Alterações Metabólicas Emergentes: Hiperferritinemia e Esteatose Hepática Não-Alcóolica

UNIVERSIDADE FEEVALE

Curso de Extensão em Interpretação Clínica e Laboratorial de Doenças Metabólicas 2017

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Objetivos

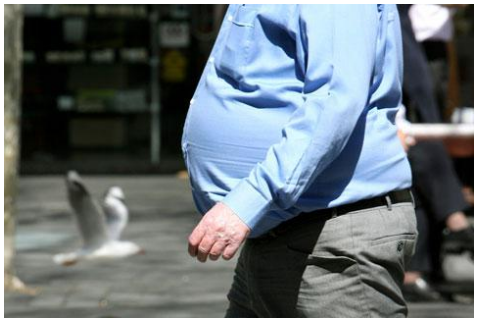
1. Apresentar conceitos recentes que envolvem a presença de ferritina elevada;
2. Relacionar alterações laboratoriais com disfunções metabólicas “clássicas” e “emergentes”, como a sobrecarga de ferro, o hipogonadismo masculino e a esteatose hepática;
3. Apresentar vias fisiopatológicas relacionadas à obesidade.

Roteiro da Aula

- Ferritina/Sobrecarga de Ferro
  - Hemocromatose Hereditária
  - Hiperferritinemia Metabólica
  - Sobrecarga de Ferro Dismetabólica
- Esteatose Hepática Não-alcóolica
  - Avaliação
  - Associação com Hipogonadismo e Sobrecarga de Ferro.
- Revisão da Literatura
  - Artigos Recentes
  - Campos de Estudo e Pesquisa

Por que falar desses assuntos?

- Crescimento da obesidade no Brasil:
  - 20,8% (24,4% mulheres)
  - Sobrepeso: 56,9%
- Marcadores de risco(?);
- Possíveis alvos terapêuticos.



IBGE, 2015

Causes and Significance of Markedly Elevated Serum Ferritin Levels in an Academic Medical Center

J Clin Rheumatol. 2013;19(6):324-328.

- Objective: A markedly elevated serum ferritin level has been associated with inflammatory conditions such as adult-onset Still's disease, systemic juvenile idiopathic arthritis, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Hyperferritinemia, however, can also be caused by a wide variety of disparate conditions, often with impressively high serum levels. The objective of this analysis was to investigate the underlying etiology of markedly elevated ferritin levels in a large group of patients treated as outpatients and inpatients in a tertiary-care medical center.
- Methods: Data of all adult patients from 2008 through 2010 with at least 1 serum ferritin level greater than **1000 µg/L** were reviewed. If a patient had multiple qualifying levels, the highest one was used. For each case, the most likely cause of the elevated ferritin was assessed based on the available clinical data using a simple algorithmic approach.

- Results: **Six hundred twenty-seven** patients were found. The average serum ferritin level was **2647 µg/L**.
- The most frequent condition was malignancy (153/627), with iron-overload syndromes the second most common (136/627). There were 6 cases of adult-onset Still's disease, systemic juvenile idiopathic arthritis, or hemophagocytic lymphohistiocytosis/macrophage activation syndrome. The average ferritin level in these syndromes was 14242 µg/L. Seven patients appeared to have anemia of chronic inflammation, and in 5 patients, there was no clearly definable cause for hyperferritinemia.
- Conclusions: Although extremely elevated ferritin levels may be associated with rheumatologic diseases, more often they are found in patients with other conditions such as malignancy or infection. In addition, extremely high ferritin levels can be found in patients with seemingly indolent disease or levels of chronic inflammation.

Introdução: Síndrome Metabólica

- Dobra o risco de doença aterosclerótica e quintuplica o de DM2;
- Aglomeração de fatores de risco múltiplos e inter-relacionados, que estão fortemente associados e parecem promover o desenvolvimento de DM2;

- Alteração-chave: resistência insulínica;

Definição de Síndrome Metabólica (OMS, EGIR e NCEP-ATPIII)

- Resistência insulínica (OMS);
- **Alteração de glicemia (>110 – 100 ou DM2)**;
- Mais dois dos abaixo:
  - Obesidade (circunferência abdominal);
  - Hipertrigliceridemia (150);
  - HDL baixo;
  - Pressão arterial;
  - Outros (OMS):

Aspectos Introdutórios

- Sobrepeso e obesidade cursam com esteatose hepática não-alcóolica (EHNA) – 30% EUA/Mundo;
- 18-19% (São Paulo e Salvador);
- Prevalência da síndrome da sobrecarga de ferro dismetabólica (SSFD/DIOS) é de 30% dos pacientes com esteatose hepática não-alcóolica;
- A DIOS está relacionada com esteatose hepática, resistência insulínica (RI), inflamação subclínica e alterações genéticas;
- O excesso de ferro predispõe à RI por alterar o metabolismo de carboidratos e a função dos adipócitos;

Journal of Hepatology 2011

- A SSFD/DIOS também predispõe:
  - à diabetes do tipo 2 por alterar o funcionamento das células beta pancreáticas;
  - a doenças cardiovasculares por contribuir para o recrutamento e ativação de macrófagos na parede arterial;
  - a doenças hepáticas por induzir estresse oxidativo nos hepatócitos e ativação das células estreladas, o que pode levar à transformação maligna (HCC).

Journal of Hepatology 2011

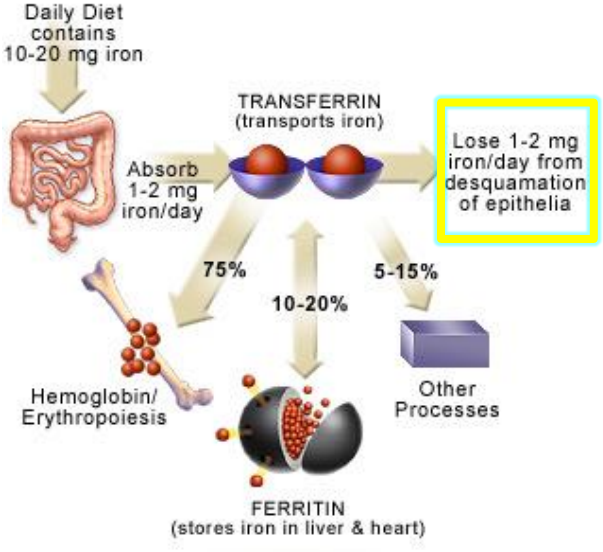
- Nos últimos anos, houve um aumento no diagnóstico de sobrecarga de ferro **não** relacionada à hemocromatose hereditária (HH), associada a diversas manifestações da síndrome metabólica, em especial à **esteatose hepática**.

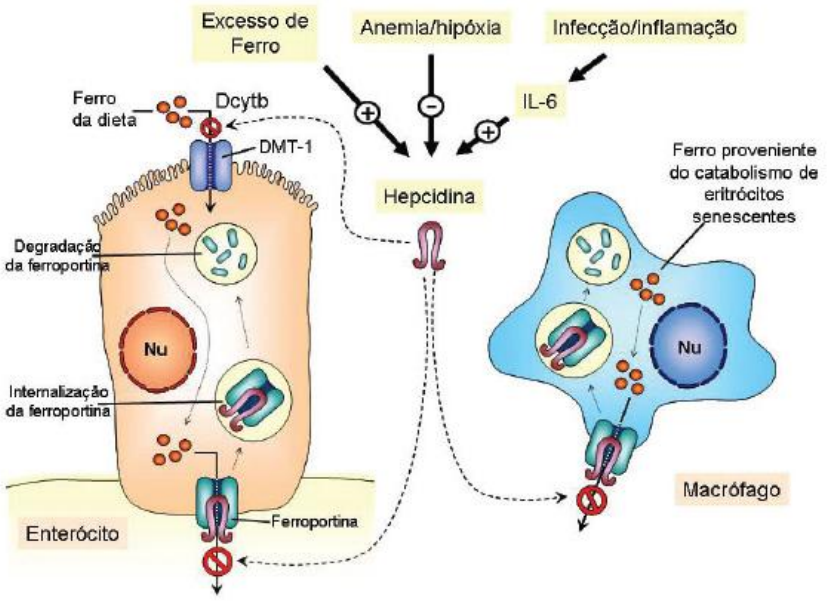
Journal of Hepatology 2011

Metabolismo do Ferro

Ferro total: 3-4 g

Dieta "ocidental": 6 mg a cada 1.000 kcal.





Rev. Bras. Hematol. Hemoter, 2008

Ferritina

- Proteína hidrossolúvel, presente em quase todas células e fluidos,
- Funções de armazenamento de ferro (proporcionalidade) – 10 a 20%;
- Dividida em duas subunidades (leve e pesada), com a capacidade de armazenar ferro livre (Fe^2 em Fe^3);
- Protege lipídios, DNA e proteínas dos efeitos tóxicos do excesso de ferro;
- Participa da fase aguda da inflamação;
- Geralmente é encontrada em baixas concentrações plasmáticas.

Valores Normais de Ferritina Sérica

- Homens: até 300
- Mulheres: até 200

Sobrecarga de ferro

É verificada quando:

- 1) a saturação de transferrina está acima de 45-50%;
- 2) presença de acúmulo de ferro na biópsia hepática ou RNM(ex. FerriScan ou com protocolos para a finalidade) – isso porque 90% do ferro do organismo se encontra depositado no fígado;
- 3) por flebotomia quantitativa (ausência de anemia após 16 “sangrias” semanais – que equivale a retirada de pelo menos 4 g de ferro).

Sobrecarga de ferro

- Causa dano celular por estresse oxidativo e desregulação metabólica;

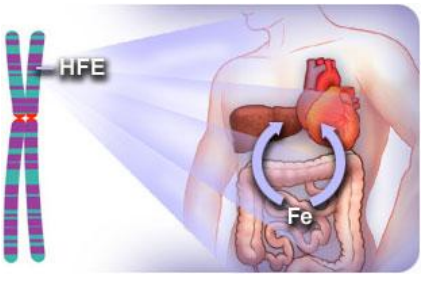
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + {}^{\cdot}OH \qquad k = 76\ L\ mol^{-1}\ s^{-1},\ T = 25\ ^{\circ}C$$

(1, reação de Fenton)

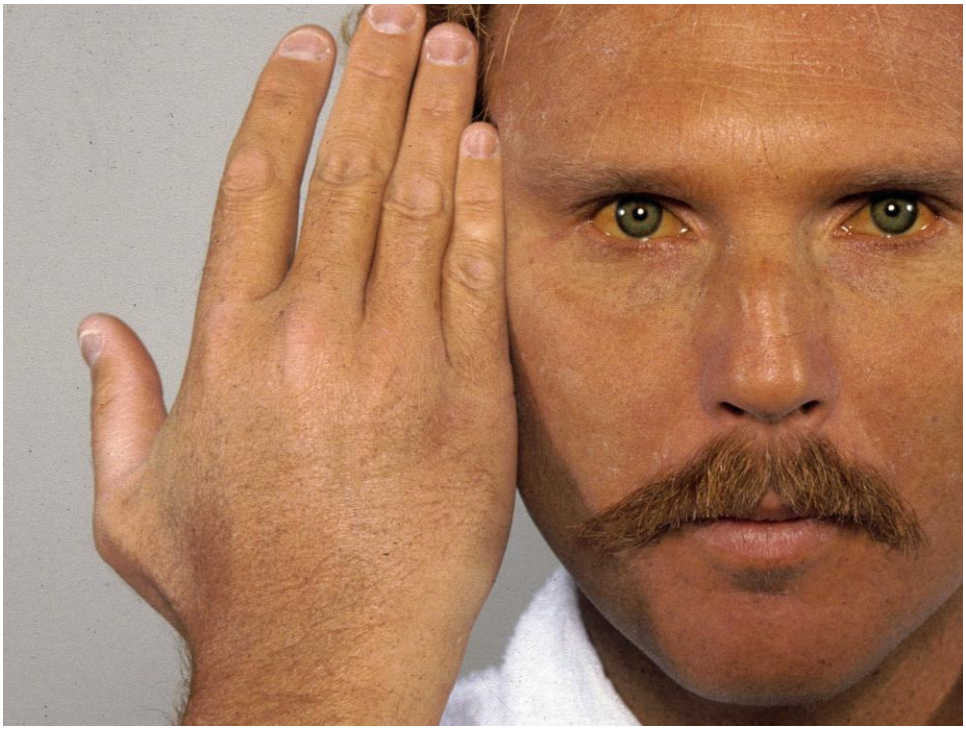
Radicais hidroxil (OH): peroxidação de fosfolipídeos, oxidação de AA, quebra em DNA e fragmentação de proteínas.

Hemocromatose Hereditária

- Definição;
- 1865 – Trousseau
  - Cirrose;
  - Diabetes;
  - Pigmentação bronzeada
- Gene/proteína HFE
- Cromossomo 6;
- Genes envolvidos
  - C282Y, H63D
  - Atuam na hepcidina



- Alterações mais raras



A Clínica da Hemocromatose Hereditária Tipo 1 (HFE)

- Sintomas manifestam-se na quarta e quinta décadas de vida;
- Predomínio de sintomas em homens;

Table 5. Symptoms in Patients with HH

Asymptomatic
Abnormal serum iron studies on routine screening chemistry panel
Evaluation of abnormal liver tests
Identified by family screening
Nonspecific, systemic symptoms
Weakness
Fatigue
Lethargy
Apathy
Weight loss
Specific, organ-related symptoms
Abdominal pain (hepatomegaly)
Arthralgias (arthritis)
Diabetes (pancreas)
Amenorrhea (cirrhosis)
Loss of libido, impotence (pituitary, cirrhosis)
Congestive heart failure (heart)
Arrhythmias (heart)

HEPATOLOGY, Vol. 54, No. 1, 2011

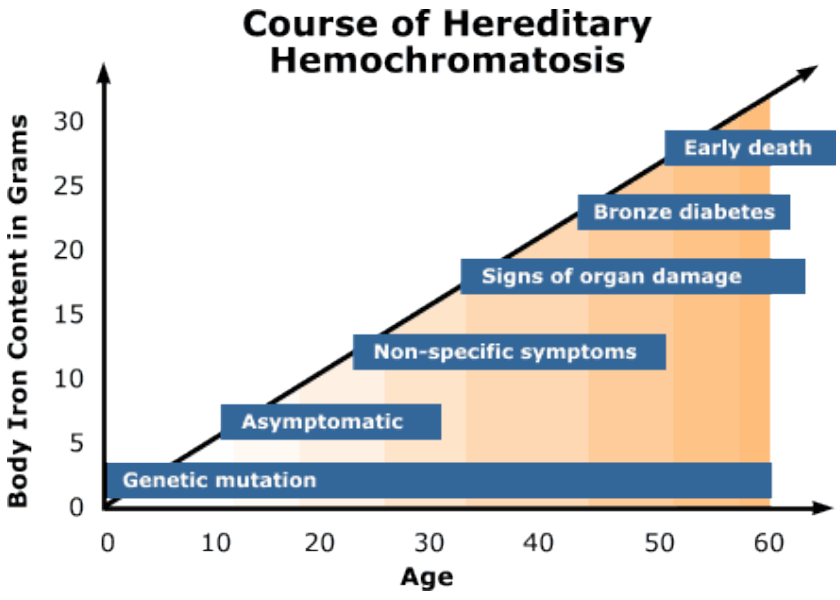


Tabela 2 – Formas hereditárias de sobrecarga de ferro

HH associada ao HFE (tipo 1)	Homozigose C282Y
	Heterozigose composta C282Y/H63D
HH não associada ao HFE	Variantes da hemojuvelina (tipo 2A)
	Variantes da hepcidina (tipo 2B)
	Variantes do receptor de transferrina (tipo 3)
	Variantes da ferroportina (tipo 4)
Outras formas HH	Síndrome catarata congênita e hiperferritinemia familiar
	Sobrecarga neonatal de ferro
	Aceruloplasminemia
	Hipo ou atransferrinemia
	Deficiência de heme oxigenase
	Variantes do Transportador de Metal Divalente 1 (DMT1)

Protocolo H. Albert Einstein, 2012

Sobrecarga de Ferro Genética	Sobrecarga de Ferro Adquirida
(1) Type 1 hemochromatosis – HFE hemochromatosis. (2) (2) Type 2 hemochromatosis – juvenile hemochromatosis: (a) type 2A – mutation in hemojuvelin gene; (b) type 2B – mutation in hepcidin gene. (3) Type 3 hemochromatosis – transferrin receptor 2 hemochromatosis. (4) Type 4 hemochromatosis – ferroportin disease: (a) type 4A – with low transferrin saturation; (b) type 4B – with high transferrin saturation. (5) A(hypo)transferrinemia. (6) Aceruloplasminemia.	**(1) Iatrogenic:** (a) multiple blood transfusions; (b) parenteral iron therapy; (c) oral iron therapy. **(2) Chronic liver disease:** (a) alcoholic liver disease; (b) hepatitis B and C; (c) porphyria cutanea tarda. **(3) Anemias:** (a) thalassemia major; (b) chronic hemolytic anemia; (c) pyruvate kinase deficiency. (4) Others: **(a) dysmetabolic hyperferritinemia.**

Case Reports in Gastroenterology, 2015

Até aqui, muitos questionamentos:

- Qual o significado clínico da hiperferritinemia?
- Com quais níveis devo me preocupar?
- Em quem e quais tipos de exames solicitar?
- De quais doenças estamos falando?

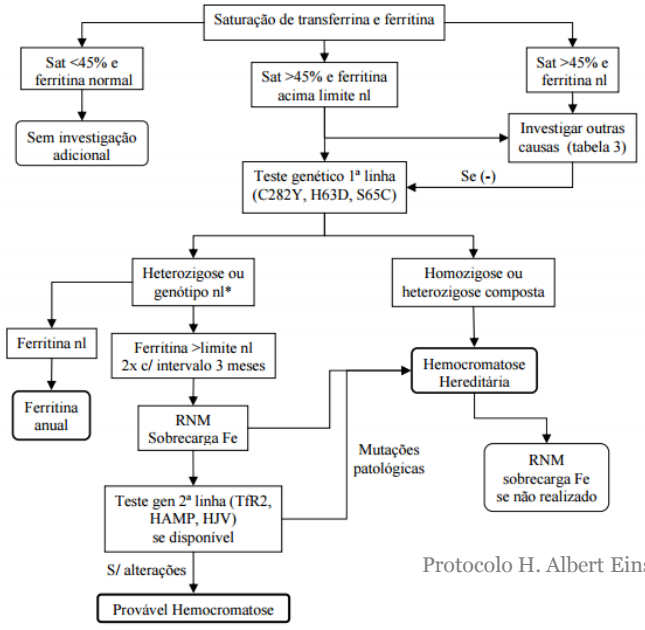
Onde estamos:

(1) Desvalorização de achados ou tratamento “aleatório”;

(2) Algoritmos clínicos.

Algoritmos Clínicos para Hemocromatose (Hiperferritinemia)

Fluxograma de diagnóstico de HH



Protocolo H. Albert Einstein, 2012

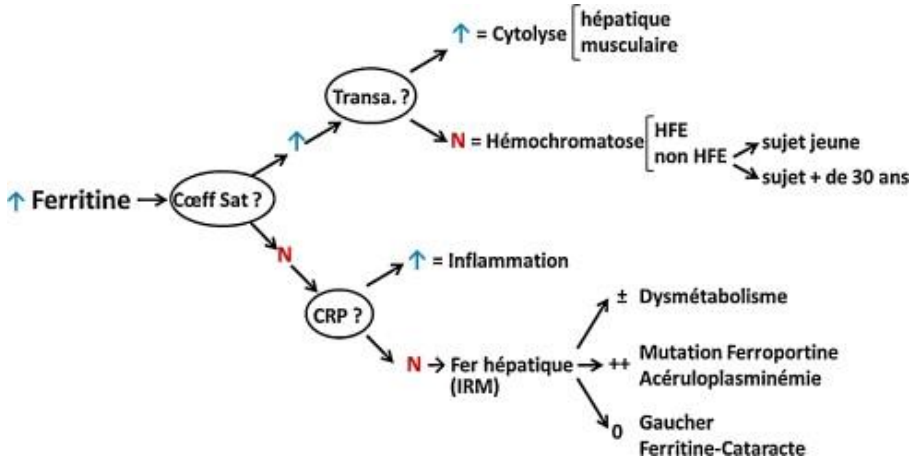


Fig. 2. Étiologies d'une hyperferritinémie et coefficient de saturation de la transferrine.

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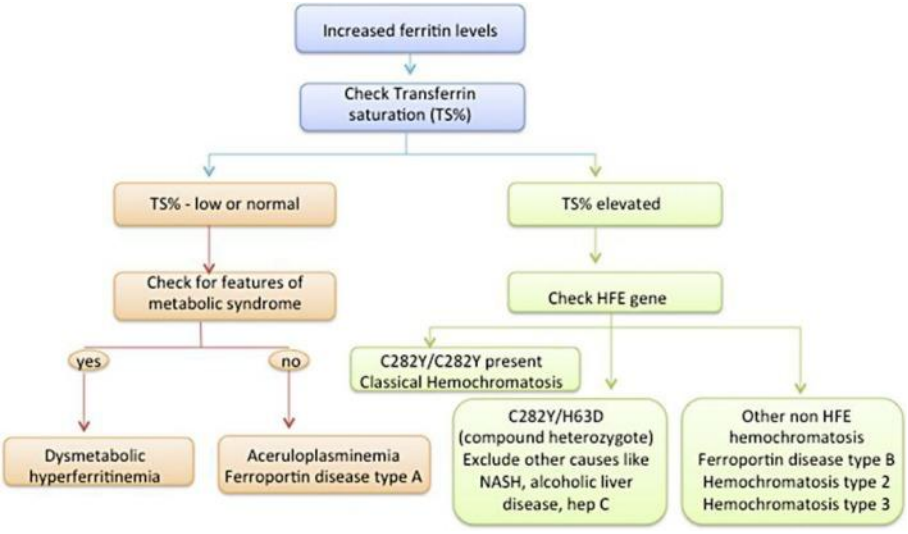
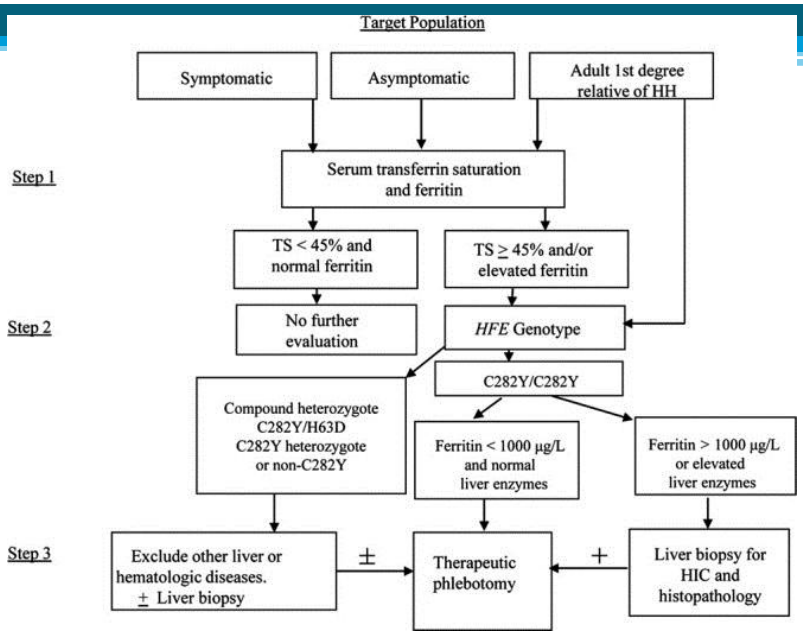
2016

Démarche diagnostique devant une hyperferritinémie
La Revue de Médecine Interne, 2015



Case Reports in Gastroenterology, 2015



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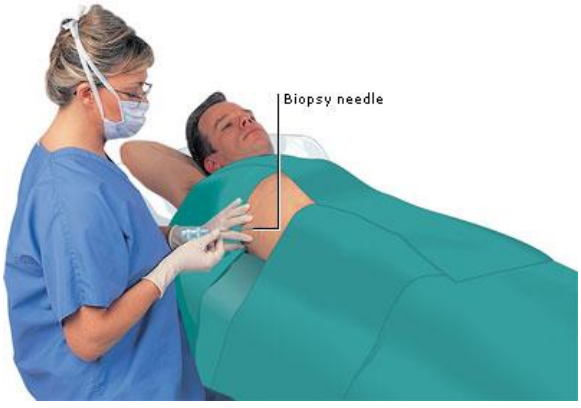
Diagnosis and Management of Hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases. Hepatology, 2011.

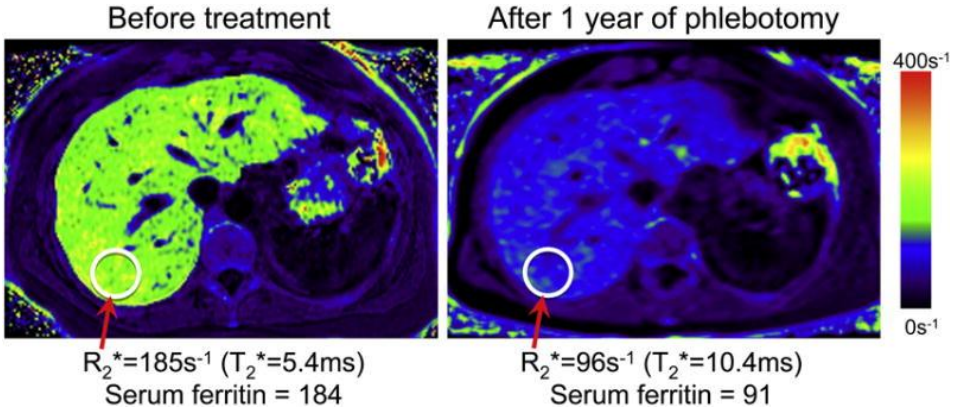
Biópsia Hepática

- Indicações
- O que possibilita



RNM para quantificação de ferro hepático

- Vantagens
  - Método não-invasivo;
- Limitações
  - Novo, caro;
  - Protocolos diferentes (cálculos e referências);
  - Precisão quando da presença de esteatose (?);



Magn Reson Imaging Clin N Am., 2010

Teste Genético para Hemocromatose Hereditária

- Devem ser solicitados segundo os algoritmos – saturação de transferrina >45%;
- Em estudo feito em Natal-RN, com 299 hiperferritinemia, apenas **2,6%** dos pacientes eram homozigóticos C282Y e **5,0%** eram apresentavam heterozigoze composta C282Y/H63D.

J Clin Lab Anal., 2014

Interpretação do Teste Genético para Hemocromatose Hereditária

Análise dos Algoritmos

- Valorizam a saturação de transferrina (ponto de corte 45%);
- Indicam a realização do teste genético HFE;
- Já indicam também a quantificação de ferro hepático por RNM;
- Indicam a biópsia quando elevação de transaminases;
- Não avaliam a possibilidade de comorbidade HH e DIOS.

Dr. Leandro Minozzo

Hiperferritinemia Metabólica

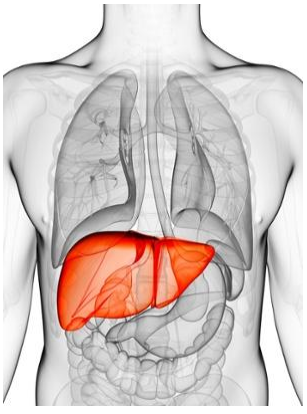
- Em 1997 foi descrita a IR-HIO (sobrecarga hepática de ferro ligada à resistência insulínica);
- Pacientes que não preenchem critérios para H. Hereditária, no entanto, possuem componentes da síndrome metabólica;
- Até agora vem sendo descrita em alguns algoritmos, porém como causa eventual de sobrecarga de ferro ou de hiperferritinemia.

Hiperferritinemia Metabólica

- Hiperferritinemia metabólica e sobrecarga (DIOS): diferentes faces do mesmo problema?
  - Compartilham a maioria das manifestações clínicas;
  - Presença de alterações metabólicas típicas da síndrome metabólica
  - Presença de esteatose hepática
  - Hiperferritinemia com saturação de transferrina normal ou levemente aumentada
  - No caso da DIOS, há a comprovação da sobrecarga de ferro por biópsia, espectrometria (RNM) ou teste com flebotomia quantitativa

Fisiopatologia da hiperferritinemia metabólica

- Hepcidina
- Ferroportina
- Ceruloplasmina (cobre)
- Adipócitos
- Estresse oxidativo
- Inflamação



Hepcidina

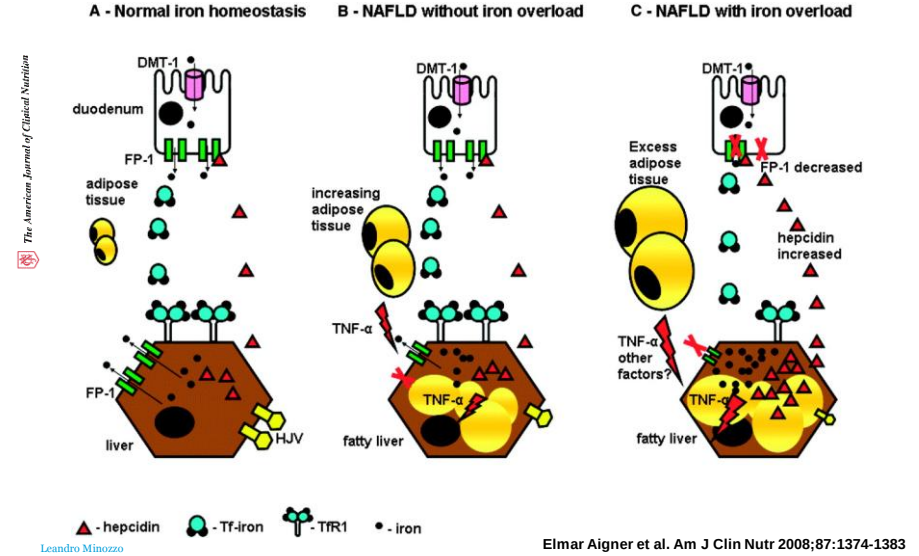
- Regulador-chave no metabolismo do ferro (“regulador negativo”);
- Produzida pelo fígado;
- Secreção aumentada em resposta ao ferro e à inflamação;
- Diminuída em resposta à eritropoese;
- Estudos relacionam aumento com Síndrome da Hipopneia e Apneia Obstrutiva do Sono.

Hepcidina

- Atua regulando o receptor ferroportina (proteína transmembrana no RE de macrófagos e enterócitos);
  - RE de macrófagos – reciclagem de 20-25 mg de Fe/dia;
  - Enterócitos – 1 a 2 mg;

- É regulada por moléculas como HFE, hemojuvelina (HJV), receptor de transferrina 2 (TfR2).

Proposed model of perturbations occurring in nonalcoholic fatty liver disease (NAFLD) iron homeostasis.



The American Journal of Clinical Nutrition

Elmar Aigner et al. Am J Clin Nutr 2008;87:1374-1383

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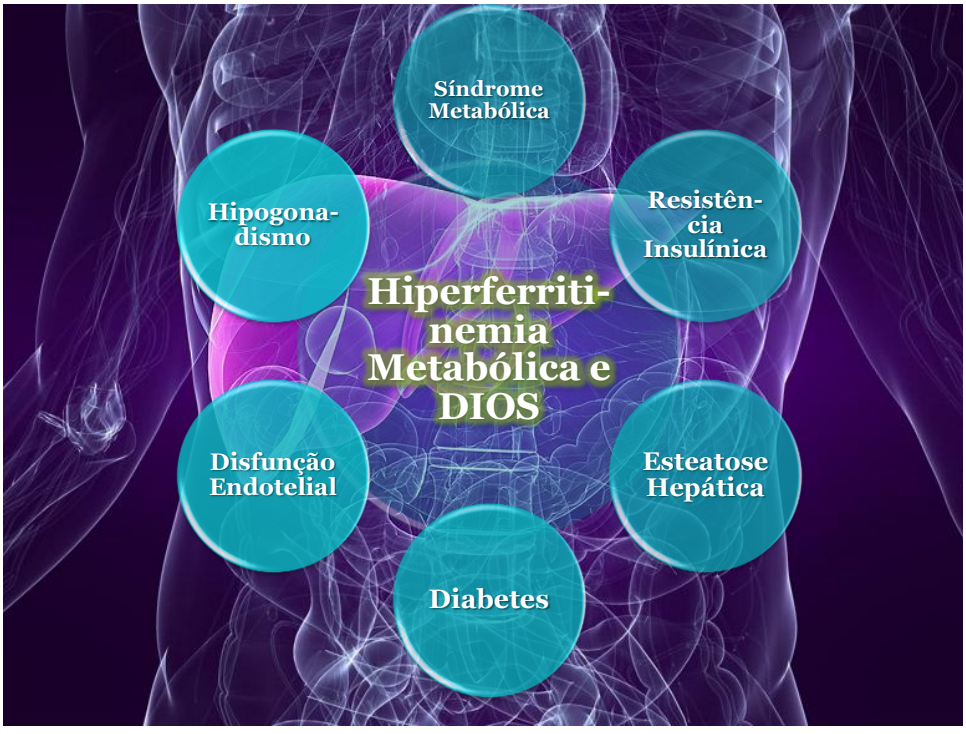
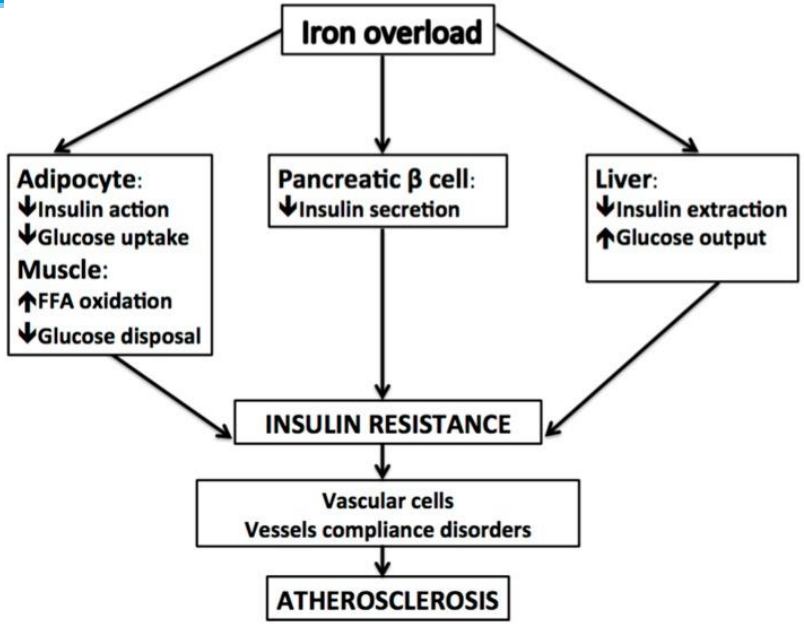




Int J Mol Sci. 2016 May; 17(5): 675.

Diabetol Metab Syndr. 2014 Oct 26;6(1):114.

Serum ferritin levels and the development of metabolic syndrome and its components: a 6.5-year follow-up study.

Hämäläinen P[1], Saltevo J[2], Kautiainen H[3], Mäntyselkä P[4], Vanhala M[5].

METHODS:

Adults born in Pieksämäki, Finland, in 1942, 1947, 1952, 1957, and 1962 (n = 1294) were invited to health checkups between 1997 and 1998 and 2003 and 2004. All of the required variables for both checkups were available from 691 (53%) subjects (289 men and 402 women). MetS was defined by the National Cholesterol Education Program criteria.

RESULTS:

During the 6.5-year follow-up period, 122 (18%) subjects developed incident cases of MetS. Increases in serum ferritin levels were significantly higher in both women and men with incident MetS compared with women and men without MetS (p = 0.04, p = 0.03). Also, serum ferritin levels increased significantly less in women in whom the criteria for MetS resolved during the follow-up period (p = 0.01). Increases in serum ferritin levels were significantly lower in women in whom the glucose criterion for MetS resolved, and higher in women for whom the waist criterion developed (p = 0.01 and p <0.001, respectively). Serum ferritin levels decreased significantly more in men in whom the triglyceride criterion for MetS resolved during the follow-up period (p = 0.01). There was a clear and significant correlation between change in serum ferritin level and change in waist circumference both in men and women (p <0.001, p <0.01).

CONCLUSIONS:

Increases in serum ferritin over a 6,5 year period are associated with development of MetS in both men and women. Whereas, lower increases in serum ferritin over the same timeframe are associated with resolution of hypertriglyceridemia in men and hyperglycemia in women. Increases in waist circumference was positively correlated with increases in serum ferritin in both men and women.

BMC Public Health. 2014 May 21;14:483.

Ferritin levels and risk of metabolic syndrome: meta-analysis of observational studies.

Abril-Ulloa V, Flores-Mateo G, Solà-Alberich R, Manuel-y-Keenoy B, Arija V[1].

BACKGROUND:

Elevated ferritin levels have been associated with single cardiovascular risk factors but the relationship to the presence of metabolic syndrome is inconclusive. The aim of this systematic review and meta-analysis of published observational studies was to estimate the association between serum ferritin levels and metabolic syndrome in adults.

METHODS:

The Pubmed, SCOPUS and the Cochrane Library databases were searched for epidemiological studies that assessed the association between ferritin levels and metabolic syndrome and were published before September 2013. There were no language restrictions. Two investigators independently selected eligible studies. Measures of association were pooled by using an inverse-variance weighted random-effects model. The heterogeneity among studies was examined using the I2 index. Publication bias was evaluated using the funnel plot.

RESULTS:

Twelve cross-sectional, one case-control and two prospective studies met our inclusion criteria including data from a total of 56,053 participants. **The pooled odds ratio (OR) for the metabolic syndrome comparing the highest and lowest category of ferritin levels was 1.73 (95% CI: 1.54, 1.95; I2 = 75,4%). Subgroup analyses indicate that pooled OR was 1.92 (95% CI: 1.61, 2.30; I2 = 78%) for studies adjusting for C-reactive protein (CRP), and 1.52 (95% CI:1. 36, 1.69; I2 = 41%) for studies that did not adjust for CRP (P = 0.044).** This finding was remarkably robust in the sensitivity analysis. We did not find publication bias.

CONCLUSIONS:

The meta-analysis suggests that increased ferritin levels are independently and positively associated with the presence of the metabolic syndrome with an odds ratio higher than 1.73.

J Diabetes Complications. 2016 Jun 23.

Association of serum ferritin levels with metabolic syndrome and insulin resistance in a Chinese population.

Chen L[1], Li Y[2], Zhang F[3], Zhang S[4], Zhou X[5], Ji L[6].

AIMS:
Increased iron is associated with type 2 diabetes, dyslipidemia, and high blood pressure. Therefore, serum ferritin may be a suitable biomarker to detect metabolic syndrome (MetS). We investigated the relationship between serum ferritin, and the prevalence of MetS and insulin resistance (IR).
METHODS:
This cross-sectional study assessed 2,786 Chinese participants, aged 25-75 years. MetS was defined using the 2006 International Diabetes Federation guidelines. IR was assessed with homeostasis model assessment estimated IR (HOMA-IR). Regression analysis was used to estimate the association between serum ferritin and the prevalence of MetS and IR.
RESULTS:
MetS prevalence within each serum ferritin quartile (Q1-4) was 31.7%, 37.1%, 43.6%, and 55.4%, respectively in men (P<0.001), and 30.1%, 34.8%, 48.2%, and 66.9%, respectively in women (P<0.001). Increased serum ferritin correlated with the number of MetS components (P<0.001). The odds ratio for MetS in the ferritin Q4 group was 1.95 (1.39-2.73) for men and 1.66(1.12-2.47) for women, compared with Q1. Serumferritin correlated positively with HOMA-IR in men (regression coefficient: 0.058, P=0.009) and women (regression coefficient: 0.082, P=0.001).
CONCLUSION:
MetS prevalence increased with elevated serum ferritin levels, and serum ferritin levels were independently associated with MetS and IR.

Hiperferritinemia e Diabetes

- Um estudo coreano, de 2013, acompanhou 2 mil homens ao longo de 4 anos. Aqueles que apresentavam níveis elevados de ferritina tiveram um risco 2 vezes maior de se tornarem diabéticos.
- Duas meta-análises, também desse ano, só que vindas da China e da Inglaterra, confirmaram a mesma tendência: um risco 1,6 a 1,7 vez maior de desenvolver diabetes naqueles pacientes com níveis mais elevados de ferritina.
- Essa última pesquisa, realizada pela Universidade de Cambridge, analisou 12 estudos e um total de 185.462 participantes.

- Em pesquisa de 2013, do tipo revisão sistemática e meta-análise (de 12 estudos), com uma população total de 185 462 participantes, concluiu-se que para cada 5 ng/mL de ferritina aumentada, o risco para o desenvolvimento de diabetes aumentou em 1%.
- Traduzindo para uma realidade de compreensão mais fácil, alguém com 800 de ferritina tem 80% maior risco de desenvolver diabetes quando comparado a quem tem 400.

Int J Obes (Lond). 2008 Nov;32(11):1665-9.; World J Gastroenterol. 2012 Aug 7;18(29):3782-6.; Haematologica March 2009 94: 307-309; Clin Nutr. 2012 Dec 28. pii: S0261-5614(12)00281-6, Diabetes Metab Res Rev. 2013 May;29(4):308-18

- Exp Clin Endocrinol Diabetes. 2016 Oct 17.
- **Serum Ferritin, Insulin Resistance, and β-cell Dysfunction: A Prospective Study in Normoglycemic Japanese Men.**
- Nakamura K[1], Sakurai M[2], Morikawa Y[3], Nagasawa SY[4], Miura K[5], Ishizaki M[2], Kido T[6], Naruse Y[7], Nakashima M[3], Nogawa K[8], Suwazono Y[8], Nakagawa H[9].
- **Author information**
- **Abstract**
- **Objectives:** The present cohort study investigated the relationship between serum ferritin levels and indices of insulin resistance and β-cell dysfunction in a normoglycemic population without iron overload disorders. **Methods: The study participants included 575 normoglycemic Japanese men aged 35-57 years with serum ferritin levels of 400 μg/L or less. Insulin resistance and β-cell dysfunction were estimated at baseline and after 3 years by the homeostasis model assessments of insulin resistance and β-cell function (HOMA-IR and HOMA-β, respectively).** To compare the subsequent changes in HOMA-IR and HOMA-β over a 3-year follow-up period among 3 groups based on tertiles of baseline serum ferritin levels (4.9-87.1, 87.2-140.5, and 140.6-396.8 μg/L), the geometric mean HOMA-IR and HOMA-β values at year 3 were calculated for each group using analysis of covariance, incorporating the respective log-transformed parameters at baseline in addition to age, body mass index and major confounding factors. **Results: The multivariate-adjusted geometric mean HOMA-IR at year 3 was significantly higher in those in the highest and middle serum ferritin tertiles (1.24 and 1.22, respectively), compared with the lowest tertile (1.07) (p=0.009).** When the total study participants were stratified by median body mass index (22.72 kg/m^2), similar positive relationships were observed between serum ferritin levels and HOMA-IR for both obese and non-obese participants. However, the adjusted geometric mean HOMA-β at year 3 was similar among the 3 serum ferritingroups. **Conclusions:** Elevated serum ferritin levels predicted a subsequent increase in HOMA-IR in normoglycemic Japanese men without iron overload disorders.
-

BMJ Open. 2014 Dec 11;4(12):e006491

Prediabetes, elevated iron and all-cause mortality: a cohort study.

. Mainous AG et al.

PRIMARY OUTCOME VARIABLE:

Mortality was measured as all-cause mortality.

RESULTS:

Adjusted analyses show that prediabetes has a small increased mortality risk (HR=1.04; 95% CI 1.00 to 1.08). Persons who had prediabetes and elevated serum ferritin had an increased HR for death (HR=1.14; 95% CI 1.04 to 1.24) compared with those who had normal ferritinand normal glucose. Among persons with prediabetes who had elevated TS, they had an increased mortality risk (HR=1.88; 95% CI 1.06 to 3.30) compared with those with normal TS levels and normal glucose.

CONCLUSIONS:

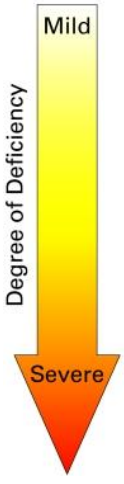
The mortality risk of prediabetes is low. However, among individuals who have coexisting elevated iron markers, particularly TS, the risk rises substantially.

DAEM, Andropausa ou Hipogonadismo

- **O Distúrbio Androgênico do Envelhecimento Masculino (DAEM), popularmente conhecido como andropausa, é uma redução gradual dos níveis sanguíneos da testosterona que acompanha o envelhecimento e que pode estar associado a uma significante diminuição da qualidade de vida dos homens.**

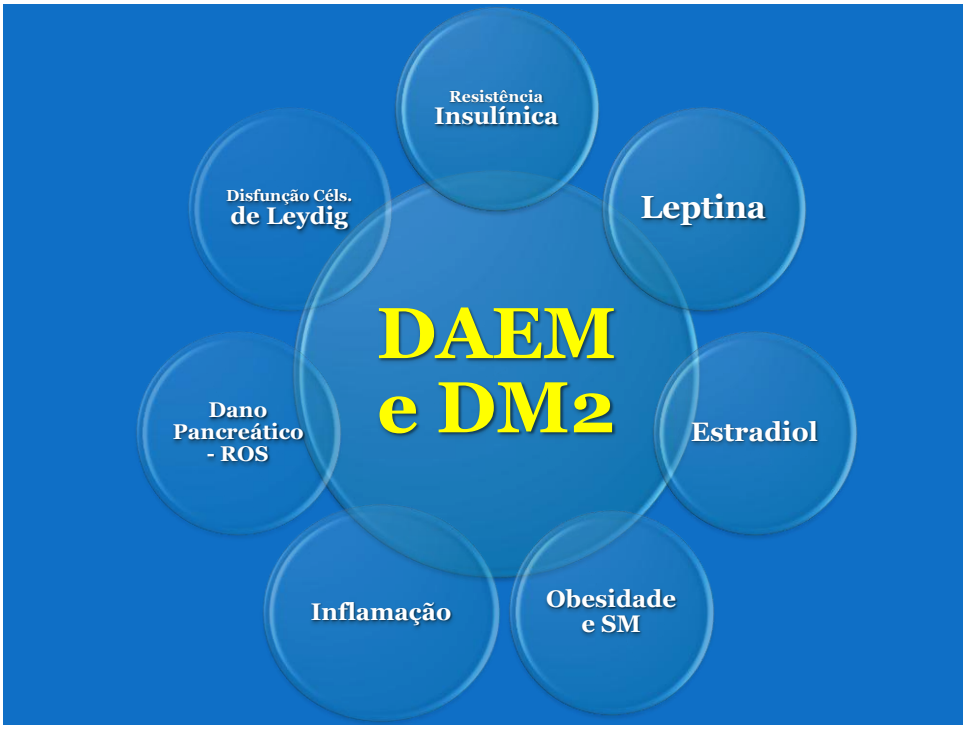
Sociedade Brasileira de Urologia

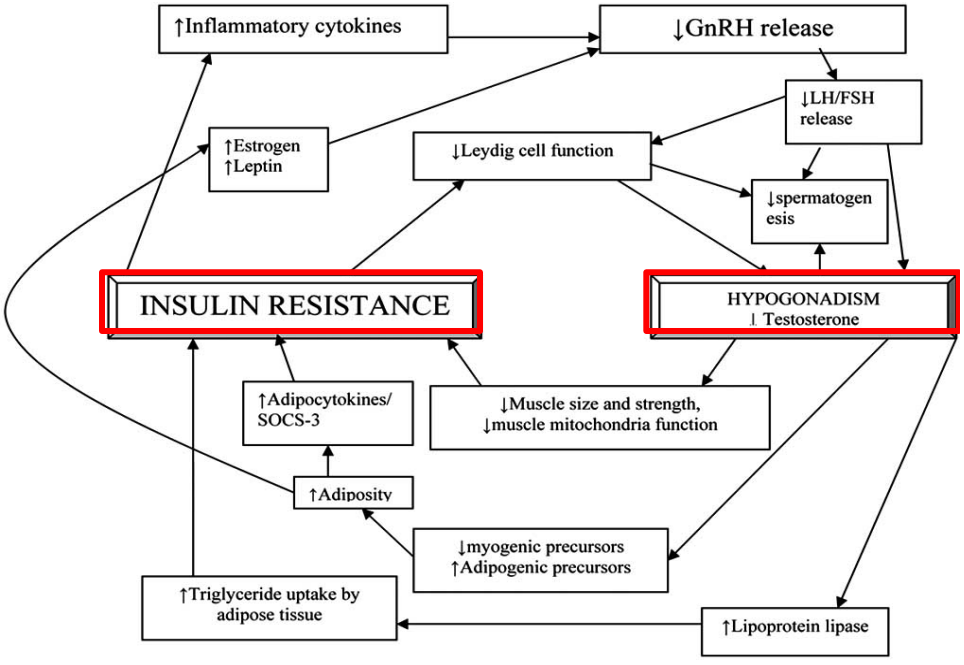
Sinais e Sintomas do DAEM



- *Decreased libido*
- *Decreased vitality*
- Fatigue
- *Mood changes*
- *Insomnia*
- *Anemia*
- *Delayed ejaculation*
- Flushes
- *Erectile dysfunction*
- *Decreased muscle mass*
- *Increased visceral body fat*
- *Testicular atrophy*
- *Weakness*
- *Osteopenia/osteoporosis*
- *Loss of facial, axillary and pubic hair*

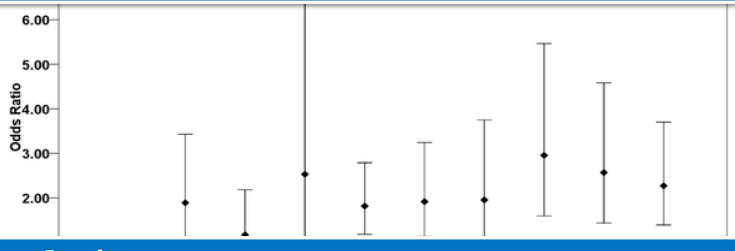
Can Urol Assoc J. 2010 August; 4(4): 269–275.





Dandona P, et al. Curr Mol Med 2008;8:816-828.

Prediabetes Is Associated with an Increased Risk of Testosterone Deficiency, Independent of Obesity and Metabolic Syndrome.



Conclusions

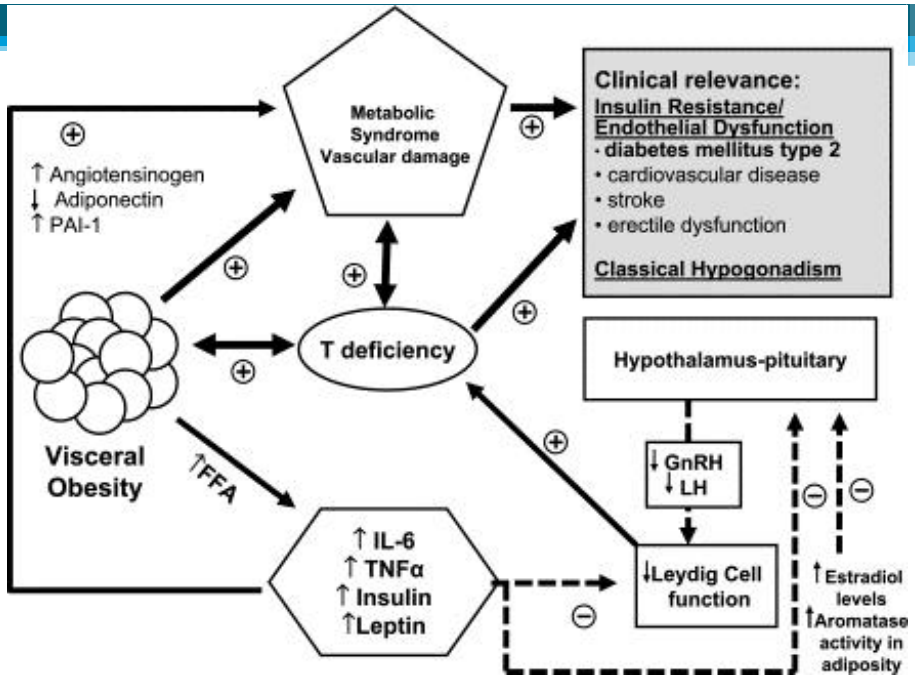
Prediabetes is associated with an increased risk of testosterone deficiency, independent of obesity and MetS. After adjusting for MetS, **the risk equals** that of diabetes. Our data suggest that testosterone should be measured routinely in men with prediabetes.

All were adjsuted for age; Groups 1-7 denote the various conditions of prediabetes; Norm.: normoglycemia; NDM: newly detected diabetes; KDM: known diabetes; IFG: Impaired fasting glucose; IPG: Impaired postprandial glucose; FPG: fasting plasma glucose; PPG: 2-hour postprandial glucose.

Ho C-H, Yu H-J, Wang C-Y, Jaw F-S, et al. (2013) **Prediabetes Is Associated with an Increased Risk of Testosterone Deficiency, Independent of Obesity and Metabolic Syndrome.** PLoS ONE 8(9): e74173.

Leandro Minozzo 2016

PLOS | ONE



Diabetes Care. 2011 July; 34(7): 1669–1675.

Clin Endocrinol (Oxf). 2016 Jun 13.

Effect of testosterone on hepcidin, ferroportin, ferritin and iron binding capacity in patients with hypogonadotropic hypogonadism and type 2 diabetes.

Dhindsa S[1,2], Ghanim H[1], Batra M[1], Kuhadiya ND[1], Abuaysheh S[1], Green K[1], Makdissi A[1], Chaudhuri A[1], Dandona P[1].

CONTEXT:
As the syndrome of hypogonadotropic hypogonadism (HH) is associated with anaemia and the administration of testosterone restores haematocrit to normal, we investigated the potential underlying mechanisms.
DESIGN:
Randomized, double-blind, placebo-controlled trial.
METHODS:
We measured basal serum concentrations of erythropoietin, iron, iron binding capacity, transferrin (saturated and unsaturated), ferritin and hepcidin and the expression of ferroportin and transferrin receptor (TR) in peripheral blood mononuclear cells (MNC) of 94 men with type 2 diabetes. Forty-four men had HH (defined as subnormal free testosterone along with low or normal LH concentrations) while 50 were eugonadal. Men with HH were randomized to testosterone or placebo treatment every 2 weeks for 15 weeks. Blood samples were collected at baseline, 3 and 15 weeks after starting treatment. Twenty men in testosterone group and 14 men in placebo group completed the study.
RESULTS:
Haematocrit levels were lower in men with HH (41·1 ± 3·9% vs 43·8 ± 3·4%, P = 0·001). There were no differences in plasma concentrations of hepcidin, ferritin, erythropoietin, transferrin or iron, or in the expression of ferroportin or TR in MNC among HH and eugonadal men. **Haematocrit increased to 45·3 ± 4·5%, hepcidin decreased by 28 ± 7% and erythropoietin increased by 21 ± 7% after testosterone therapy (P < 0·05). There was no significant change in ferritin concentrations, but transferrin concentration increased while transferrin saturation and iron concentrations decreased (P < 0·05). Ferroportin and TR mRNA expression in MNC increased by 70 ± 13% and 43 ± 10%, respectively (P < 0·01), after testosterone therapy.**
CONCLUSIONS:
The increase in haematocrit following testosterone therapy is associated with an increase in erythropoietin, the suppression ofhepcidin, and an increase in the expression of ferroportin and TR.

Diabetes Care. 2016 Jan;39(1):82-91.

Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction AfterTestosterone Replacement in Men With Type 2 Diabetes.

Dhindsa S[1], Ghanim H[2], Batra M[2], Kuhadiya ND[2], Abuaysheh S[2], Sandhu S[2], Green K[2], Makdissi A[2], Hejna

One-third of men with type 2 diabetes have hypogonadotropic hypogonadism (HH). We conducted a randomized placebo-controlled trial to evaluate the effect of testosterone replacement on insulin resistance in men with type 2 diabetes and HH.

RESEARCH DESIGN AND METHODS:

A total of 94 men with type 2 diabetes were recruited into the study; 50 men were eugonadal, while 44 men had HH. Insulin sensitivity was calculated from the glucose infusion rate (GIR) during hyperinsulinemic-euglycemic clamp. Lean body mass and fat mass were measured by DEXA and MRI. Subcutaneous fat samples were taken to assess insulin signaling genes. Men with HH were randomized to receive intramuscular testosterone (250 mg) or placebo (1 mL saline) every 2 weeks for 24 weeks.

RESULTS:

Men with HH had higher subcutaneous and visceral fat mass than eugonadal men. GIR was 36% lower in men with HH. GIR increased by 32% after 24 weeks of testosterone therapy but did not change after placebo ($P = 0.03$ for comparison). There was a decrease in subcutaneous fat mass (-3.3 kg) and increase in lean mass (3.4 kg) after testosterone treatment ($P < 0.01$) compared with placebo. Visceral and hepatic fat did not change. The expression of insulin signaling genes (IR-β, IRS-1, AKT-2, and GLUT4) in adipose tissue was significantly lower in men with HH and was upregulated after testosterone treatment. Testosterone treatment also caused a significant fall in circulating concentrations of free fatty acids, C-reactive protein, interleukin-1β, tumor necrosis factor-α, and leptin ($P < 0.05$ for all).

CONCLUSIONS:

Testosterone treatment in men with type 2 diabetes and HH increases insulin sensitivity, increases lean mass, and decreases subcutaneous fat.

PLoS One. 2013 Oct 11;8(10).

The association between the levels of serum ferritin and sex hormones in a large scale of Chinese male population.

Liu Z[1], Ye F, Zhang H, et al.

METHODS: 1999 Chinese men in the Fangchenggang Area Male Health and Examination Survey (FAMHES);

RESULTS: The age, BMI and alcohol consumption significantly affected serum ferritin levels, but there was no significant difference between smokers and nonsmokers. Ferritin levels were significantly and negatively associated with total testosterone ($R = -0.205$, $P < 0.001$), sex hormone-binding protein ($R = -0.161$, $P<0.001$) and free testosterone ($R = -0.097$, $P<0.001$). After age and alcohol consumption were adjusted, the above associations were still significant ($R = -0.200$, -0.181 and -0.083, respectively, all $P<0.001$). However, there was only borderline negative association between ferritin levels and estradiol (adjusted $R = -0.039$, $P = 0.083$).

CONCLUSION:

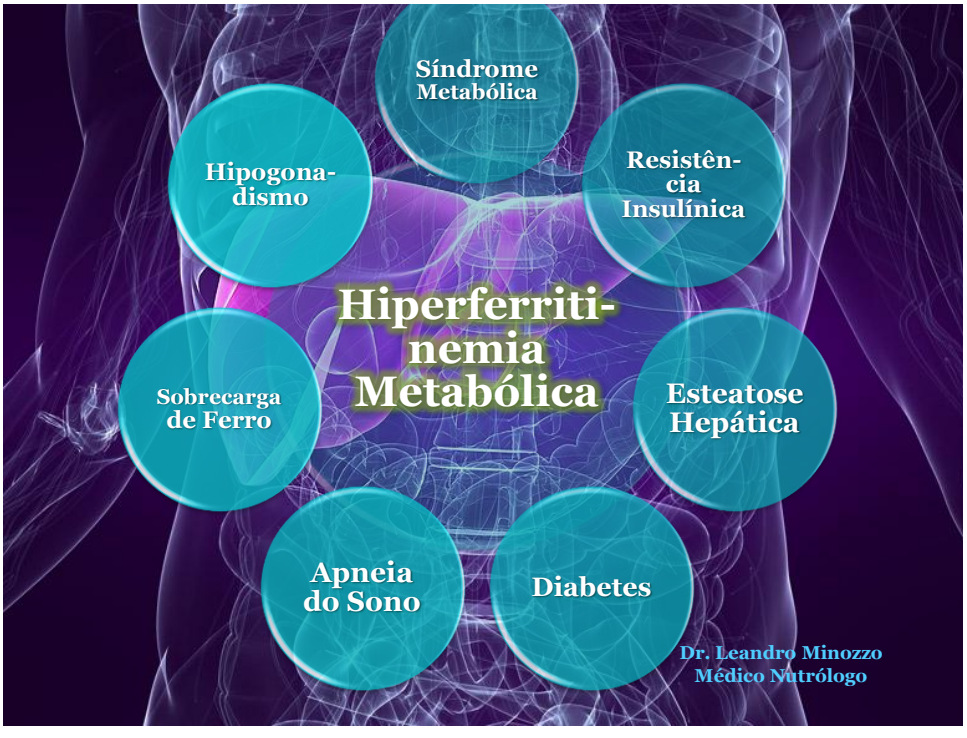
The large scale of epidemic results showed the significantly negative associations between serum ferritin levels and sex hormones, which may provide more clues to explore the potential regulation and biological mechanism of ferritin.

Liver iron overload is associated with elevated SHBG concentration and moderate hypogonadotrophic hypogonadism in dysmetabolic men without genetic haemochromatosis.

- Eur J Endocrinol. 2011 Aug;165(2):339-43.

- Gautier A[1], Lainé F, Massart C, Sandret L, Piguel X, Brissot P, Balkau B, Deugnier Y, Bonnet F.

- To assess the relation between moderate iron overload on sex hormone binding globulin (SHBG) levels and gonadotroph function in men with dysmetabolic iron overload syndrome and the effects of phlebotomy.
- **METHODS:**
- The relationship between magnetic resonance imaging assessed liver iron concentration (LIC) and plasma ferritin levels with total testosterone, bioavailable testosterone (BT), SHBG and LH levels, were studied in 50 men with moderate dysmetabolic ironexcess, in the absence of genetic haemochromatosis, who were randomised to phlebotomy therapy or to normal care.
- **RESULTS:**
- Four patients (8%) had low total testosterone (<10.4 nmol/l) and 13 patients (26%) had low BT (<2.5nmol/l). In the entire population, those with LIC above the median (90 µmol/l) had a higher mean SHBG (P=0.028), lower LH (P=0.039) than those with LIC below the median. In multivariable analysis (adjusted for age, and fasting insulin) LIC was significantly associated with SHBG (positively) and LH (negatively). Patients in the highest quartile of SHBG had higher LIC (P=0.010) and higher ferritinaemia (P=0.012) than those in the three other quartiles. Iron depletion by venesection did not significantly improve any hormonal levels.
- **CONCLUSIONS:**
- Hypogonadism is not infrequent in men with dysmetabolic iron overload syndrome. Liver iron excess is associated with increased plasma SHBG and moderate hypogonadotrophic hypogonadism. Phlebotomy therapy needs further investigation in symptomatic hypogonadal men with dysmetabolic iron excess.



Finalizando, os impactos metabólicos da sobrecarga de ferro:

- Esqueleto;
- Sistema Nervoso Central.

Immunol Res. 2016 Aug 9.

Elevated ferritin and circulating osteoprotegerin levels as independent predictors of hip fracture in postmenopausal women admitted for fragility fracture: time for new screening strategies?

Lipovetzki Y[1], Zandman-Goddard G[1,2], Feldbrin Z[3,2], Shargorodsky M[4,5].

Identification of risk factors may help us to understand the pathogenesis of osteoporotic hip fracture as well as to formulate development of better diagnostic, prevention and treatment strategies. The present study was designed to determine the impact of multiple metabolic risk factors such as markers of systemic inflammation (C-reactive protein), immune responses-acute phase reactants (ferritin), insulin resistance (HOMA-IR) and bone remodeling (osteoprotegerin), for the prediction of hip fractures in postmenopausal osteoporotic women. The study group consisted of 115 postmenopausal women divided into two groups: Group 1 consisted of 49 women hospitalized in the Orthopedic Department, Wolfson Medical Center for the diagnosis of non-traumatic hip fracture and Group 2 contained 66 postmenopausal osteoporotic women without a history of hip fracture. Metabolic parameters were determined. Circulating OPG was significantly higher in Group 1 than in Group 2 (205.2 ± 177.1 vs 60.0 =/- 22.3, $p < 0.0001$). While levels of hemoglobin (Hbg) as well as MCV and MCH did not differ between groups, circulating ferritin was significantly increased in Group 1 compared to the control Group 2 (217.9 ± 195.1 vs 49.7 ± 31.3, $p < 0.0001$). In multiple linear regression analysis, which explains about 40 % of the variability in CRP, 42 % in OPG, and 28 % in ferritin, significant by-group differences in terms of these parameters persisted even after adjustment.

Elevated serum ferritin concentrations and bone remodeling marker, osteoprotegerin, are independent predictors of hip fracture in postmenopausal women hospitalized for fragility fracture.

Review Iron misregulation in the brain

Iron misregulation in the brain: a primary cause of neurodegenerative disorders

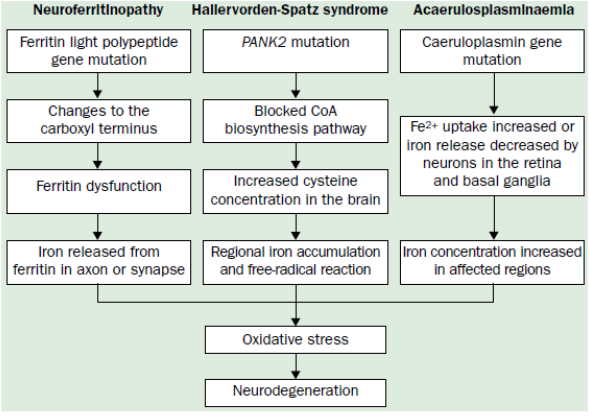


Figure 1. The role of genetic factors in iron misregulation in the development of neurodegenerative disorders.

Tratamento

- Diminuição da ingestão de ferro;
- Diminuição da ingestão de frutose e excesso de gordura;
- Retirada de ferro;
  - Doação de sangue?
- Quelação;
- Acrescento:
  - Perda de peso (dieta + exercício físico);
  - Tratamento da EHNA e Resistência Insulínica;

Nutr Res Pract. 2016 Feb;10(1):81-8.

Dietary factors associated with high serum ferritin levels in postmenopausal women with the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V), 2010-2012.

Ju SY[1], Ha AW[1].

BACKGROUND/OBJECTIVES:

Serum ferritin levels are significantly increased after menopause and greatly affect women's health. The aim of this study was to investigate the dietary and non-dietary factors associated with high ferritin levels in postmenopausal women.

SUBJECTS/METHODS:

Among adult women in 2010-2012, qualified postmenopausal women (n = 3880) were separated into quartiles of serumferritin. The variable differences among the quartiles of ferritin were determined using either procsurvey chi-square test (χ(2)-test) among categorical variables, or GLM (Generalized Linear Model) among continuous variables. The odds ratio for high ferritin in relation to dietary factors was also determined using procsurvery logistic analysis.

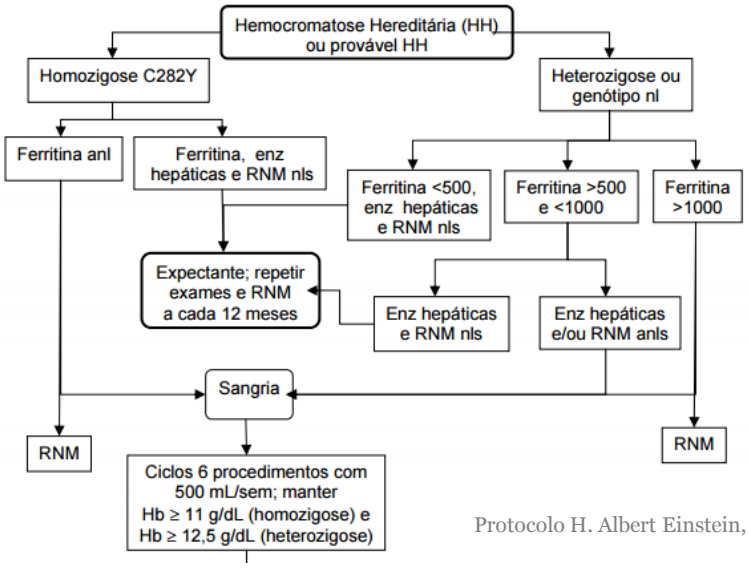
RESULTS:

Age, obesity, drinking habit, and blood glucose levels were found to be significant indicators of high serum ferritin level after adjusting for all confounding factors. Among the food groups, grain, milk, vegetable, and seaweed intakes were significantly associated with high ferritinlevels, but after adjusting for all confounding factors, only grains and vegetables remained significant factors. Among the nutrient groups, calcium, vitamin A, and vitamin C intake were significant factors, but after adjustment, none of the nutrient groups analyzed were associated with a highrisk of ferritin.

CONCLUSION:

Age, obesity, drinking habit, and glucose levels, as well as inadequate intakes of grains and vegetables, were found to be significantly associated with high serum ferritin levels in postmenopausal Korean women.

Fluxograma de Conduta e Seguimento na HH



Protocolo H. Albert Einstein, 2012

Eur J Gastroenterol Hepatol. 2014 Apr;26(4):418-21.

Long-term course after initial iron removal of iron excess in patients with dysmetabolic iron overload syndrome.

Bardou-Jacquet E[1], Lainé F, Morcet J, Perrin M, Guyader D, Deugnier Y.

Initial venesection therapy in dysmetabolic iron overload syndrome (DIOS) was shown to improve insulin resistance. However, no data are available on the long-term outcome of iron store, thus questioning the relevance of maintenance therapy.

AIM:

The aim of the study was to describe the long-term evolution of iron overload after successful iron removal in patients with DIOS.

PATIENTS AND METHODS:

Patients diagnosed with DIOS from 1998 to 2003 and having completed venesection therapy were proposed an outpatient visit in 2009. Inclusion criteria were as follows: confirmation of the DIOS diagnosis, absence of iron-related treatment or bloodletting since the end of the initial venesection treatment, at least 2 years of follow-up since last phlebotomy. Clinical and biological data were recorded at diagnosis and at inclusion.

RESULTS:

A total of 58 patients were included. The mean liver iron content at diagnosis was 80±43 µmol/g and the mean amount of iron removed was 2.2±1.2 g. The mean follow-up time was 71±23 months since end of treatment. **At inclusion, 64% of patients had recurrence of iron overload. Serum ferritin at diagnosis was the only parameter associated with recurrence of iron overload.**

CONCLUSION:

In patients with DIOS, the course of iron loading after initial iron removal supports periodical follow-up to detect those patients with recurrence of iron overload who could benefit from maintenance therapy.

World J Gastroenterol. 2014 Mar 21;20(11):3002-10. doi: 10.3748/wjg.v20.i11.3002.

A randomized trial of iron depletion in patients with nonalcoholic fatty liver disease and hyperferritinemia.

Valenti L[1], Fracanzani AL[1], Dongiovanni P[1], Rovida S[1], Rametta R[1], Fatta E[1], Pulixi EA[1], Maggioni M[1], Fargion S[1].

To compare iron depletion to lifestyle changes alone in patients with severe nonalcoholic fatty liver disease (NAFLD) and hyperferritinemia, a frequent feature associated with more severe liver damage, despite at least 6 mo of lifestyle changes.

METHODS:

Eligible subjects had to be 18-75 years old who underwent liver biopsy for ultrasonographically detected liver steatosis and hyperferritinemia, ferritin levels ≥ 250 ng/mL, and NAFLD activity score > 1. Iron depletion had to be achieved by removing 350 cc of blood every 10-15 d according to baseline hemoglobin values and venesection tolerance, until ferritin < 30 ng/mL and/or transferrin saturation (TS) < 25%. Thirty-eight patients were randomized 1:1 to phlebotomy (n = 21) or lifestyle changes alone (n = 17). The main outcome of the study was improvement in liver damage according to the NAFLD activity score at 2 years, secondary outcomes were improvements in liver enzymes [alanine aminotransferases (ALT), aspartate aminotransferase (AST), and gamma-glutamyl-transferases (GGT)].

RESULTS:

Phlebotomy was associated with normalization of iron parameters without adverse events. In the 21 patients compliant to the study protocol, the rate of histological improvement was higher in iron depleted vs control subjects (8/12, 67% vs 2/9, 22%, P = 0.039). There was a better improvement in steatosis grade in iron depleted vs control patients (P = 0.02). In patients followed-up at two years (n = 35), ALT, AST, and GGT levels were lower in iron-depleted than in control patients (P < 0.05). The prevalence of subjects with improvement in histological damage or, in the absence of liver biopsy, ALT decrease ≥ 20% (associated with histological improvement in biopsied patients) was higher in the phlebotomythan in the control arm (P = 0.022). The effect of iron depletion on liver damage improvement as assessed by histology or ALT decrease ≥ 20% was independent of baseline AST/ALT ratio and insulin resistance (P = 0.0001).

CONCLUSION:

Iron depletion by phlebotomy is likely associated with a higher rate of improvement of histological liver damage than lifestyle changes alone in patients with NAFLD and hyperferritinemia, and with amelioration of liver enzymes.

Am J Gastroenterol. 2007 Jun;102(6):1251-8.

Iron depletion by phlebotomy improves insulin resistance in patients with nonalcoholic fatty liver disease and hyperferritinemia: evidence from a case-control study.

Valenti L[1], Fracanzani AL, Dongiovanni P, Bugianesi E, Marchesini G, Manzini P, Vanni E, Fargion S.

Hyperferritinemia is frequently observed in nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome characterized by hepatic insulin resistance and considered high cardiovascular risk. Iron depletion by phlebotomy has been reported to decrease insulin resistance in NAFLD in small, uncontrolled studies. Aims of this study were to define the relationship between ferritin and iron stores in patients with NAFLD, the effect of iron depletion on insulin resistance, and whether basal ferritin levels influence treatment outcome.

METHODS:

Subjects were included if ferritin and/or ALT were persistently elevated after 4 months of standard therapy. Sixty-four phlebotomized subjects were matched 1:1 for age, sex, ferritin, obesity, and ALT levels with patients who underwent lifestyle modifications only. Insulin resistance was evaluated by insulin levels, determined by RIA and the HOMA-R index, at baseline and after 8 months.

RESULTS:

Baseline ferritin levels were associated with body iron stores (P<0.0001). **Iron depletion produced a significantly larger decrease in insulin resistance (P=0.0016 for insulin, P=0.0042 for HOMA-R) compared with nutritional counseling alone, independent of changes in BMI, baseline HOMA-R, and the presence of the metabolic syndrome. Iron depletion was more effective in reducing HOMA-R in patients in the top two tertiles of ferritin concentrations (P<0.05 vs controls), and in carriers of the mutations in the HFE gene of hereditary hemochromatosis (P<0.05 vs noncarriers).**

CONCLUSIONS:

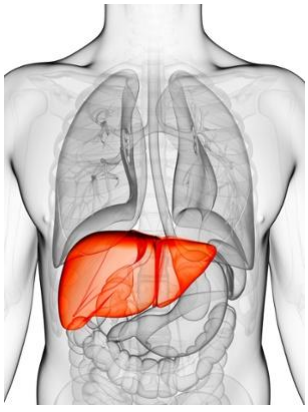
Given that phlebotomy reduces insulin resistance, which is associated with liver tissue damage, future studies should evaluate the effect of iron depletion on liver histology and cardiovascular end points.

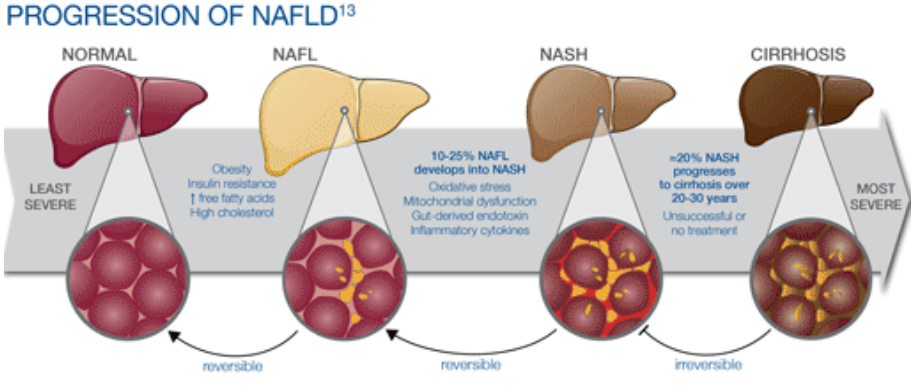
Até aqui, muitos questionamentos:

- Qual o significado clínico da hiperferritinemia?
  - Definitivamente um marcador de risco!
- Com quais níveis devo me preocupar?
  - Homens acima de 300 e mulheres acima de 200;
- Em quem e quais tipos de exames solicitar?
  - Síndrome metabólica, esteatose hepática, obesos, histórico familiar, alterações em órgãos-alvo; solicitar: ferritina, saturação de transferrina, enzimas hepáticas;
- De quais doenças estamos falando?
  - Hiperferritinemia metabólica

Esteatose Hepática Não-Alcóolica

- É doença! E tem até CID-10:
  - K76.0





Esteatose Hepática Não-Alcóolica

- Esteatose hepática é definida como o acúmulo de gordura no fígado, principalmente na forma de triglicérides, excedendo 5% do peso do órgão. (Sherlock S, Dooley J, 1997);
- Pode ser do tipo micro, macrovesicular e misto;
- Descrita a primeira vez em 1980 (Ludwig);
- Prevalência estimada:
- 30% EUA – mundo;
- 18-19% Brasil (São Paulo e Salvador);

- 85 a 95% dos casos são casos primários, ou seja, não relacionados a outras doenças (hepatites virais ou autoimunes, hemocromatose ou doença de Wilson, ou medicamentosa);
- Casos primários são associados à sindrome metabólica e de resistência insulínica periférica;
- Doença Hepática Gordurosa Não-Alcóolica (justificativa do emprego desse termo);

Classificação da DHNG

Primária	Secundária			
Associadas à RI e à SM	**Medicamentos**	**Procedimentos cirúrgicos e proliferação bacteriana**	**Doenças Familiares**	**Miscelânea**
DM2	Amiodarona e Bloqueadores de Canal de Cálcio	Gastroplastias e Bypass jejunoileal	Abeta ou hipobetalipoproteinemia, Lipodistrofia parcial	NPP
Obesidade	Estrógenos sintéticos Corticóides	Ressecção intestinal extensa e cir. biliopancreática		Desnutrição aguda Toxinas
Hiperlipidemia	Tamoxifeno Cloroquina	Diverticulose com supercrescimento bacteriano		
HAS	MTX, tetraciclinas e isoniazida			

Table I. Classification of different causes associated with NAFLD

Genetic and metabolic diseases
- Obesity
- Diabetes mellitus
- Hyperlipidaemia
- Wilson disease
- Lipodystrophy
- Christian disease Weber
- Hemochromatosis
- Storage disease cholesterol esters

Drugs
- Corticosteroids
- Estrogens
- NSAIDs
- Calcium antagonists
- Amiodarone
- Tamoxifen
- Tetracyclines
- Chloroquine
- Antiretrovirals
- Perhexiline

Environmental toxins

Extrahepatic conditions
- Heart failure
- Inflammatory bowel disease
- Bacterial overgrowth syndrome
- Hypothyroidism
- Polycystic ovary syndrome
- Pregnancy
- Neoplastic diseases

Nutritional conditions
- Jejunoileal bypass
- Total parenteral nutrition
- Prolonged fasting
- Protein malnutrition
- Carbohydrate diet

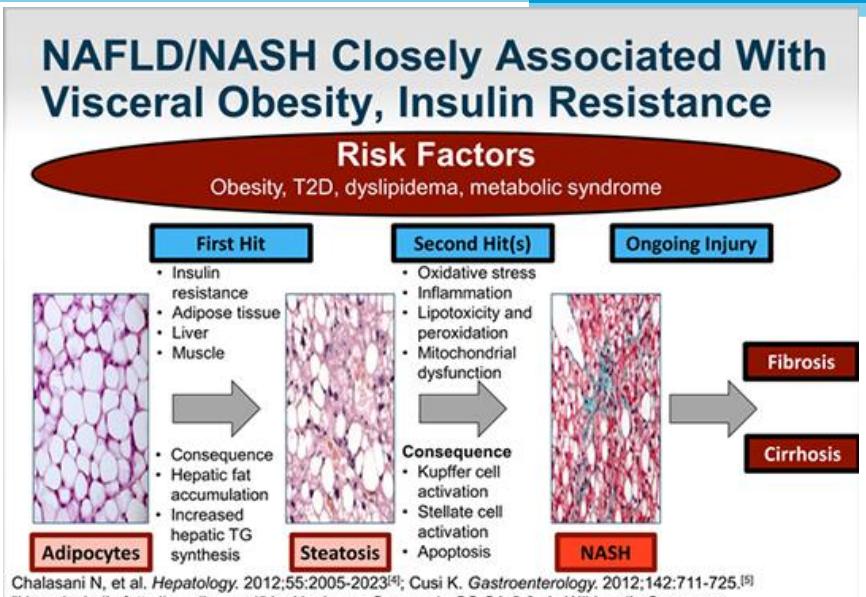
Infections
- Hepatitis B and C
- HIV infection

Fisiopatologia da Esteatose Hepática Não-Alcóolica

- Resistência insulínica (80%)
- Favorece a lipogênese e inibe a lipólise – aumenta excessivamente aporte de AG para fígado;
- Beta-oxidação (mitocôndrias);
- Estresse oxidativo; estresse do retículo endoplasmático, disfunção mitocondrial.
- Fígado se torna vulnerável
- Pode desencadear:
  - lesão – inflamação – cirrose;

Pathogenesis, diagnosis and treatment of non-alcoholic fatty liver disease

- The pathogenic mechanism of NAFLD is associated with insulin resistance and can be explained as the 'double impact theory;
- In the "first impact", the reduction in cellular capacity to respond to the action of insulin causes compensatory hyperinsulinaemia. In adipose tissue it acts on the hormone-sensitive lipase (HSL) increasing the risk of lipolysis with the consequent release of free fatty acids (FFA) to the liver. Glucose absorption decreases in the skeletal muscle, while in the hepatocyte hyperinsulinaemia **increases gluconeogenesis, decreases glycogen synthesis and increases uptake of FFA, alters the transport of triglycerides such as VLDL and inhibits beta-oxidation.**
- These alterations in the metabolism of fats are the basis of FLD;
- This "first impact" results from the interaction of various factors, such as hepatic resistance to leptin or the reduction of adiponectin levels, it would therefore be more correct to speak of "multiple impacts", with a predominance of one or the other, depending on the patient.



Chalasani N, et al. *Hepatology.* 2012;55:2005-2023[4]; Cusi K. *Gastroenterology.* 2012;142:711-725.[5]
"Non-alcoholic fatty liver disease1" by Nephron - Own work. CC-SA-3.0 via Wikimedia Commons.
"Liver steatosis fatty change" by Laboratory of Experimental Pathology, Division of Intramural Research, NIEHS (NIH) via Wikimedia Commons.

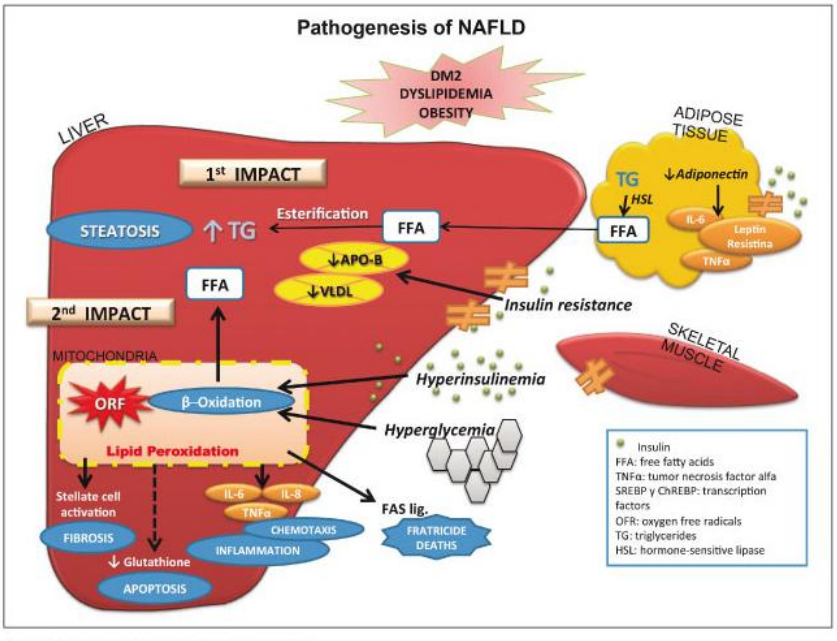


Fig. 1. Pathogenesis of NAFLD (author: Verónica Martín).

Diagnóstico da EH/DHGNA

- Maioria dos casos assintomáticos;
- Quando sintomas: fadiga, dor HD;
- Ultrassonografia (sensibilidade 80% e especificidade 90%) para detecção de infiltração gordurosa quando esteatose acomete > 10% dos hepatócitos;
- RNM – excluindo água corporal é o melhor método de imagem para quantificação de gordura – por espectroscopia;

Dificuldade em Diferenciar Esteatose de esteatohepatite

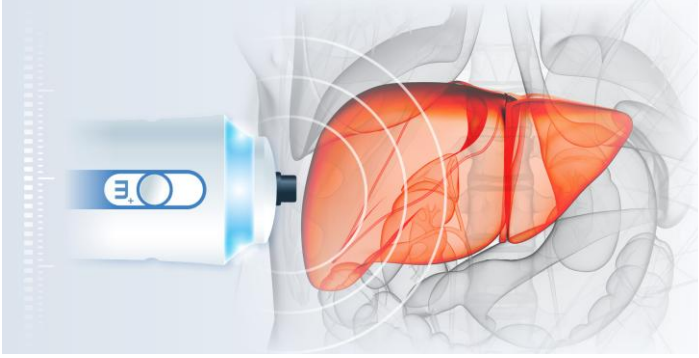
- Na prática, apenas com biópsia;
- Porém, devido à prevalência e aos riscos – busca-se métodos não-invasivos;
- Temos métodos bioquímicos e mecânicos;
- Elastometria (FibroScan) – elastografia avalia a elasticidade hepática através de um transdutor que mede a velocidade de propagação da onda através do fígado – relação com grau de fibrose.

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)
BMI (kg/m²)
IGF/diabetes
AST
ALT
Platelets (x10⁹/l)
Albumin (g/l)
calculate score

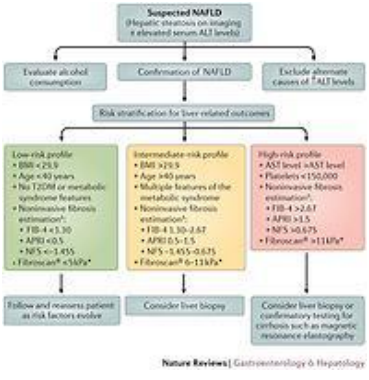
BMI: body mass index
IGF: impaired fasting glucose

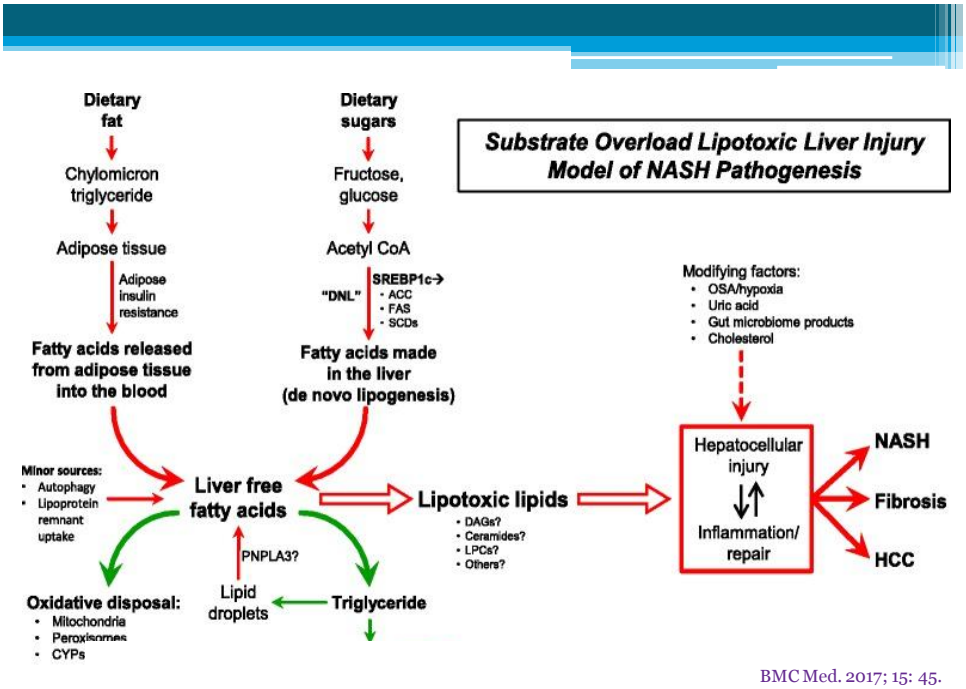


Quando realizar biópsia hepática?

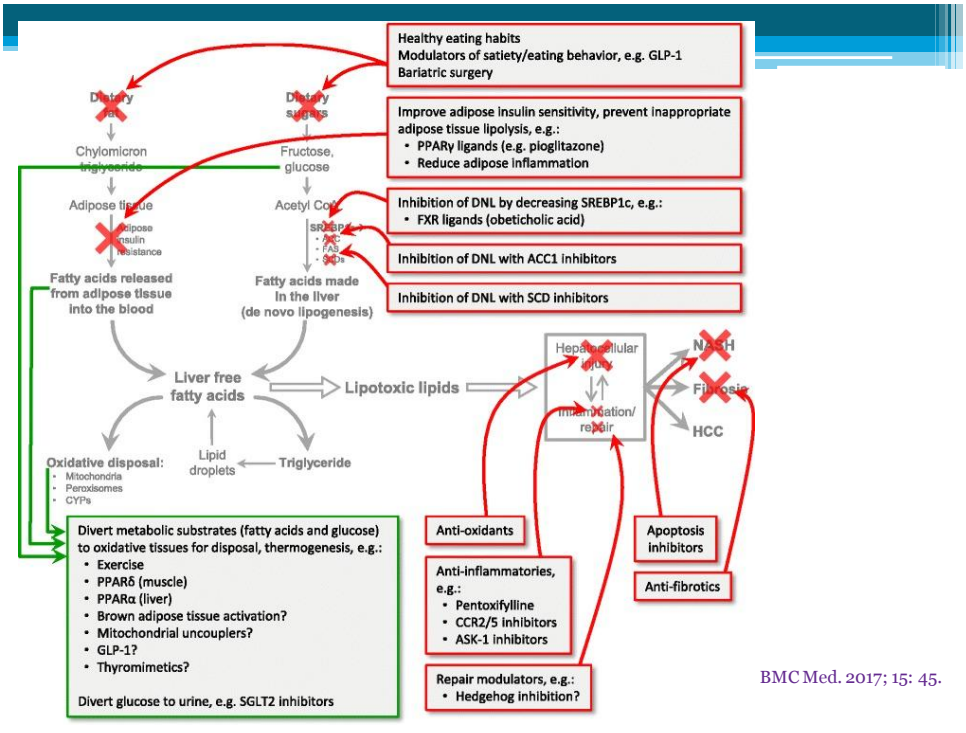
- Risco baixo;
- Risco moderado;
- Riscos elevado;

- IMC > 29,9;
- Idade > 60 anos;
- Síndrome Metabólica;
- FibroScan ou NFS;
- Plaquetas < 150 mil;
- Alteração em transaminases;





BMC Med. 2017; 15: 45.



BMC Med. 2017; 15: 45.

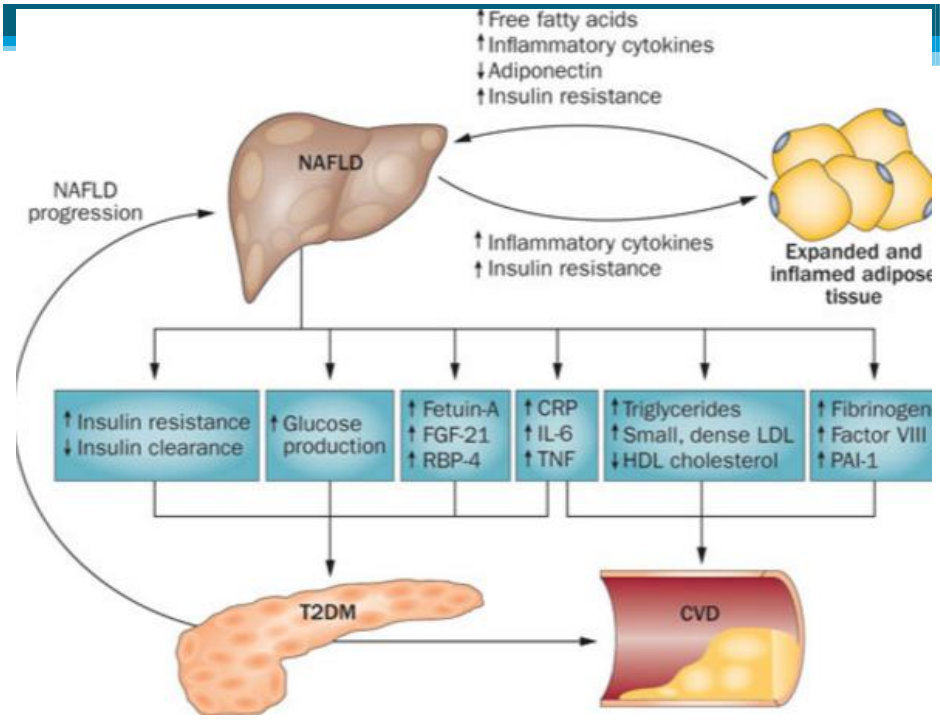
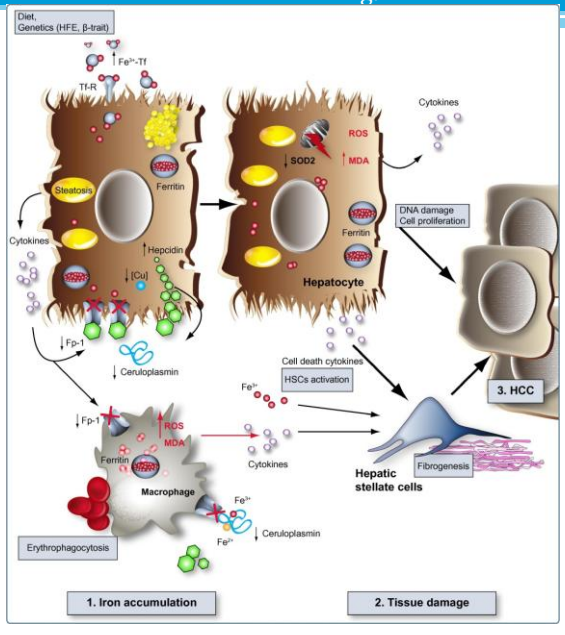


Fig. 2



Leandro Minozzo
2016

Journal of Hepatology 2011 55, 920-932DOI: (10.1016/j.jhep.2011.05.008)

Liver Int. 2016 Apr 11.

Elevated serum ferritin is associated with increased mortality in NAFLD after 16 years of follow-up.

Hagström H[1], Nasr P[2], Bottai M[3], Ekstedt M[2], Kechagias S[2], Hultcrantz R[1], Stål P[1].

High levels of ferritin in patients with non-alcoholic fatty liver disease (NAFLD) are associated with significant fibrosis and higher NAFLD activity score (NAS). It is unclear if this association has an impact on mortality. We investigated if high levels of ferritin, with or without iron overload, were associated with an increased mortality in NAFLD.

METHODS:

We included 222 patients between 1979 and 2009 with biopsy-proven NAFLD and available serum ferritin concentrations. The cohort was divided into "high" (n = 89) and "normal" (n = 133) ferritin values, using a cut-point of 350 µg/L in males, and 150 µg/L in females, and stratified upon iron overload status. Data on mortality was obtained from a national, population based register. Poisson regression was used to estimate hazard ratios for mortality. The estimates were adjusted for age at biopsy, sex, smoking, BMI, diabetes, hypertension, cardiovascular disease and fibrosis stage at the time of biopsy.

RESULTS:

The median follow-up time was 15.6 years (range: 0.5-34.2). Patients with high ferritin had more advanced fibrosis and higher NAS than patients with normal ferritin ($p < 0.05$).

Fifteen years after diagnosis, and after adjusting for confounders, the high-ferritin group showed an increasingly higher mortality that was statistically significant (Hazard ratio = **1.10** per year, 95% Confidence interval 1.01-1.21, $p < 0.05$). There was no difference in mortality between patients with different iron overload patterns.

CONCLUSIONS:

High levels of ferritin are associated with a long-term increased risk of death.

Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease.

- Hepatology. 2012 Jan;55(1):77-85.

- Kowdley KV[1], Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, Sanyal AJ, Nelson JE; NASH Clinical Research Network.

- Serum ferritin (SF) levels are commonly elevated in patients with nonalcoholic fatty liver disease (NAFLD) because of systemic inflammation, increased iron stores, or both. The aim of this study was to examine the relationship between elevated SF and NAFLD severity. Demographic, clinical, histologic, laboratory, and anthropometric data were analyzed in 628 adult patients with NAFLD (age, ≥ 18 years) with biopsy-proven NAFLD and an SF measurement within 6 months of their liver biopsy. A threshold SF >1.5 × upper limit of normal (ULN) (i.e., >300 ng/mL in women and >450 ng/mL in men) was significantly associated with male sex, elevated serum alanine aminotransferase, aspartate aminotransferase, iron, transferrin-iron saturation, iron stain grade, and decreased platelets ($P < 0.01$). **Histologic features of NAFLD were more severe among patients with SF >1.5 × ULN, including steatosis, fibrosis, hepatocellular ballooning, and diagnosis of NASH ($P < 0.026$). On multiple regression analysis, SF >1.5 × ULN was independently associated with advanced hepatic fibrosis (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.05-2.62; P = 0.028) and increased NAFLD Activity Score (NAS) (OR, 1.99; 95% CI, 1.06-3.75; P = 0.033).**
- **CONCLUSIONS:**
- A SF >1.5 × ULN is associated with hepatic iron deposition, a diagnosis of NASH, and worsened histologic activity and is an independent predictor of advanced hepatic fibrosis among patients with NAFLD. Furthermore, elevated SF is independently associated with higher NAS, even among patients without hepatic iron deposition. We conclude that SF is useful to identify NAFLD patients at risk for NASH and advanced fibrosis.

Curr Hepatol Rep. 2016 Jun;15(2):75-85.

Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease.

VanWagner LB[1], Rinella ME[2].

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide with an increased prevalence of metabolic, macro- and microvascular complications. The primary causes of mortality in NAFLD are cardiovascular disease (CVD), malignancy and liver disease. NAFLD is a multisystem disease that affects a variety of extra-hepatic organ systems.

The main focus of this review is to summarize the reported extra-hepatic associations, which include CVD, chronic kidney disease, obstructive sleep apnea, osteoporosis, psoriasis, colorectal cancer, iron overload and various endocrinopathies (e.g. type 2 diabetes mellitus, thyroid dysfunction, and polycystic ovarian syndrome).

Due to the systemic manifestations of NAFLD patients require a multidisciplinary assessment and may benefit from more rigorous surveillance and early treatment interventions to decrease mortality related to malignancy or cardiometabolic diseases.

Hepatology. 2014 Mar;59(3):1174-97.

Extrahepatic complications of nonalcoholic fatty liver disease.

Armstrong MJ[1], Adams LA, Canbay A, Syn WK.

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease, and is strongly associated with the metabolic syndrome. In the last decade, it has become apparent that the clinical burden of NAFLD is not restricted to liver-related morbidity or mortality, and the majority of deaths in NAFLD patients are related to cardiovascular disease (CVD) and cancer. These findings have fuelled concerns that NAFLD may be a new, and added risk factor for extrahepatic diseases such as CVD, chronic kidney disease (CKD), colorectal cancer, endocrinopathies (including type 2 diabetes mellitus [T2DM] and thyroid dysfunction), and osteoporosis. In this review we critically appraise key studies on NAFLD-associated extrahepatic disease. There was marked heterogeneity between studies in study design (cross-sectional versus prospective; sample size; presence/absence of well-defined controls), population (ethnic diversity; community-based versus hospital-based cohorts), and method ofNAFLD diagnosis (liver enzymes versus imaging versus biopsy).

Taking this into account, **the cumulative evidence to date suggests that individuals with NAFLD (specifically, nonalcoholic steatohepatitis) harbor an increased and independent risk of developing CVD, T2DM, CKD, and colorectal neoplasms.** We propose future studies are necessary to better understand these risks, and suggest an example of a screening strategy.

Campos para estudo e pesquisa em hiperferritinemia e doença hepática gordurosa não-alcóolica:

- Epidemiologia;
- Fisiopatologia;
- Exames diagnósticos;
  - Laboratoriais;
  - Imagem;
- Pesquisa clínica – intervenção.

Obrigado!

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