros estudos que estão em andamento ou na fase de elaboração de projetos.

Este estudo, no entanto, tem algumas limitações, entre elas a amostra selecionada a partir de pacientes referenciados pelo Sistema Único de Saúde (SUS) o qual é mais utilizado por pacientes de menor poder aquisitivo, cujos hábitos e costumes podem ter contribuído para os resultados. Outro aspecto a se considerar é a utilização da USG como método diagnóstico para esteatose pela razão já mencionada anteriormente.

8 PERSPECTIVAS DE ESTUDO

Em face da elevada frequência de DAC e DHGNA na população estudada, a maior frequência de DHGNA em pacientes com DAC, a possibilidade de associação de DHGNA à gravidade de DAC e à mortalidade cardiovascular, surgem novos questionamentos que precisam ser respondidos.

São propostos, portanto, os seguintes estudos:

1. **Título:** Gravidade da Doença Arterial Coronariana e sua relação com Doença Hepática Gordurosa Não Alcoólica.

   Tipo de estudo: Corte transversal

   Objetivo principal: avaliar a associação de gravidade de DAC e a presença de DHGNA em pacientes dessa amostra.

2. **Título:** Doença Hepática Gordurosa Não Alcoólica e risco Cardiovascular.

   Tipo de estudo: Caso-controle

   Objetivo principal: Determinar o risco cardiovascular em pacientes com DHGNA comparados a indivíduos sem DAGNA.

3. **Título:** Doença Hepática Gordurosa Não Alcoólica e mortalidade Cardiovascular.

   Tipo de estudo: Estudo de coorte.

   Objetivo principal: Avaliar mortalidade cardiovascular, após cinco anos, e sua relação com DHGNA em pacientes dessa amostra.

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10 ANEXOS

Anexo A - Parecer do Comitê de Ética em Pesquisa em Seres Humanos

UNIVERSIDADE FEDERAL DE CAMPINA GRANDE
HOSPITAL UNIVERSITARIO ALCIDES CARNEIRO
Comitê de Ética em Pesquisas com Seres Humanos
Rua: Drº. Carlos Chagas, s/ n, São José.
Cep: 58107 – 670.
Tel: 2101 – 5545, e-mail: cep@huac.ufcg.edu.br

DECLARAÇÃO

Declaro para os devidos fins que o protocolo nº. 20090603 – 011, titulo: Correlação entre Doença Hepática Não – Gordurosa (DHGNA) e Cardiopatia Isquêmica, foi aprovado com ressalvas em reunião de 11/ 03/ 2009 e que foram cumpridas as exigências do relator (a), retornando a este Comitê de Ética em Pesquisa em 23 de Março de 2009.

Após conclusão da pesquisa deve ser encaminhada ao CEP/ HUAC, em 30 dias (trinta dias), relatório final de conclusão, antes de envio do trabalho para publicação. Haverá apresentação pública do trabalho no Centro de Estudos HUAC em data a ser acordada entre pesquisador e CEP/HUAC.

Relator (a),
Maria Luisa Souto Porto

Maria das Graças Vieira de Souza e Cavalcanti de Castro
Coordenadora CEP/ HUAC/ UFCG.

Campina Grande - PB, 24 de Março de 2009.

CARTORIO DO 8º OFÍCIO DE NOTAS
Rua Marques do Herval, 83 - Centro - Fone 3341-6085
CNPJ: 09.365.545/0001-76
Pedro Oliveira de Lucena
Tabelião
Certifico e dou fé que a presente cópia fotostática é a
Reprodução fiel do original que me foi exibido.
Campina Grande 09 JUL 2009
Pedro Oliveira de Lucena
Tabelião

CARTÓRIO DO 8º OFÍCIO
Pedro Oliveira de Lucena
TABELIÃO
CAMPINA GRANDE - PB

COMITÊ DE ÉTICA EM PESQUISA COM SERES HUMANOS - CEP
UNIVERSIDADE FEDERAL DE CAMPINA GRANDE - UFCG
HOSPITAL UNIVERSITÁRIO ALCIDES CARNEIRO - HUAC

DECLARAÇÃO

Declaro para fins de comprovação, que foi analisado e aprovado neste Comitê de Ética em Pesquisa – CEP em 2009, bem como enviado a Plataforma Brasil em 2013, para adequação do título o projeto de número CAAE: 12540913.0.0000.5182 intitulado: **CORRELAÇÃO ENTRE DOENÇA HEPÁTICA GORDUROSA NÃO-ALCOÓLICA (DHGNA) E CARDIOPATIA ISQUÊMICA.**

Estando o pesquisador ciente de cumprir integralmente os itens da Resolução nº. 196/ 96 do Conselho Nacional de Saúde – CNS, que dispõe sobre Ética em Pesquisa que envolve seres humanos, podendo sofrer penalidades caso não cumpra com um dos itens da resolução supra citada.

Após conclusão da pesquisa deve ser encaminhado ao CEP/ HUAC em 30 dias, relatório final de conclusão, antes do envio do trabalho para publicação. Haverá apresentação pública do trabalho no Centro de Estudos do HUAC em data a ser acordada entre o CEP e o pesquisador.

Profª. Maria Teresa Nascimento Silva
Coordenadora CEP/HUAC/UFCG

Campina Grande - PB, 25 de Março de 2013.

Rua.: Dr. Carlos Chagas, s/ n, São José, Campina Grande – PB.
Telefone.: (83) 2101 – 5545. E-mail.: cep@huac.ufcg.edu.br

Anexo B - Termo de Consentimento

Universidade Federal de Campina Grande
HUAC - Hospital Universitário Alcides Carneiro

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

ESTUDO: CORRELAÇÃO ENTRE DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA (DHGNA) E CARDIOPATIA ISQUÊMICA

Você está sendo convidado(a) a participar do projeto de pesquisa acima citado. O documento abaixo contém todas as informações necessárias sobre a pesquisa que estamos fazendo. Sua colaboração neste estudo será de muita importância para nós, mas se desistir a qualquer momento, isso não causará nenhum prejuízo a você.

Eu,.....profissão.....
residente e domiciliado na .....,
portador da Cédula de identidade, RG.....e inscrito no CPF/MF.....
nascido(a) em _____ / _____ /_____ , abaixo assinado(a), concordo de livre e espontânea vontade em participar como voluntário(a) do estudo "CORRELAÇÃO ENTRE DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA (DHGNA) E CARDIOPATIA ISQUÊMICA**"**. Declaro que obtive todas as informações necessárias, bem como todos os eventuais esclarecimentos quanto às dúvidas por mim apresentadas.

Estou ciente que:

O estudo se faz necessário para que se possam descobrir as possíveis causas da doença denominada "CORRELAÇÃO ENTRE DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA (DHGNA) E CARDIOPATIA ISQUÊMICA"

I) Correlacionar a presença de gordura no fígado e com doença nos vasos do coração.
II) Será feita 01 coleta de 15 ml de sangue;
III) Será feita ultrassonografia da minha barriga
IV) Essa (s) coleta(s), bem como a ultrassonografia, serão feitas apenas para este estudo e em nada influenciará (influenciarão) o meu tratamento; não vai (vão) me curar; não vai (vão) me causar nenhum problema, exceto o pequeno incômodo de dor no momento da coleta (introdução da agulha para retirada do sangue)

V) A participação neste projeto não tem objetivo de me submeter a um tratamento, bem como não me acarretará qualquer ônus pecuniário com relação aos procedimentos médico-clínico-terapêuticos efetuados com o estudo;

VI) Tenho a liberdade de desistir ou de interromper a colaboração neste estudo no momento em que desejar, sem necessidade de qualquer explicação;

VII) A desistência não causará nenhum prejuízo à minha saúde ou bem estar físico. Não virá interferir no atendimento ou tratamento médico;

VIII) Os resultados obtidos durante este ensaio serão mantidos em sigilo, mas concordo que sejam divulgados em publicações científicas, desde que meus dados pessoais não sejam mencionados;

IX) Caso eu desejar, poderei pessoalmente tomar conhecimento dos resultados, ao final desta pesquisa.

( ) Desejo conhecer os resultados desta pesquisa.

( ) Não desejo conhecer os resultados desta pesquisa.

IX) Observações Complementares.

X) Caso me sinta prejudicado (a) por participar desta pesquisa, poderei recorrer ao CEP/HUAC, do Comitê de Ética em Pesquisas em Seres Humanos do Hospital Universitário Alcides Carneiro, ao Conselho Regional de Medicina da Paraíba e a Delegacia Regional de Campina Grande.

Campina Grande, de de 20.....

( ) Paciente / ( ) Responsável

.....

Testemunha 1:_____
Nome / RG / Telefone

Testemunha 2**:**_____
Nome / RG / Telefone

Responsável pelo Projeto: Dra. Consuelo Padilha Vilar Salvador
(Medica CRM 2846) **Telefone para contato: (083) 88856901**

Anexo C - Questionário de Coleta dos Dados

ESTUDO: CORRELAÇÃO ENTRE DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA (DHGNA) E CARDIOPATIA ISQUÊMICA

DATA DO PREENCHIMENTO DA FICHA:___/___/_____

INDICAÇÃO DO CATETERISMO:
DOR PRECORDIAL TÍPICA: ☐ SIM ☐ NÃO; SEM DOR; ☐
ALTERAÇÃO AO ECG: ☐ SIM ☐ NÃO
ALTERAÇAO AO TESTE ERGOMÉTICO: ☐ SIM ☐ NÃO
ALTERAÇAO AO ECOCARDIOGRAMA: ☐ SIM ☐ NÃO

MÉDICO RESPONSÁVEL: _____
SERVIÇO: _____
NOME DO PACIENTE:
_____
SEXO:_____DATA NASC: _____
NATURALIDADE:_____NACIONALIDADE:_____
PROFISSÃO:_____

DADOS CLÍNICOS:

- Diabetes ☐ SIM ☐ NÃO
- Antecedente IAM ☐ SIM ☐ NÃO
- Dislipidemia ☐ SIM ☐ NÃO
- HAS ☐ SIM ☐ NÃO
- Medicamentos ☐ SIM; Quais:_____ Tempo de uso : _____ ☐ NÃO
- Drogas ilícitas ☐ SIM; Quais:_____ Tempo de uso : _____ ☐ NÃO
- Exp. a petroq. ☐ SIM; Duração:_____ Tempo de afastamento:_____ ☐ NÃO
- Etilismo ☐ SIM; Duração:_____ Tipo:_____ ☐ NÃO

Quantidade: ☐ ≤ 20 g/dia ☐ > 20 g/dia
Tabagismo: ☐ SIM; Duração_____ Ex;tabagismo: ☐ SIM; Duração_____ ☐ NÃO

- Hemotransfusão: ☐ SIM; Tempo: _____ ☐ NÃO

História familiar de doenças metabólicas: ☐ SIM Quais:_____ ☐ NÃO

- Realiza atividades Físicas: ☐ SIM Tempo: _____ Frequência:_____ ☐ NÃO
- Outros: _____

EXAME FÍSICO:

Peso: _____ Altura: _____ IMC (Peso/altura^2): _____
Circunferência Abdominal: _____(cm)
PA: _____X_____ (mmHg)
Dados positivos do exame físico segmentar (pele, cardiorrespiratório, abdome, neurológico, etc):_____
_____

DIAGNÓSTICOS NA ULTRASSONOGRAFIA;

Data			
Esteatose:			
Grau de Esteatose:	Grau I	Grau: II	Grau III
Síndrome Hipertensão Portal			
Ascite			
Cirrose			

Obs: Preencher Sim / Não

EXAMES LABORATORIAIS:

Data						
Plaquetas						
TP/INR						
Glicemia						
Insulina						
AST						
ALT						
FA						
GGT						
PT/ALB						
BT/BD						
Colesterol Total						
HDL						
LDL						
Triglicerídeos						
Ferritina						
Sat. transferrina						
HBsAg						
Anti;HCV						
Anti;Mitocôndra						
Anti;Músculo Liso						
FAN						
HOMA-IR						

Cálculo do HOMA:

HOMA-IR=insulina jejum (mU/mL) x glicose jejum (mmol/L*)[1] . 22,5

[1] O índice HOMA é um cálculo de execução simples, que se fundamenta nas dosagens de insulinemia e glicemia, ambas em jejum, descrito em 1985 por David Matheus. Sua finalidade é determinar a resistência à insulina e a capacidade funcional das células pancreáticas. *Para conversão da glicose de mg/dL para mmol/L, multiplica-se o valor em mg/dL por 0,0555. Referência: Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: IR and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–19.

Anexo D - Resumos Publicados em Anais de Congressos

1. CONSUÊLO PADILHA VILAR; HELMA PINCHEMEL COTRIM; GESIRA SOARES DE ASSIS FLORENTINO; MOURIBE ARRUDA FELINTO ARAÚJO; CIBELLE PADILHA VILLAR BARRETO; GERSON BRAGAGNOLI. DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA & DOENÇA CORONARIANA: RELEVÂNCIA DA ASSOCIAÇÃO. Oral NA-011. In: Congresso da Associação Latino-Americana para o Estudo do Fígado, 12-14 ago. 2010, Porto Alegre, Brasil. **Annals of Hepatology**, v. 9, n. 2, p. 329, 2010.

2. GESIRA SOARES DE ASSIS FLORENTINO, HELMA PINCHEMEL COTRIM, CONSUÊLO PADILHA VILAR, ANDRÉ VINICIUS DE ASSIS FLORENTINO, CLAUDIA DANTAS GADELHA, ALEXANDRE MAGNO DE N. MARINHO. DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA EM MULHERES MENOPAUSADAS: HÁ INFLUÊNCIA DA TERAPIA DE REPOSIÇÃO HORMONAL? Pôster NA-014. In: Congresso da Associação Latino-Americana para o Estudo do Fígado, 12-14 ago. 2010, Porto Alegre, Brasil. **Annals of Hepatology**, v. 9, n. 2, p. 330, 2010.

3. CONSUÊLO P. SALVADOR; HELMA P. COTRIM; GESIRA S. FLORENTINO; CIBELLE BARRETO; GERSON BRAGAGNOLI; PAULO A. SCHWINGEL; ANDRÉ V. FLORENTINO. RELEVANCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN INDIVIDUALS UNDERGOING CORONARY ANGIOGRAPHY. In: Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), 04-08 Nov. 2011, San Francisco, California (USA). **Hepatology** v. 54, n. 4 (suppl), p. 1141A, 2011.

4. FLORENTINO G.S.A., COTRIM H.P., SALVADOR C.P., FLORENTINO A.V.A., GADELHA C.D., SCHWINGEL P. Nonalcoholic Fatty Liver disease in Menopausal Women: Influence Hormone Replacement Therapy. Poster PP0851. In: XXI conference of the Asian Pacific Association for the Study of Liver (APASL), 17-23 fev. 2011, Bangkok, Thailand. **Hepatology International** v.5, p.197, 2011.

tes con HGNA. **MATERIAL Y MÉTODO:** Cincuenta y cuatro pacientes con diagnóstico histológico de HGNA, incluidos en "Viusid trial" publicado en Alimentary Phamacology and Therapeutics 2009; 30:999-1009 y que fueron tratados con dieta hipocalórica de 1620 kcals y ejercicio físico durante 24 semanas de tratamiento, fueron seleccionados para el análisis. **MATERIAL Y MÉTODO:** Se definió un punto de corte de 5% para la pérdida del porciento del peso corporal. Se evaluó la asociación entre una pérdida mayor o menor al 5% con la mejoría histológica, los parámetros bioquímicos y metabólicos. Para el análisis de las variables cuantitativas fue empleado el test de Wilcoxon para la comparación de medias y el ji cuadrado para las variables cualitativas, con una significación estadística $\alpha = 0,05$. **RESULTADOS:** Hubo una mejoría histológica significativa del NAS score, de la esteatosis y la fibrosis, pero no de la inflamación y el balonamiento en aquellos pacientes con una reducción del porcentaje peso corporal superior al 5% (P = 0,001). Se observó una reducción siganificativa en los valores medios de aminotransferasa (ALAT) en aquellos pacientes con una reducción del porciento del peso corporal superior al 5% (-22,7±7) en comparación a aquellos pacientes con una reducción menor al 5% (15,7±6,9) en los que hubo un incremento de los valores medios (P < 0,0001). No hubo cambios significativos en los parámetros metabólicos (glucemia, HOMA-IR e insulinemia) entre los que perdieron más o menos del 5% del peso corporal. **CONCLUSIONES:** Nuestros resultados sugieren que una pérdida igual o mayor al 5% del peso corporal es capaz de reducir significativamente el NAS score, la esteatosis, la fibrosis y los valores de aminotransferasa en pacientes con HGNA.

ORAL NA-011

DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA & DOENÇA CORONARIANA: RELEVÂNCIA DA ASSOCIAÇÃO

CONSUÊLO PADILHA VILAR,*,** HELMA COTRIM PINCHIMEL,** GESIRA SOARES DE ASSIS FLORENTINO,*,** MOURIBE ARRUDA FELINTO ARAUJO,*** CIBELLE PADILHA VILLAR BARRETO,* GERSON BRAGAGNOLI*

*UFCG, UNIVERSIDADE FEDERAL DE CAMPINA GRANDE-PB. **UFBA, PROGRAMA DE POS-GRADUAÇÃO EM MEDICINA E SAÚDE - FACULDADE DE MEDICINA DA BAHIA. ***FCM, FACULDADE DE CIÊNCIAS MÉDICAS-PB.

INTRODUÇÃO: A Doença Hepática Gordurosa Não Alcoólica (DHGNA) está associada a fatores de risco como dislipidemia, diabetes mellitus e obesidade. Recentemente, vem sendo também associada a doenças cardiovasculares, que podem aumentar a morbidade e mortalidade dos pacientes. **OBJETIVO:** avaliar a correlação entre DHGNA e doença coronariana (DAC) em indivíduos submetidos a cineangiocoronariografia (CAT). **METODOLOGIA:** Estudo transversal onde foram avaliados indivíduos submetidos a CAT entre abril de 2009 e abril de 2010, com suspeita diagnóstica de DAC, em hospitais referenciados para atendimento em cardiologia em Campina Grande – Paraíba, Nordeste do Brasil. Todos os pacientes foram submetidos à avaliação clínico–laboratorial (colesterol, triglicérides, ALT, AST, GGT, glicemia, insulina), ultrassonografia abdominal (USAB) e CAT. Critérios para DHGNA: ingestão alcoólica < 140 g/semana para os homens e < 70 g/semana para as mulheres; exclusão de outras doenças hepáticas; presença de esteatose na USAB. Análise estatística dos dados foi realizada com a utilização do programa SPSS 17.0. As variáveis contínuas foram descritas como médias ± desvio padrão. Nível de significância (p) < 0,05. **RESULTADOS:** Foram avaliados 102 indivíduos com média de idade de 60,7 ± 9,3 anos, 52,9% eram mulheres, 70,2% (71) dos casos apresentavam sobrepeso/obesidade, 20,6% (21) eram diabéticos, 52,9% (54) tinham dislipidemia. A freqüência de DHGNA foi de 43,1% (44) e 58,8% (60) desses indivíduos apresentaram doença coronariana. A associação DAC e DHGNA foi observada em 41,6% (25/60) dos casos dos quais 28% eram diabéticos, 68% dislipidêmicos, 80% hipertensos, e 88% apresentavam sobrepeso e/ou obesidade, sendo que 60% apresentavam obesidade central. RI foi observada em 48% desses casos. **CONCLUSÕES:** a) foi elevada a freqüência de DHGNA (43,1%) e de DAC (58,8%) na amostra estudada; b) foi relevante a associação DAC e DHGNA (41,6%); c) foi freqüente a presença de fatores de risco comuns para DHGNA e DAC; d) o estudo mostra a importância de se avaliar a correlação entre a DGHNA com a gravidade da DAC na cineangiocoronariografia para melhor entendimento dessa correlação e melhor orientação dos pacientes.

POSTER NA 012

PAPEL ETIOLÓGICO DA ESTEATOHEPATITE NÃO ALCOÓLICA NA CIRROSE CRIPTOGÊNICA

ANDREA BENEVIDES LEITE LIMA VERDE,* ANGELO ALVES DE MATTOS,* SANDRO ALEX,* IDÍLIO ZAMIN JÚNIOR,* GABRIELA PERDOMO CORAL*

*UFCSPA, UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE.

INTRODUÇAO: A relação entre esteatohepatite não alcoólica (EHNA) e cirrose criptogênica (CC) é sugerida principalmente pelo estudo de fatores de risco para EHNA, ou seja, sexo, índice de massa corpórea (IMC), glicemia de jejum alterada (GJA), triglicerídios (TG) >150 mg/dL, HDL colesterol (HDLc) < 40 mg/dL para homens e < 50 mg/dL para mulheres, PA > 130x85 mmHg e obesidade central. **OBJETIVO:** Determinar a prevalência de fatores de risco para EHNA nos pacientes portadores de CC e compará-la com a dos pacientes com EHNA, cirrose por álcool e por hepatite C no nosso meio. **MATERIAL E MÉTODO:** Pacientes maiores de 18 anos, portadores de EHNA comprovada por biópsia hepática ou de cirrose por hepatite C, por álcool ou criptogênica, foram avaliados quanto ao sexo, IMC, glicemia, TG e HDLc. Medidas de associação foram feitas entre os dados de todos os grupos. Resultados: No grupo com CC (47 pacientes): 48,9% sexo feminino; IMC >3 0 em 31,8%; glicemia > 100 em 75%, sendo ≥ 126 em 40,9%; TG > 150 em 25,6%; homens com HDL < 40 em 38,4% e mulheres com HDL < 50 em 81%. No grupo com EHNA (47 pacientes): 68,1% sexo feminino; IMC > 30 em 73,8%; glicemia > 100 em 72,1%, sendo ≥ 126 em 34,9%; TG>150 em 82,1%; homens com HDL < 40 em 53,8% e mulheres com HDL < 50 em 36%. No grupo com cirrose por álcool (75 pacientes), HCV (70 pacientes) e álcool+HCV (50 pacientes): 35,2% sexo feminino; IMC>30 em 20,6%; glicemia >100 em 48,9%, sendo ≥ 26 em 20,5%; TG > 150 em 20,1%; homens com HDL < 40 em 42,1% e mulheres com HDL< 50 em 55,6%. Não houve diferença estatística entre os grupos com CC e EHNA quanto ao sexo e GJA e/ou DM. Houve diferença estatisticamente significativa entre os cirróticos por HCV e álcool e aqueles com EHNA e CC quanto à GJA. Para as demais variáveis, o grupo com CC se mostrou diferente do grupo com EHNA. **CONCLUSÃO:** Os resultados mostram concordância com a literatura quanto à prevalência de glicemia de jejum alterada e/ou DM naqueles com CC ser semelhante à apresentada pelos pacientes com EHNA, sugerindo uma possível associação de CC com EHNA prévia. No entanto, a comparação da prevalência do IMC, de hipertrigliceridemia e níveis reduzidos de HDLc na CC e EHNA não se mostrou semelhante.

POSTER NA-013

PADRÃO AO DOPPLER DA VEIA HEPÁTICA DIREITA NA CARACTERIZAÇÃO DA DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA: COMPARAÇÃO COM BIÓPSIA

VALERIA FERREIRA DE ALMEIDA E BORGES,* ANGELICA LEMOS DEBS DINIZ,* HELMA PINCHEMEL COTRIM,** MARCIO HENRIQUE ALVES,* MIRELA REBOUÇAS FERNANDES DE LIMA*
*UFU, UNIVERSIDADE FEDERAL DE UBERLANDIA.
**UFBA, UNIVERSIDADE FEDERAL DA BAHIA.

INTRODUÇÃO: A utilização mais clássica da ultrassonografia (USG) com Doppler das veias hepáticas é nas causas pós hepáticas de hipertensão portal. Além destas situações, estudos em obesidade e em doença hepática gordurosa não alcoólica (DHGNA) têm demonstrado que a esteatose e a fibrose são as causas principais de padrão anormal ao Doppler da veia hepática direita. **OBJETIVO**: Avaliar a correlação entre o padrão ao Doppler da veia hepática direita e o grau de esteatose, inflamação e fibrose à biópsia na DHGNA. **PACIENTES E MÉTODOS**: USG com Doppler da veia hepática direita foi realizada em 82 voluntários. Dentre estes, 42 eram portadores de DHGNA e foram também submetidos à biópsia hepática percutânea por agulha (*Tru-cut*). Os demais 40, sem fatores risco para DHGNA e sem esteatose à USG, foram incluídos como controles. O padrão ao Doppler da veia hepática direita foi classificado em trifásico (normal, regular, com fluxo reverso curto), bifásico (sem fluxo reverso, mas com flutuação de mais de 10% da amplitude fásica média) e monofásico (patológico, plano, com oscilação da onda menor que 10% da amplitude média). Os espécimes obtidos por biópsia hepática por agulha foram corados com Tricrômio de Masson e Hematoxilina-Eosina (H&E) e classificados em esteatose discreta (até 33% dos hepatócitos com esteatose), moderada (de 33 a 66%) e acentuada (mais de 66%). A fibrose e a inflamação foram classificadas de acordo com sua intensidade e localização no lóbulo hepático. **RESULTADOS**: O padrão foi trifásico em 38 (95%) dos controles; e em 9 (56,3%) do subgrupo com esteatose discreta enquanto no subgrupo com esteatose acentuada o padrão foi monofásico em 60% encontrando-se diferença significante na distribuição dos padrões ao Doppler (teste de Mann-Whitney, $P < 0,01$). Houve uma correlação inversa e significante entre o padrão de fluxo da veia hepática direita e o grau de esteatose e ($r = -0,57$, $P < 0,01$). A correlação com o grau de inflamação ($r = -0,48$) e com o grau de fibrose ($r = -0,44$) foram menos evidentes, mas ainda significantes ($P<0,01$). **CONCLUSÃO:** A alteração do padrão de fluxo da veia hepática em pacientes com DHGNA pode sugerir redução da complacência vascular devido à infiltração gordurosa.

POSTER NA-014

DOENÇA HEPÁTICA GORDUROSA NÃO ALCOÓLICA EM MULHERES MENOPAUSADAS: HÁ INFLUÊNCIA DA TERAPIA DE REPOSIÇÃO HORMONAL?

GESIRA SOARES DE ASSIS FLORENTINO,*,** HELMA COTRIM PINCHIMEL,* CONSUELO PADILHA VILAR,*,** ANDRÉ VINÍCIUS DE ASSIS FLORENTINO,*** CLAUDIA DANTAS GADELHA,** ALEXANDRE MAGNO DA N. MARINHO**
*UFBA, PROGRAMA DE PÓS GRADUAÇÃO EM MEDICINA E SAÚDE – FACULDADE DE MEDICINA DA BAHIA. **UFCG, UNIVERSIDADE FEDERAL DE CAMPINA GRANDE.
***FCM-CG, FACULDADE DE CIÊNCIAS MÉDICAS DE CAMPINA GRANDE.

INTRODUÇÃO: A Doença Hepática Gordurosa Não Alcoólica(DHGNA) é freqüente em mulheres nas 5ª e 6ª décadas, e, portanto, na menopausa. Nessa fase também é mais freqüente a obesidade, diabetes tipo 2 e dislipidemia. Entretanto, as características clínicas da DHGNA nessas mulheres não estão bem definidas. **OBJETIVOS:** Avaliar a freqüência e características clínicas e bioquímicas da DHGNA em mulheres menopausadas (MMP); avaliar a correlação entre utilização de terapia de reposição hormonal (TRH) e DHGNA. **METODOLOGIA:** Estudo de corte transversal onde foram avaliadas MMP entre abril/ 2009 a abril/2010 procedentes da Região Nordeste do Brasil. As participantes submeteram-se a avaliação clínica, ultrassonografia de abdomen (US) e exames laboratoriais (glicemia, triglicérides(TG), colesterol, LDL, HDL, ALT, AST, GGT, insulina, ferritina, saturação transferrina, antinúcleo. AgHBs, anti-HCV e foram divididas em 2 grupos: Critérios para DHGNA: presença de esteatose ao US; exclusão de ingestão alcoólica(> 70g/semana); e outras doenças hepáticas. Resistência a Insulina: HOMA_IR ≥ 3,0. Excluído diabéticas. Análises estatísticas: programa SPSS 17.0 para windows: teste t para comparar os dois grupos com e sem DHGNA, teste qui-quadrado para as variáveis categóricas, nível de significância estatística de 5%. **RESULTADOS:** Participaram do estudo 179 MMP, e dessas 60(33,5%) que tiveram diagnóstico de DHGNA foram incluídas nesse estudo. A média de idade foi de 57,0 ± 6,7 e as médias de IMC e a cintura foram 30,6 ± 4,4, 99,0 ± 9,3 respectivamente. Fatores de risco para DHGNA: obesidade em 30(51,8%),TG elevado 35(60,3%) e HDL 37(66,1%); hipertensão arterial 22(36,7%). ALT estava elevada em 4(7,8%), AST em 5(8,6%) e GGT em 27(45,8%). Média de HOMA foi 2,79 + 1,65. Esteatose na US foi observada em 100%. Das 179 mulheres menopausadas avaliadas 12, 8% (23) referiram uso contínuo de TRH (> 12 meses) (Grupo 1), e dessas 8,7% (2/23) tinham DHGNA. Entre aquela que não faziam uso de TRH (Grupo 2), DHGNA foi observada em 37,2% (58/156). **CONCLUSÕES:** a) foi elevada a freqüência de DHGNA e de síndrome metabólica em mulheres menopausadas (MMP); b) associação da terapia de reposição hormonal (TRH) com a DHGNA não foi relevante. A freqüência de DHGNA foi maior entre as mulheres que não utilizavam TRH; c) nesse estudo a TRH não influenciou freqüência de DHGNA em mulheres na menopausa.

POSTER NA-015

SUPLEMENTAÇÃO COM BETAÍNA EM PACIENTES COM NASH: DIMINUIÇÃO DA ESTEATOSE HEPÁTICA

FERNANDA A DOMENICI,* MARIA J BROCHADO,* ANA DE LOURDES CANDOLO MARTINELLI,* JORGE ELIAS,* SÉRGIO ZUCOLOTO,* HELIO VANNUCCHI*
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INTRODUÇÃO: A doença hepática gordurosa não-alcoólica (NAFLD) é uma doença de desordem metabólica caracterizada pela infiltração de gordura no fígado na ausência de consumo de álcool. O espectro da doença varia desde esteatose pura, esteatohepatite não-alcoólica (NASH) e cirrose. São comumente relacionados à NASH distúrbios metabólicos como obesidade, dislipidemia, diabetes mellitus tipo II e desnutrição. O tratamento da NASH ainda não está estabelecido e a betaína que é um componente normal do ciclo da metionina, com características hepatoprotetoras podendo diminuir a esteatose hepática, tem sido proposta. **MATERIAL E MÉTODOS:** Participaram do estudo 14 indivíduos com diagnóstico histológico de NASH [8 mulheres (52,38 ± 8,7 anos) e 6 homens

analysis showed that in comparison to lean NAFLD, non-lean NAFLD patients were more likely to be male [OR (95% CI): 1.71 (1.08 - 2.71)] and insulin resistant [(OR: 5.95 (3.40 - 10.41)] but less likely to report excellent or very good health status [OR:0.51 (0.29 - 0.89)]. CONCLUSIONS: Although both lean and non-lean NAFLD are more likely to have components of MS than their weight-matched non-NAFLD controls, lean NAFLD patients have different clinical, nutritional and health status profile than the non-lean NAFLD patients.

Disclosures:

Zobair M. Younossi - Advisory Committees or Review Panels: Vertex, Biolex, Tibotec; Consulting: Salix

Francesco Negro - Advisory Committees or Review Panels: Roche, MSD, Gilead, Boehringer Ingelheim, Novartis

The following people have nothing to disclose: Maria Stepanova, Youssef Younossi, Brian P. Lam, Fatema Nader

1647
ASSOCIATION BETWEEN NONALCOHOLIC FATTY LIVER DISEASE AND SERUM URIC ACID IN THE US POPULATION

Ming-Hsiung Shih[1,2], Mariana Lazo[3], Su-Hsun Liu[3], Jeanne Clark[3,4]; [1]Family Medicine, Cardinal-Tien Hospital Yung Ho Branch, New Taipei City, Taiwan; [2]Master of Public Health Progrm, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [4]Department of Medicine and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University School of Medicine, Baltimore, MD

Context: Studies conducted in Eastern Asia revealed that serum uric acid (SUA) level is highly related to nonalcoholic fatty liver disease (NAFLD). However, limited information is available in the United States. Our objective was to determine the association between NAFLD and SUA level in the US and to determine if this was independent of age, sex, and components of metabolic syndrome (MetS). Methods: We analyzed data from 7003 men and women aged 20-74 in the Third National Health and Nutrition Examination Survey (1988-1994) who received an ultrasound exam of the gallbladder and had it reviewed for hepatic steatosis, had fasted at least 8 hours before the blood collection, and had complete information on the components of the metabolic syndrome, serum uric acid and liver enzymes. We defined NAFLD as the presence of steatosis without alcohol overconsumption or the use of zydovudine or didanosine. We defined hyperuricemia as SUA > 7.0 mg/dL for men and > 5.7 mg/dL for women. We calculated the prevalence and odds ratio (OR) of NAFLD by SUA, adjusting for sex, age, race, alcohol consumption, body mass index, systolic blood pressure, fasting plasma glucose, high-density lipoprotein cholesterol, and serum triglycerides. We conducted similar analyses using sex-specific quintiles of SUA. Results: The overall prevalence of NAFLD was 16.7% (95%CI: 15.3-18.1%). The prevalence of NAFLD among individuals with hyperuricemia was 30.6% vs. 13.6% in those with normal SUA (p<0.001). Additionally, the prevalence of NAFLD was higher in participants with higher serum uric acid levels (10.1%, 9.9%, 14.2%, 20.6%, and 30.3%, respectively from the second (women: 3.8-4.2 mg/dL; men: 5.2-5.7 mg/dl) to the fifth quintile of SUA(women ≥5.7 mg/dL; men ≥7.2 mg/dL). After adjustment, individuals with hyperuricemia were significantly more likely to have NAFLD (OR: 1.4, 95% CI: 1.1-1.8). Similarly, the adjusted odds of NAFLD were significantly higher in a stepwise fashion from the third to the fifth quintile of SUA (ORs: 0.9, 1.3, 1.5, and 1.6, respectively; p-value for trend <0.01) as compared to the lowest quintile. Conclusion: NAFLD and SUA level were strongly and independently associated in this nationally representative sample of men and women after adjustment for multiple factors. However, whether elevated uric acid level is in the causal pathway, a marker or a consequence of NAFLD cannot be determined from this cross-sectional study, and prospective studies are needed to further clarify the association.

Disclosures:

The following people have nothing to disclose: Ming-Hsiung Shih, Mariana Lazo, Su-Hsun Liu, Jeanne Clark

1648
RELEVANCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN INDIVIDUALS UNDERGOING CORONARY ANGIOGRAPHY

Consuelo P. Salvador[2,1], Helma P. Cotrim[1], Gesira S. Florentino[2,1], Cibelle Barreto[2], Gerson Bragagnoli[2], Paulo A. Schwingel[1], André V. Florentino[3]; [1]Medicine, Universidade Federal Bahia, Salvador-Bahia, Brazil; [2]Medicine, Universidade Federal de Campina Grande, Campina Grande - Paraiba, Brazil; [3]Medicine, Faculdade de Ciências Médicas - Campina Grande, Campina Grande - Paraiba, Brazil

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) are associated with obesity, diabetes, dyslipidemia and metabolic syndrome (MS). However, the relationship between NAFLD and CAD remains controversial and this study aimed to evaluate: a) the relevance of NAFLD individuals undergoing coronary angiography (CAG); b) the relationship between CAG severity and the presence of NAFLD. Methodology: From April 2009 to April 2011, individuals undergoing CAG due to a suspected CAD at University Hospital were enrolled. All of them performed abdominal ultrasound (AUS), clinical and laboratorial evaluation (HBsAg, anti-HCV, ALT, AST, GGT, lipids, glucose, insulin, ferritin and auto antibodies). NAFLD criteria included: history of ethanol intake ≤20g/day; exclusion of other liver diseases; presence of hepatic steatosis on AUS. CAD criteria: obstructive lesions in epicardial arteries or their major branches. Severity of CAD was assessed by stenosis ≥70% on at least one main vessel. ATP-III criteria were used to MS diagnosis. HOMA-IR≥3 was considered insulin resistance (IR). Data were processed using SPSS software. Continuous variables were summarized with means and standard deviations while categorical variables were presented as absolute frequencies and percentages. Unpaired (T) test was used to assess the differences in mean and the chi-square test for comparison of frequency data. All statistical methods were two-tailed and significance level was set to 5%. Results: Totally 244 individuals were included and 63.5% (155) had diagnosis of CAD. NAFLD was observed in 43.8% (68/155) of these cases. The mean age of the patients was 62.3±9.4 years and 64% were men. Patients with CAD and NAFLD, when compared those without NAFLD presented a significantly higher BMI, waist circumference, insulin levels and triglycerides (p<0.05). HOMA-IR≥3.0 was found in 50% of these individuals in contrast to 19.3% in non-NAFLD patients (p<0.0001). MS was observed in 64.7% of NAFLD cases: elevated measurement of waist, arterial hypertension, elevated triglycerides and low levels of HDL were observed in 66%, 78%, 86.8% and 76.5% of the cases respectively. Stenosis ≥70% on CAG was observed in 78% of patients with NAFLD and in 79% of non-NAFLD cases. Conclusions: The frequency of NAFLD in individuals with CAD was elevated; obesity, central obesity, elevated index of IR, triglycerides and insulin levels were relevant risk factors associated with NAFLD and CAD. The results showed that in patients who have coronary artery disease, NAFLD should be investigated, independently of the CAD severity.

Disclosures:

prospective study, with a larger sample and liver biopsy is needed to clarify the findings. This is the first report from our area.

PP08-51

Nonalcoholic Fatty Liver Disease in Menopausal Women: Influence Hormone Replacement Therapy

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Background: Alterations in body composition, fat distribution and/or hormonal or metabolic changes occur following menopause and obesity, dyslipidemia, diabetes and metabolic syndrome (MS) are common. However, the characteristics of nonalcoholic fatty liver disease (NAFLD) in menopause need to be better understood.

Aim: To evaluate the frequency of NAFLD in postmenopausal women; the correlation of menopause with features of MS; the association of hormone replacement therapy (HRT) with NAFLD.

Methodology: A series-case study evaluated menopausal women from April/2009 to April/2010. All the participants had clinical and laboratorial evaluations (HBsAg, anti-HCV, ALT, AST, GGT, CPK, lipids, glucose, insulin, auto antibodies, ferritin, transferring saturation), abdominal ultrasound (AUS). HOMA-IR≥3 was considered insulin resistance (IR). NAFLD criteria: negative or occasional history of ethanol intake (≤20 g/day); exclusion of others liver diseases; hepatic steatosis on AUS.

Results: The study included 179 menopausal women. NAFLD criteria were observed in 60 (33, 5%) and they presented: the mean age of 57.0 ± 6.7 years and the means of BMI and waist circumference of 30.6 ± 4.4 and 99.0 ± 9.3 respectively. Hepatic steatosis was observed in 100% of these cases on AUS. Metabolic syndrome features observed were: central obesity in 30 (51.8%), hypertension in 22(36.7%), elevated triglycerides in 35(60.3%) and low HDL-C in 37(66.1%) respectively. History of HRT used was referred by 12.8% (23/179) of the menopausal women and 8.7% (2/23) of them had NAFLD. The presence of MS features was similar in women with and without history of HTR.

Conclusions: The frequency of NAFLD in menopausal women (MMP) was high; it was associated with features of metabolic syndrome; the correlation of NAFLD with hormone replacement therapy (TRH) was not observed. The results suggest that the frequency of NAFLD in menopausal women was not influenced by the TRH.

PP08-52

LDL-cholesterol Serum Levels Inversely Correlate with Oxysterols Plasma Levels in HCV Infected Patients

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Background/aims: Hepatitis C virus (HCV) infection is characterized by increased oxidative stress (OS), which is well evaluable testing oxysterols plasma concentration. These molecules, interfering with different cellular functions, may affect lipid metabolism through Liver X Receptors (LXRs) modulation. HCV exploits host lipid metabolism to facilitate its replication and its diffusion; however, their plasma levels have not yet been studied in chronically HCV infected patients (CHC). Thus, we aimed to evaluate and highlight the potential pathogenetic role of oxysterols, 7-ketocholesterol (7KC) and 7-beta-hydroxycholesterol (7betaOH), in HCV-related lipid dysmetabolism.

Methods: The study was carried out on 80 consecutive patients, 42 Chronic Hepatitis C infected (93% of which by HCV genotype 1b) and 38 Non Alcoholic Fatty Liver Disease (NAFLD). Plasma oxysterols, 7KC and 7betaOH, levels were determined by isotope dilution gas chromatography/ mass spectrometry (GC-MS).

Results: GC-MS revealed higher 7KC (71.2 ± 77.3 vs. 30.4 ± 14.5, $p < 0.005$) and 7betaOH (23.7 ± 20.6 vs. 11.5 ± 4.9, $p < 0.001$) plasma levels in HCV respect to NAFLD patients. Furthermore, multivariate regression analysis highlighted an inverse independent correlation between high oxysterols and low LDL-cholesterol ($p = 0.01$ for 7betaOH; $p = 0.02$ for 7KC) plasma levels in HCV group; in contrast, NAFLD group showed a direct correlation between oxysterols levels and LDL-cholesterol ($p < 0,001$ for 7betaOH; $p = 0.002$ for 7KC).

Conclusions: Our work for the first time correlates oxysterols plasma levels, markers of oxidative stress, to lipid dysmetabolism, in HCV infected patients. In addition, our data further support a different regulation of lipid metabolism in HCV infected and NAFLD patients, suggesting that the non alcoholic liver steatosis (NAFLD) and steatosis due to HCV-related lipid dysmetabolism, have different features, probably due to oxysterols, and thus cannot be considered equally.

PP08-53

Liver Histopathology versus Biochemical Markers in Hepatic Steatosis

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Background: Non-alcoholic fatty liver disease (NAFLD) is recognized as one of the most frequent causes of chronic liver disease and abnormal liver function tests.

Aim: To study the pattern of serum leptin, adiponectin, apolipoprotein AI, TNF alpha and hepatic tissue TNF alpha in patients with NAFLD and to assess the validity of these Biomarkers versus histopathology in diagnosis of different types of hepatic steatosis with special emphasis on the correlation with the severity of illness.

Patients and methods: A prospective study of 70 patients with NAFLD and 15 normal individuals as controls was carried out. Complete history taking, clinical examination, laboratory parameters, abdominal ultrasonography, needle liver biopsy and histopathologic examination were done for all cases. Scores of fibrosis (BAAT and modified APRI) were also done.

Results: Hepatic steatosis is a disease of both sexes with female predominance, mostly in the fourth decade. The main risk factors for NAFLD are obesity, hypertriglyceridemia and diabetes mellitus. Serum leptin, apolipoprotein AI and TNF alpha are capable to differentiate between NAFLD patients and normal individuals with specific cutoff. BMI >25.6 indicate hepatic steatosis with high sensitivity and specificity.

Conclusions: Elevated transaminases in NAFLD especially AST could indicate the development of NASH with no correlation with severity of lesion. Despite the significant correlation between high serum level of leptin, apolipoprotein AI and TNF alpha and low serum level of adiponectin in NAFLD patients; no single marker succeeded to predict the development of non-alcoholic steatohepatitis (NASH). BAAT and modified APRI scores are good diagnostic tools for diagnosis of hepatic fibrosis in NAFLD patients.

Anexo E - Trabalhos Apresentados em Congressos

1. Doença Hepática Gordurosa Não Alcoólica e uso de Estatinas: Fator de Risco ou Benefício? Apresentação oral. In: XXI Congresso Brasileiro de Hepatologia, XIV Simpósio Internacional de Terapêutica em Hepatite Viral, IV Simpósio de Terapia Intensiva em Gastroenterologia e Hepatologia da UGH-HP, I Semana Sul Americana de Fígado e III Encontro Amazônico de Hepatites Virais. 27 set. a 01 de out. 2011, Salvador, Brasil.

2. Doença Hepática Gordurosa Não Alcoólica em Pacientes com Doença Coronariana. Apresentação oral. In: XXI Congresso Brasileiro de Hepatologia, XIV Simpósio Internacional de Terapêutica em Hepatite Viral, IV Simpósio de Terapia Intensiva em Gastroenterologia e Hepatologia da UGH-HP, I Semana Sul Americana de Fígado e III Encontro Amazônico de Hepatites Virais. 27 set. a 01 de out. 2011, Salvador, Brasil.

3. Terapia de Reposição Hormonal em Mulheres na Menopausa: Fator de risco ou de Proteção para a Doença Hepática Gordurosa Não Alcoólica? Apresentação oral. In: XXI Congresso Brasileiro de Hepatologia, XIV Simpósio Internacional de Terapêutica em Hepatite Viral, IV Simpósio de Terapia Intensiva em Gastroenterologia e Hepatologia da UGH-HP, I Semana Sul Americana de Fígado e III Encontro Amazônico de Hepatites Virais. 27 set. a 01 de out. 2011, Salvador, Brasil.

CERTIFICADO

Certificamos que

Consuêlo Padilha Vilar Salvador

participou do **XXI Congresso Brasileiro de Hepatologia, XIV Simpósio Internacional de Terapêutica em Hepatite Viral, IV Simpósio de Terapia Intensiva em Gastroenterologia e Hepatologia da UGH-HP, I Semana Sul Americana de Fígado** e **III Encontro Amazônico de Hepatites Virais**, realizados no período de 27 de setembro a 01 de outubro de 2011, no Pestana Bahia Hotel

na qualidade de Autora do trabalho *"Doença Hepática Gordurosa não Alcoólica e uso de Estatinas: Fator de Risco ou Benefício?"*.

Salvador, 01 de outubro de 2011.

Dr. Raymundo Paraná
Presidente da Sociedade Brasileira de Hepatologia e do Congresso

Dr. Paulo Lisboa Bittencourt
Secretário Geral da Sociedade Brasileira de Hepatologia

CERTIFICADO

Certificamos que

Consuêlo Padilha Vilar Salvador

participou do **XXI Congresso Brasileiro de Hepatologia, XIV Simpósio Internacional de Terapêutica em Hepatite Viral, IV Simpósio de Terapia Intensiva em Gastroenterologia e Hepatologia da UGH-HP, I Semana Sul Americana de Fígado** e **III Encontro Amazônico de Hepatites Virais**, realizados no período de 27 de setembro a 01 de outubro de 2011, no Pestana Bahia Hotel na qualidade de Autora do trabalho *"Doença Hepática Gordurosa não Alcoólica em Pacientes com Doença Coronariana"*.

Salvador, 01 de outubro de 2011.

Dr. Raymundo Paraná
Presidente da Sociedade Brasileira de Hepatologia e do Congresso

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Secretário Geral da Sociedade Brasileira de Hepatologia

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Salvador, 01 de outubro de 2011.

Dr. Raymundo Paraná
Presidente da Sociedade Brasileira de Hepatologia e do Congresso

Dr. Paulo Lisboa Bittencourt
Secretário Geral da Sociedade Brasileira de Hepatologia

Anexo F - Publicação em Periódico

1. Gesira Florentino, Helma P. Cotrim, André Florentino, Consuêlo Padilha, Manoel Medeiros-Neto, Gerson Bragagnoli, Paulo Schwingel. Hormone replacement therapy in menopausal women: risk factor or protection to nonalcoholic fatty liver disease? Annals of Hepatology 2012; 11: 147-9.

ANNALS of Hepatology

LETTER TO EDITOR

January-February, Vol. 11 No.1, 2012: 147-149

Hormone replacement therapy in menopausal women: risk factor or protection to nonalcoholic fatty liver disease?

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To the Editor

Non-alcoholic fatty liver disease (NAFLD) represents a clinical condition that may progress from steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma. There are not enough information about the relationship between menopause and NAFLD, and this study evaluated the relevance of this liver disease in menopausal women (MPW), and the relationship between hormone replacement therapy (HTR) and NAFLD.

MATERIAL AND METHODS

MPW were enrolled from April/2009 to April/2011. Those who had criteria to NAFLD were included in two groups:

- Group 1 (G1) women who referred HRT use ≥ 6 months.
- Group 2 (G2) women that denied HRT use.

NAFLD criteria: history of ethanol intake ≤ 20 g/day; exclusion of other liver diseases; presence of hepatic steatosis on abdominal ultrasound. All volunteers performed clinical and laboratorial evaluation. ATP-III criteria were used to metabolic syndrome (MS)[1] and HOMA-IR ≥ 3.0 was considered insulin resistance (IR). Fischer's exact test and independent t-test were used to compare frequencies and means respectively. Proportions of NAFLD between groups were calculated to estimate the odds ratio (OR). All p-values were two tailed and the significance level was set to < 0.05.

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RESULTS

A total of 251 MPW were evaluated and 37% had criteria to NAFLD: 14 in G1 and 79 in G2 (crude OR: 0.54). Features of MS have similar frequencies except for high waist circumference in G2 (Table 1). Higher proportions of subjects with IR and elevated level of GGT and ferritin were observed in G2. Rates of elevated liver aminotransferases were similar in both groups.

COMMENT

The relationship between menopause, NAFLD and HRT needs to be understood. Features of MS are frequent in the women in the 6th and 7th decades, and these conditions may explain the elevated frequency of NAFLD in these women. Deficiency of estrogens in menopause also has been related to elevated levels of cholesterol, LDL cholesterol, triglycerides, insulin, presence of central obesity, IR and MS, and the absence of estrogen favors hepatic steatosis.[2,3] Gutiérrez-Grobe, *et al.*[4] studied the relationship between features of MS and levels of estrogens and observed normal levels of estrogens in pre menopause, lower levels in post menopause and in women with polycystic ovary syndrome (POS). Higher NAFLD prevalence also was reported in post menopause and in women with POS. The difference between men and women in the clinical course of chronic hepatitis C (CHC) has been demonstrated. The progression of fibrosis is faster

Table 1. Characteristics of menopausal women (MPW) with NAFLD (n = 93).

Variables	Group 1* (n = 14)	Group 2** (n = 79)	p
Metabolic syndrome risk factors			
Elevated glycemia	0 (0%)	9 (11.4%)	0.35
Hypertension	6 (42.9%)	49 (62.0%)	0.18
High waist circumference	6 (42.9%)	67 (84.8%)	< 0.001
High triglycerides	4 (28.6%)	40 (50.6%)	0.16
Low HDL cholesterol levels	9 (64.3%)	52 (65.8%)	0.91
Elevated liver enzymes			
AST	0 (0%)	6 (7.6%)	0.59
ALT	2 (14.3%)	16 (20.3%)	1.00
GGT	1 (7.1%)	30 (38.0%)	0.03
High ferritin levels	1 (7.1%)	36 (45.6%)	< 0.01
HOMA-IR index ≥ 3.0	0 (0%)	24 (30.4%)	0.02

*G1: women that have referred HRT use. **G2: women that denied HRT use.

in men with CHC even when potential confounding factors such as age, duration of infection, or metabolic features are accounted.[5,6] The reduced rate of fibrosis among women disappears after menopause when compared with men. However, this rate is slowed in MPW underwent by long-term estrogen exposure with hormone replacement therapy (HRT).[7] Villa, *et al.*[8] evaluated prospectively patients with CHC and observed that menopause is independently associated with the severity of liver damage, and that menopausal women have a remarkably lower likelihood of achieving sustained virologic response. The authors also identify the length of estrogen deprivation as a strong independent risk factor for fibrosis, and they have suggested that menopause could be significantly correlated with necroinflammation, steatosis, and metabolic alterations.

Few studies have addressed the relationship between HRT and NAFLD in MPW. Some experimental studies[9] have demonstrated that estrogen can influence the development of NAFLD, and the possible relationship between deficiency of estrogens, MS and NAFLD.[9,10] The relationship between estrogen deficiency and low levels of cytokines after menopause has been discussed, and attention has been done on levels of TNF-alfa and IL-6; these cytokines undergo large changes during menopause.[11,12] However, this subject deserves future investigation in NAFLD. The current study, that involved a large series of menopausal women, observed an elevated frequency of NAFLD in MPW; insulin resistance index significantly elevated in MPW who deny using HRT; low frequency of MS features in MPW, who have used HRT. In conclusion these results may suggest that HRT is not a risk factor to NAFLD, and hypothesize that HRT could be a protective factor against this liver disease. However, it is a challenge for future investigation.

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