

Percorsi
Pediatrici
del
Val di Noto
2016

Sindrome Metabolica e NAFLD: è solo alimentazione?

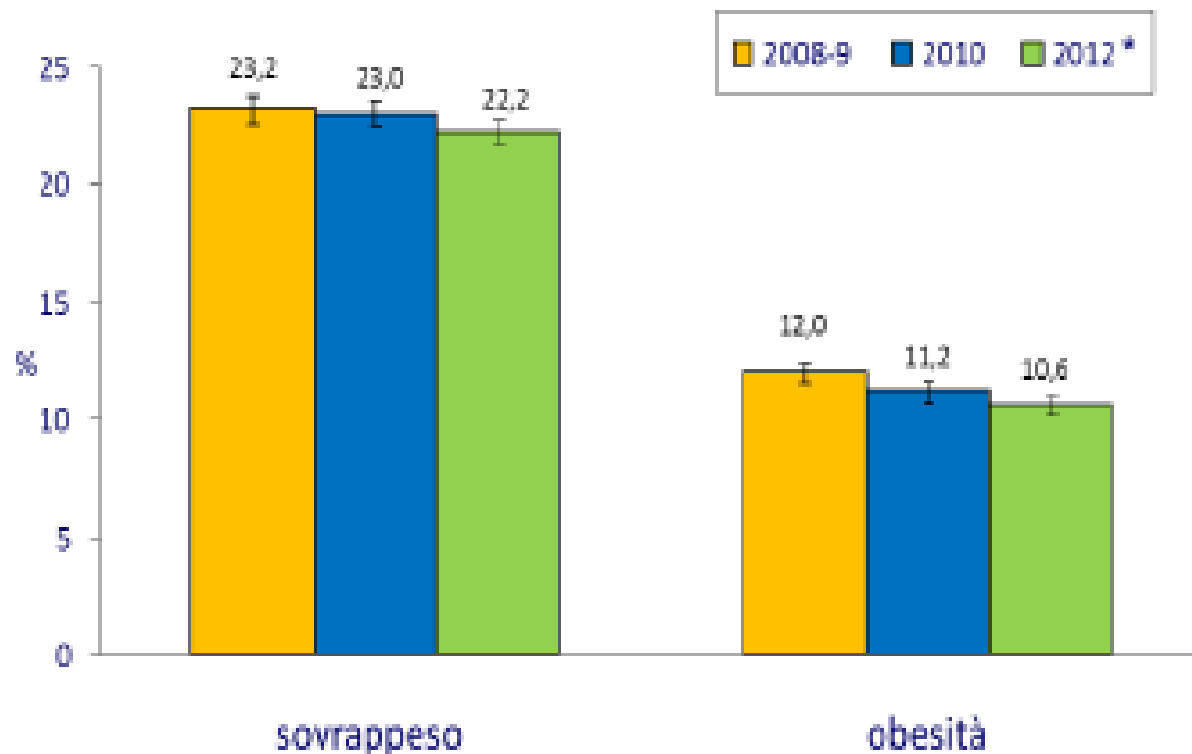
Sabato 27 febbraio 2016

Fabrizio Comisi



Obesità

Sovrappeso e Obesità nei bambini 2008/9-2012



1.1.1. Per diagnosticare l'eccesso di peso si consiglia di usare¹:

- fino a 24 mesi: rapporto peso/lunghezza (tabelle di riferimento: CDC 2000 (www.cdc.gov); valore di cut-off: 85° centile, per il sovrappeso; 95° centile, per l'obesità
- dopo i 24 mesi: BMI (tabelle di riferimento per i cut-off di BMI: Cole *et al*, BMJ 2000); valore di cut-off: percentile di BMI coincidente con il BMI di 25 all'età di 18 anni, per il sovrappeso; valore di cut-off: percentile di BMI coincidente con il BMI di 30 all'età di 18 anni, per l'obesità

Valori di cut off

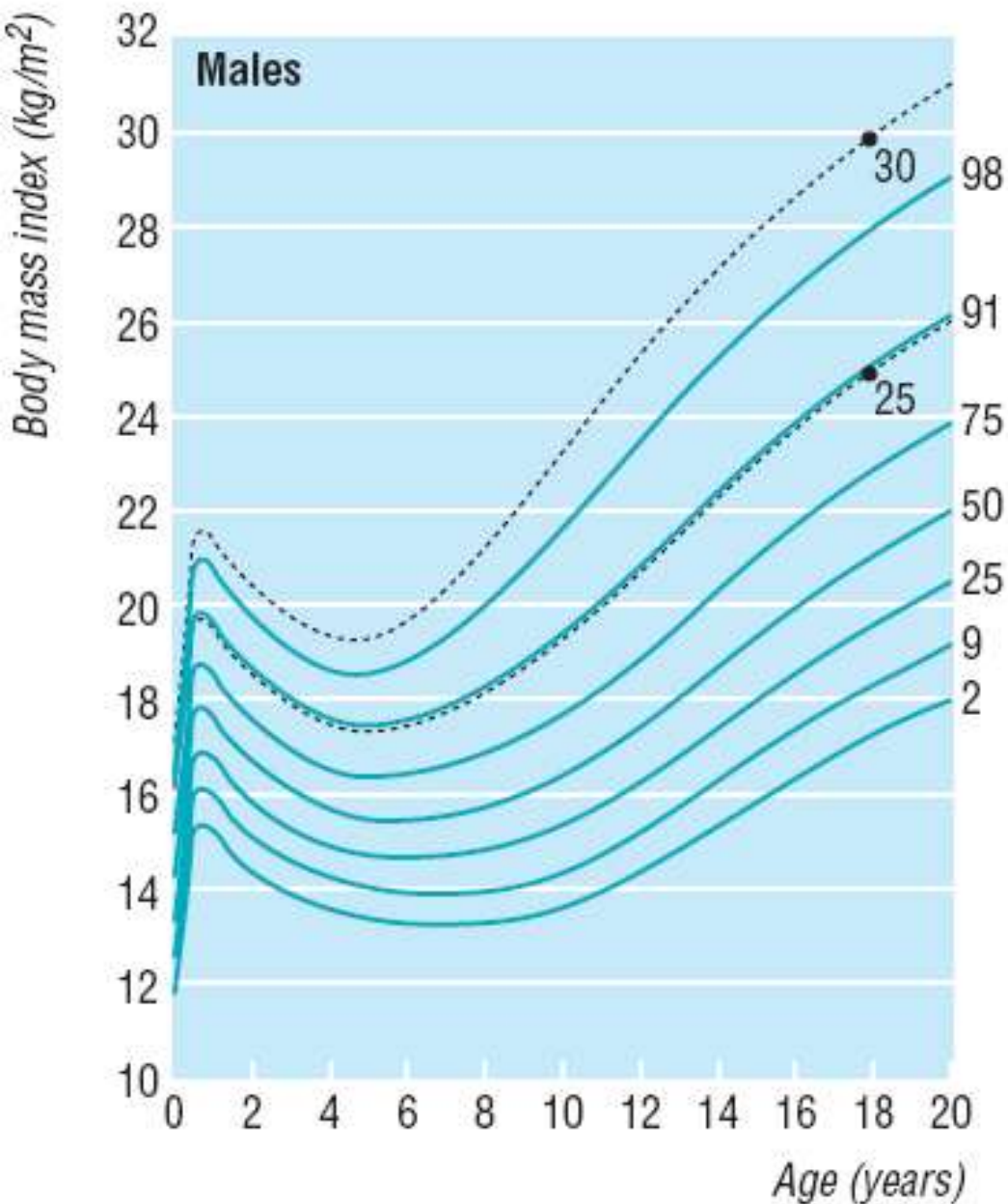
0-24 mesi (Rapporto peso/lunghezza)

- **Sovrappeso: 85° centile**
- **Obesità: 95° centile**

>24 mesi (BMI)

- **Sovrappeso: Percentile di BMI coincidente a BMI 25 a 18 anni**
- **Obesità: Percentile di BMI coincidente a BMI 30 a 18 anni**





>24 mesi (BMI)

- *Sovrappeso: Percentile di BMI coincidente a BMI 25 a 18 anni*
- *Obesità: Percentile di BMI coincidente a BMI 30 a 18 anni*

Sindrome Metabolica - Prevalenza

...For American children, the prevalence of MS was found to be 9.2% in the period from 1988 to 1994 and 12.7% from 1999 to 2000....

*In **obese** children, the prevalence is **30%** and reaches **50%** in extremely obese children.*

Pediatric Reviews 2009;volume 1:e1

**Metabolic syndrome in the
pediatric population:
a short overview**

Natasa Marcun Varda, Alojz Gregoric
Department of Paediatrics, University
Medical Centre, Maribor, Slovenia

Sindrome Metabolica

Prevalenza variabile in funzione dei criteri usati:

- 4-12% nella popolazione pediatrica generale
- 30-50% in bambini obesi
- 14-19% in bambini ipertesi

Sindrome Metabolica - Prevalenza

*.....la prevalenza della SM, sebbene indiscutibilmente in aumento, in età pediatrica varia considerevolmente sulla base del tipo di score utilizzato per la diagnosi e del tipo di popolazione valutata, con stime che oscillano **dal 2,2 al 9,4%** nella stessa popolazione a seconda del sistema diagnostico utilizzato.*

La sindrome metabolica in età pediatrica:
è tempo di ripensare i criteri diagnostici?

Area Pediatrica | Vol. 16 | n. 1 | gennaio-marzo 2015 | **31**

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Sindrome Metabolica

*.....numerosi studi hanno dimostrato come la sindrome metabolica sia oramai da considerarsi una **malattia sistemica, che colpisce diversi organi ed apparati.....***

*.....altre condizioni patologiche, come la **steatosi epatica, le apnee del sonno, uno stato pro-trombotico e pro-infiammatorio, l'iperuricemia, la disvitaminosi D, la policistosi ovarica, sono state considerate comunque manifestazioni della sindrome metabolica....***

La sindrome metabolica in età pediatrica:
è tempo di ripensare i criteri diagnostici?

Area Pediatrica | Vol. 16 | n. 1 | gennaio-marzo 2015 | **31**

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La Sindrome Metabolica

Sindrome Metabolica

*“The metabolic syndrome (MS) in adults is defined as a concurrence of **obesity, disturbed glucose and insulin metabolism, hypertension and dyslipidemia**, and is associated with **increased morbidity and mortality from cardiovascular diseases and type 2 diabetes.**”*

Pediatric Reviews 2009;volume 1:e1

**Metabolic syndrome in the
pediatric population:
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Department of Paediatrics, University
Medical Centre, Maribor, Slovenia**

Sindrome Metabolica del bambino

Table 2. Definition of pediatric metabolic syndrome according to the International Diabetes Federation.

Age (Years)	Criteria for the metabolic syndrome
< 10	Obesity (waist circumference > 90 th percentile), metabolic syndrome as entity is not diagnosed
10-16	Waist circumference > 90 th percentile or adult cut-off if lower Triglycerides \geq 1.7 mmol/L HDL-cholesterol <1.03 mmol/L Glucose \geq 5.6 mmol/L or type 2 diabetes mellitus Systolic blood pressure \geq 130 or diastolic blood pressure \geq 85 mmHg
> 16	Adult criteria

For the diagnosis, central obesity and 2 of 4 other components must be present.

Pediatric Reviews 2009;volume 1:61

**Metabolic syndrome in the
pediatric population:
a short overview**

Natasa Marcun Varda, Alojz Gregoric
Department of Paediatrics, University
Medical Centre, Maribor, Slovenia

Sindrome Metabolica = malattia sistemica

Sono considerate manifestazioni di SM:

- *NAFLD*
- *OSAS*
- *Stato protrombotico*
- *Stato proinfiammatorio*
- *Iperuricemia*
- *Disvitaminosi D*
- *Policistosi ovarica*
- *...*

La sindrome metabolica in età pediatrica:
è tempo di ripensare i criteri diagnostici?

Non alcoholic fatty liver disease - NAFLD

*“Spettro di patologia epatica che va dal semplice accumulo di grasso negli epatociti (la steatosi epatica semplice, o **NAFL**) a vari gradi di infiammazione e fibrosi fino alla cirrosi epatica (Non-Alcoholic SteatoHepatitis – **NASH**).”*

NAFLD

Fattori che conducono alla steatosi:

- Insulino-resistenza
- Obesità viscerale
- Dislipidemia

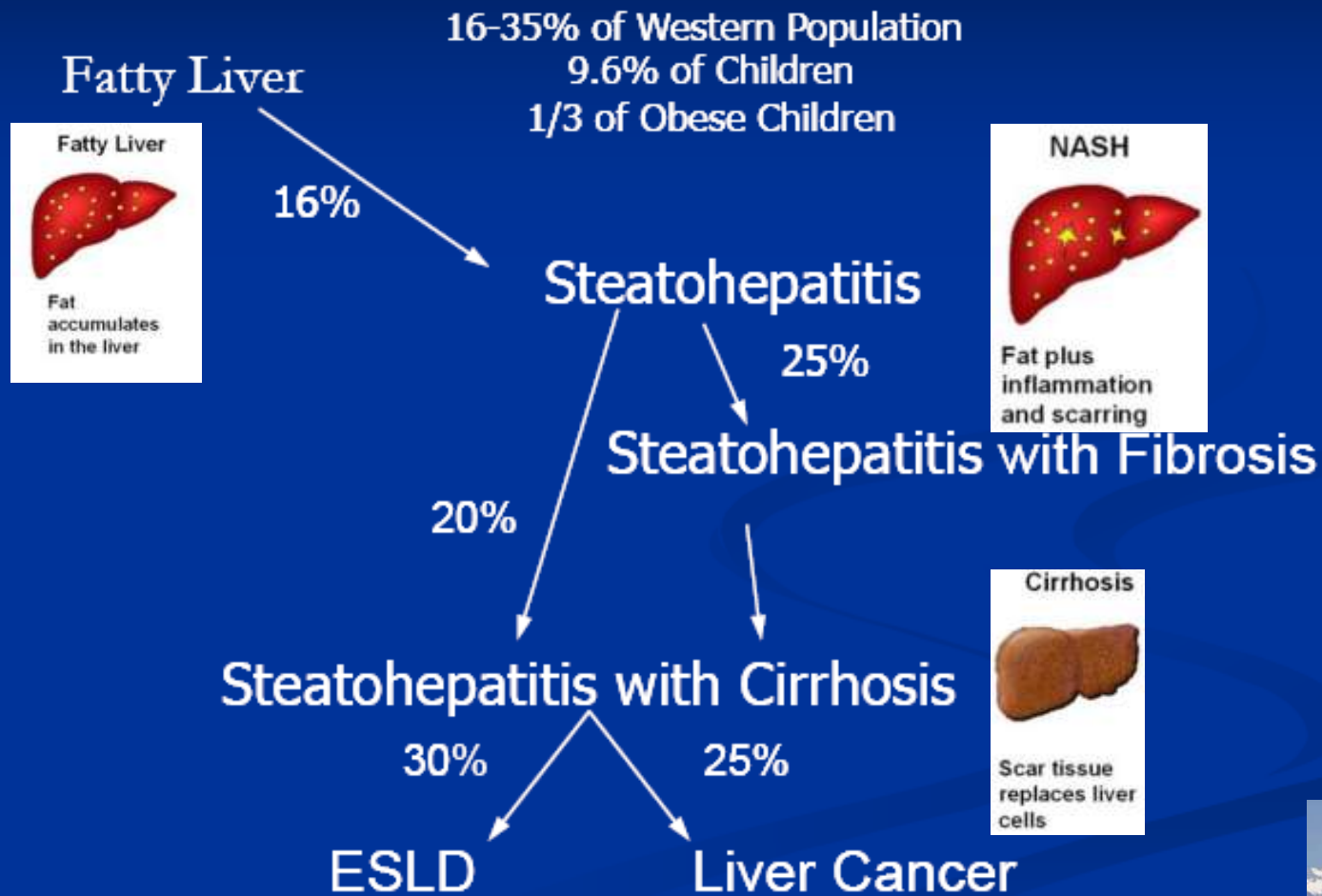
*Associazione fra steatosi epatica e danno cardiovascolare strutturale o funzionale nel bambino (ipertrofia ventricolo sin; dilatazione atrio sin.)
La severità del danno cardiaco correla con la severità della NAFLD*

**Early left ventricular abnormality/
dysfunction in obese children affected
by NAFLD**

D. Fintini ^{a,*,1}, M. Chinali ^{b,1}, G. Cafiero ^{-c}, C. Esposito ^{-b},
U. Giordano ^{-c}, A. Turchetta ^{-c}, S. Pescosolido ^{-d},
G. Pongiglione ^{-b}, V. Nobili ^{-e}

Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 72–74

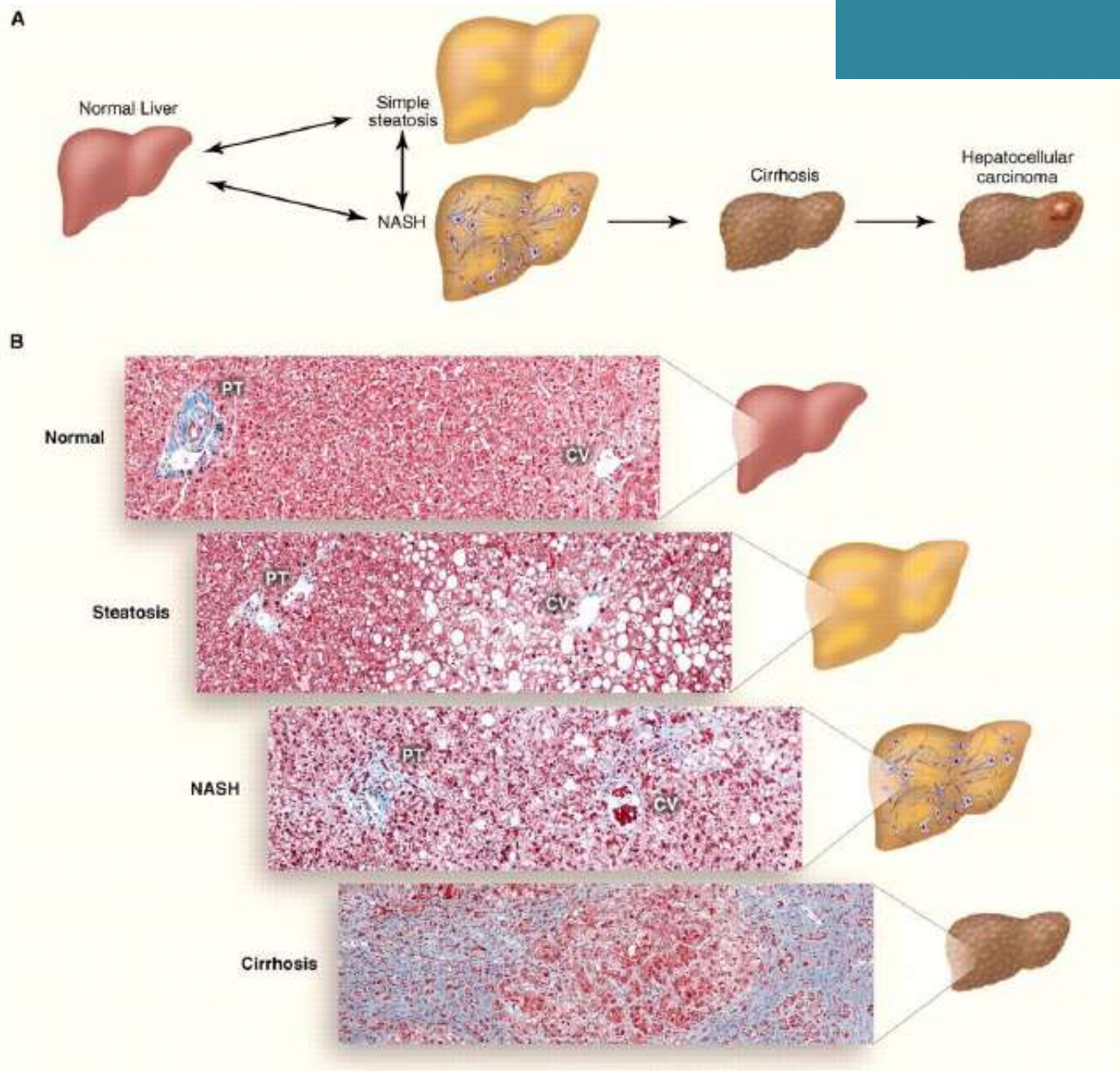
Stages of Fatty Liver Disorders



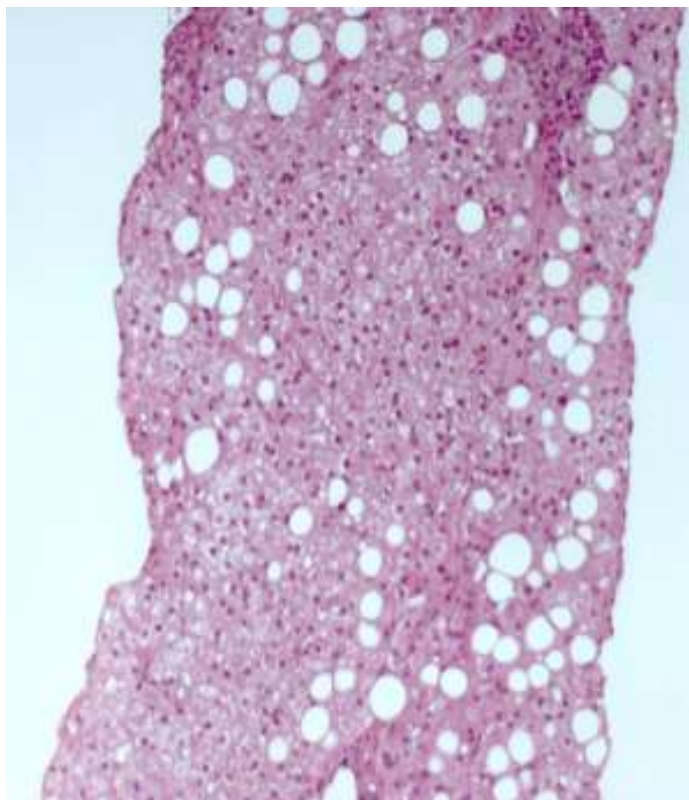
NASH in Children



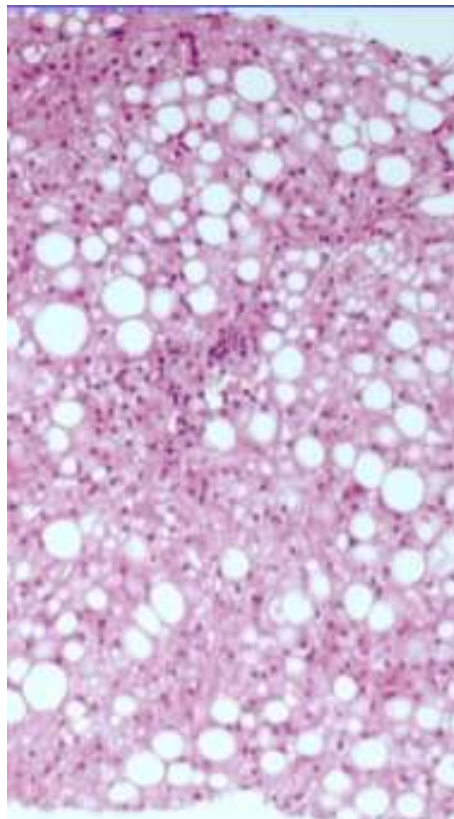
Karen F. Murray, MD
Professor of Pediatrics
Director, Hepatobiliary Program
Seattle Children's and
University of Washington School of Medicine
Seattle, Washington USA



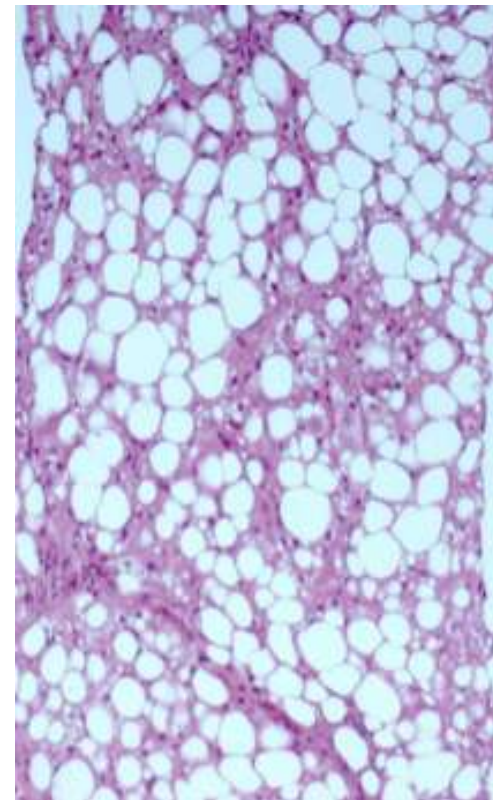
Steatosi Grado 1



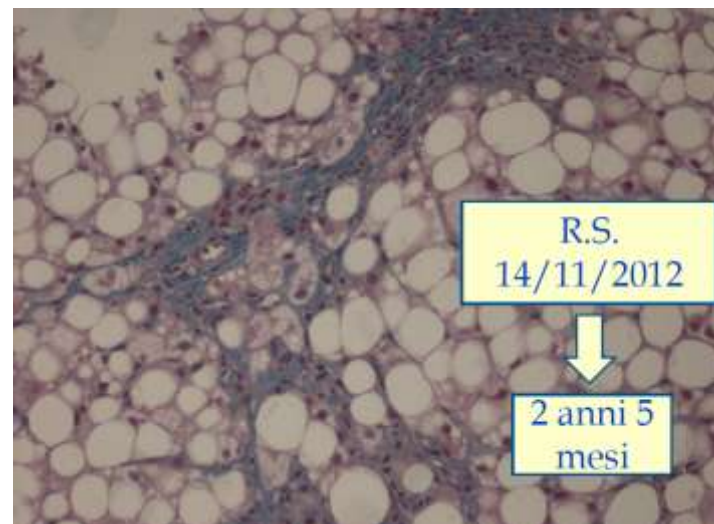
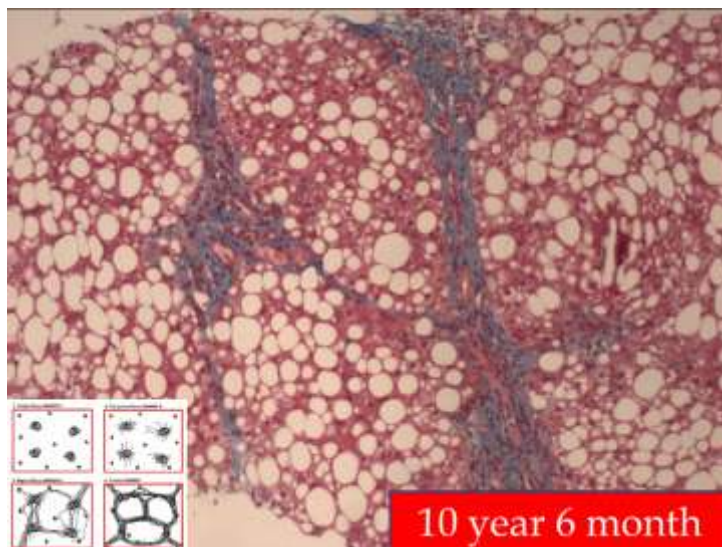
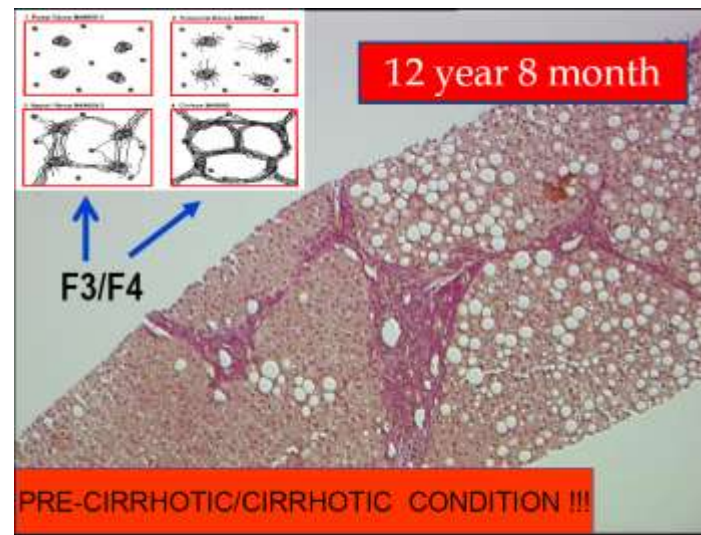
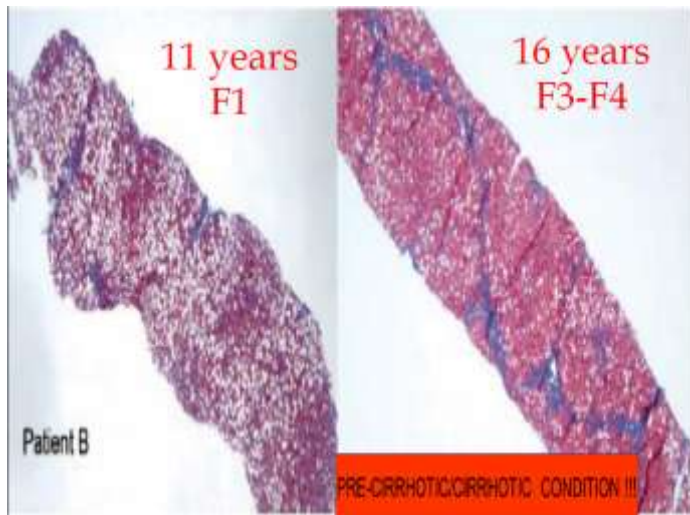
Steatosi Grado 2



Steatosi Grado 3



Thanks to Dr. Valerio Nobili

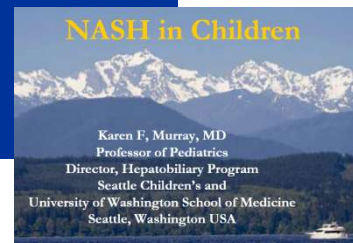


Thanks to Dr. Valerio Nobili

Pediatric NASH Epidemiology

- Obesity (90%), Acanthosis nigricans, hepatomegaly
- Boys 40% > Girls
- Ages 2-17 years (avg 12 years)
- 25-30% abdominal pain
- Autopsy data:
 - Fatty liver in 9.6% of 742 pediatric autopsies
 - Fatty liver: Hispanic 12%, Asian 10.2%, White 8.6%, African-American 1.5%
 - Fatty liver in 38% of obese children
 - NASH in 3% (23% of the subjects with fatty liver)

Patton et al, JPGN 2006;43:413; Schwimmer et al, Pediatrics 2006;118(4):1388.



In sintesi la letteratura esaminata afferma che:

Su 100 bambini obesi

- 38 hanno il fegato “grasso”
- 8,7 hanno la NASH
- 3,9 evolvono in fibrosi /cirrosi

Pediatric NASH Epidemiology

- Obesity (90%), Acanthosis nigricans, hepatomegaly
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- Ages 2-17 years (avg 12 years)
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Patton et al, JPGN 2006;43:413; Schwimmer et al, Pediatrics 2006;118(4):1388.

NASH in Children



Se l'obesità ha prevalenza del 10%, un PLS massimalista segue circa 80 bambini obesi quindi dovrebbe trovarsi nella seguente condizione:

Su 80 bambini obesi

- 30 hanno il fegato “grasso”
- 7 hanno la NASH
- 3 evolveranno in fibrosi /cirrosi

Pediatric NASH Epidemiology

- Obesity (90%), Acanthosis nigricans, hepatomegaly
- Boys 40% > Girls
- Ages 2-17 years (avg 12 years)
- 25-30% abdominal pain
- Autopsy data:
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Patton et al, JPGN 2006;43:413; Schwimmer et al, Pediatrics 2006;118(4):1388.

NASH in Children



Pausa di riflessione.....

Quanto abbiamo valutato i nostri pazienti sovrappeso / obesi?

Abbiamo elementi a sostegno o a confutazione di quanto affermato in letteratura?

Pensiamo sia utile soffermarci sul problema?



Obstructive Sleep Apnoea Syndrome

Legata all'aumento ponderale

Causa ipossia cronica -> danni cardiaci e cerebrali

L'aumento di 1 kg/mq di BMI oltre la media prevista comporta un aumento del 12% del rischio di OSAS

Risk Factors for Sleep-disordered Breathing in Children

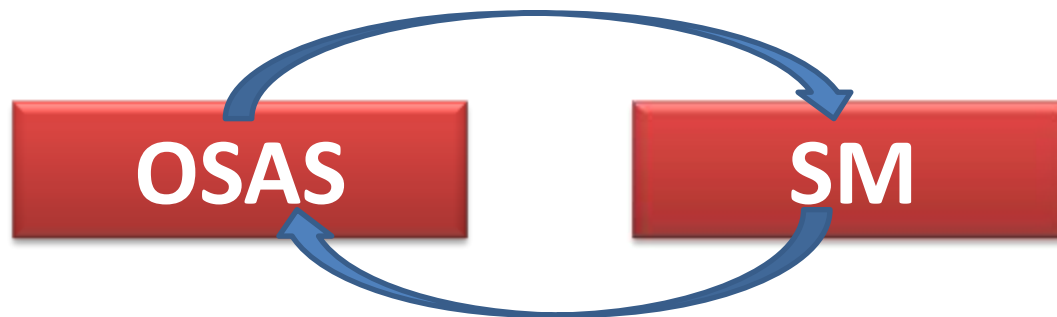
Associations with Obesity, Race, and Respiratory Problems

SUSAN REDLINE, PETER V. TISHLER, MARK SCHLUCHTER, JOAN AYLOR, KATHRYN CLARK,
and GREGORY GRAHAM

AM J RESPIR CRIT CARE MED 1999;159:1527-1532.

Obstructive Sleep Apnoea Syndrome

Features of the metabolic syndrome are more prevalent in patients with OSA, independent of obesity and a correlation has been suggested between the presence of the metabolic syndrome and increased OSA severity [25,43]. Conversely, subjects with the metabolic syndrome have also been shown to have an increased risk of having OSA (OR = 2.62 (1.37–4.50)) [44].



Sleep-disordered breathing and type 2 diabetes
A report from the International Diabetes Federation
Taskforce on Epidemiology and Prevention

Jonathan E. Shaw ^{a,c}, Naresh M. Punjabi ^b, John P. Wilding ^c,
K. George M.M. Alberti ^d, Paul Z. Zimmerman ^d

Obstructive Sleep Apnoea Syndrome

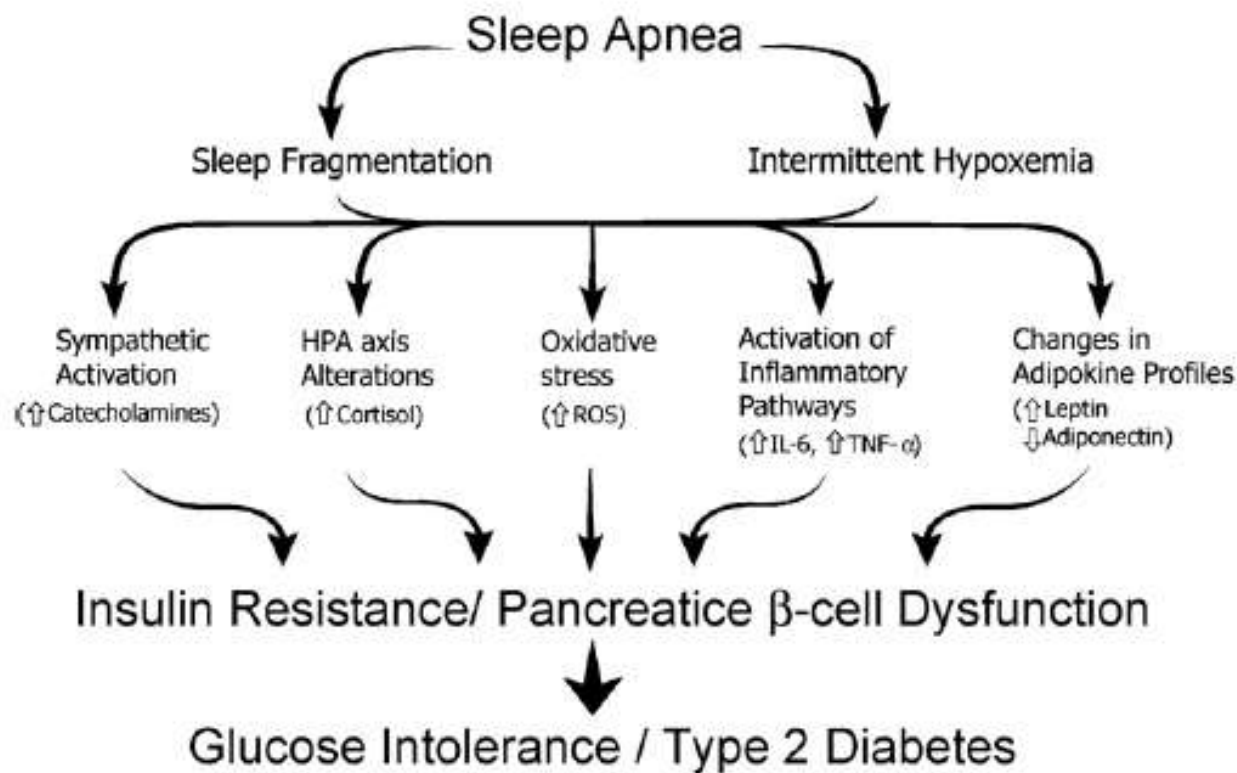


Fig. 1 – Potential mechanisms linking sleep apnoea to glucose intolerance.

Sleep-disordered breathing and type 2 diabetes
A report from the International Diabetes Federation
Taskforce on Epidemiology and Prevention

Jonathan E. Shaw^{a,c}, Naresh M. Punjabi^b, John P. Wilding^d,
 K. George M.M. Alberti^e, Paul Z. Zimmet^e

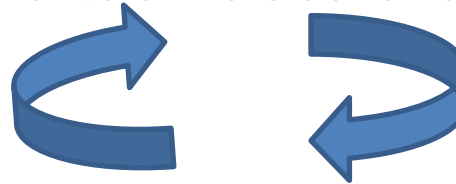
Obstructive Sleep Apnoea Syndrome

Surgical treatment for OSA in children has been shown to be at least partially effective at normalizing endothelial function, reducing levels of inflammatory markers, and improving lipid profile, the apnea-hypopnea index and sleep fragmentation.

Gozal D. Sleep, sleep disorders and inflammation in children. Sleep Med 2009;10 Suppl 1:S12–S16.

Iperuricemia

Iperinsulinismo riduce assorbimento di Na e ac. Urico dal tubulo renale



Iperuricemia limita biodisponibilità di NO essenziale per azione dell'insulina



Contributo all'insulino - resistenza

Iperuricemia nel bambino

Prevalenza del 53% in bambini con eccesso ponderale

*I pazienti con iperuricemia hanno maggiore **BMI**, maggiore **circonferenza addominale**, maggiore **insulino-resistenza**, più elevati **valori pressori** ...*

Hyperuricemia and metabolic syndrome in children with overweight and obesity

Soralla Civantos Modino^{a,*}, M. Guadalupe Guijarro de Armas^a,
Susana Monereo Mejias^a, July M. Montaña Martínez^a, Paloma Iglesias Bolaños^a,
María Merino Viveros^a, Jose Maria Ladero Quesada^b

Endocrinol Nutr. 2012;59(9):533–538

Iperuricemia nel bambino

Valutato IMT in bambini obesi e controlli sani:

*Rilevata **associazione positiva fra iperuricemia e ateroscleosi carotidea** per aumento dello stress ossidativo, della disfunzione dell'endotelio e della flogosi legati all'ac. Urico.*

CLINICAL STUDY

Serum uric acid and its association with metabolic syndrome and carotid atherosclerosis in obese children

Lucia Pacifico¹, Vito Cantelmi², Caterina Anania¹, Elisabetta Bonaiuto¹, Francesco Martino¹, Roberto Pascone¹ and Claudio Chiesa^{1,3}

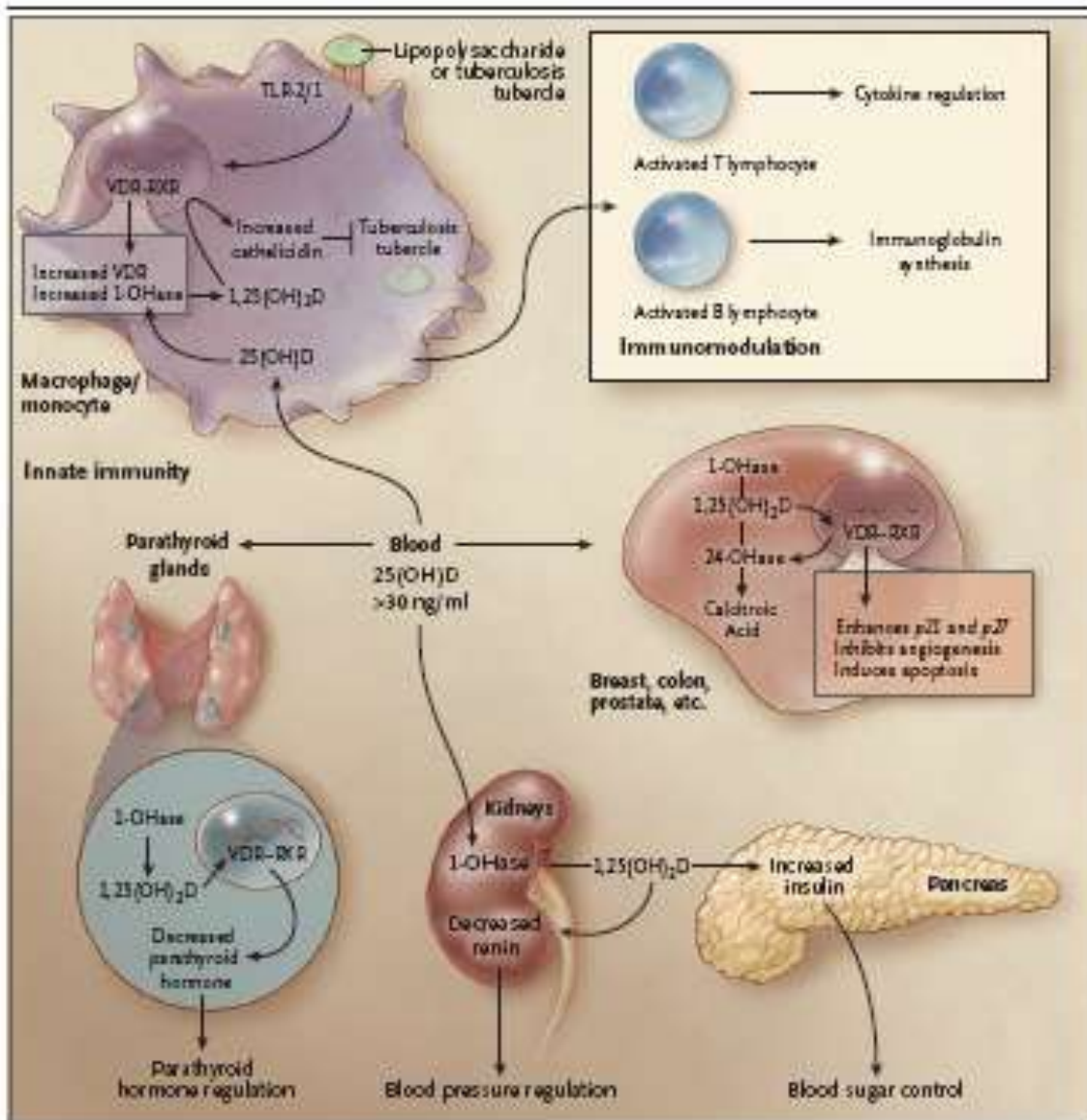
Ipovitaminosi D

Numerose le evidenze di correlazione fra bassi livelli di Vit D e malattie cardiovascolari.

Relazione inversa fra livelli di Vit D ed accumulo di adipe

- Sequestro di Vit D negli adipociti

- influenza negativa delle adipocitochine (leptina) sulla sintesi di Vit D



Vitamin D Deficiency

Michael F. Holick, M.D., Ph.D.

N Engl J Med 2007;357:266-81.

Copyright © 2007 Massachusetts Medical Society.

Ipovitaminosi D e NAFLD

Effetti Vit D3

- Modulazione dell'infiammazione
- Soppressione della proliferazione dei fibroblasti e produzione di collagene

E se la correggiamo?

.....After the trial, in the vitamin D group, serum TG concentration decreased significantly.....

.....A significant decrease was observed in serum insulin levels....

J Pediatr (Rio J). 2014;90(1):28-34



Jornal de
Pediatria

www.jpmed.com.br



ORIGINAL ARTICLE

Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial[☆]

Roya Kelishadi^{a,*}, Shadi Salek^a, Mehdi Salek^a,
Mahin Hashemipour^a, Mahsa Movahedian^b

Conclusion

Vitamin D supplementation was inversely associated with insulin resistance and some cardiometabolic risk factors. Vitamin D supplementation may have beneficial effects on controlling some complications of childhood obesity.

J Pediatr (Rio J). 2014;90(1):28-34



Jornal de
Pediatria

www.jpmed.com.br



ORIGINAL ARTICLE

Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial[☆]

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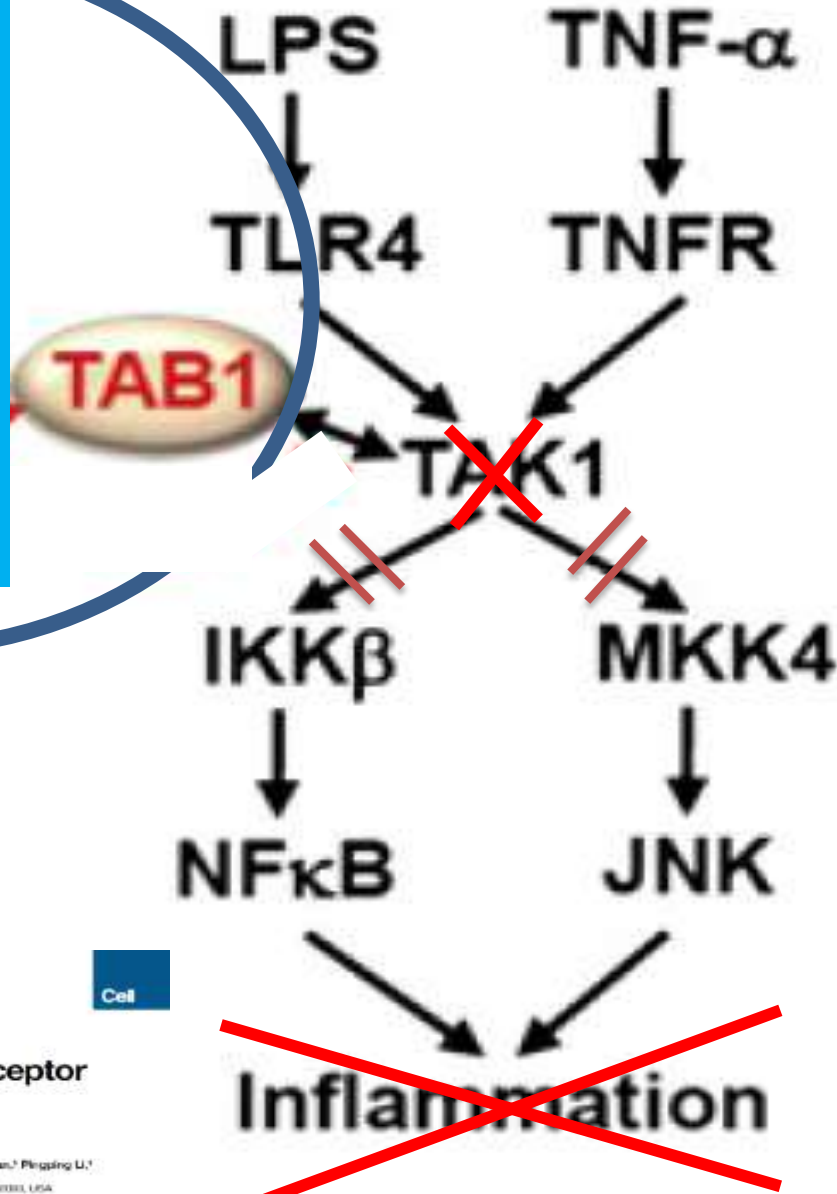
Role of Docosahexaenoic Acid Treatment in Improving Liver Histology in Pediatric Nonalcoholic Fatty Liver Disease

Valerio Nobili^{1*}, Guido Carpino^{2*}, Anna Alisi¹, Rita De Vito³, Antonio Franchitto^{4,5}, Gianfranco Alpini⁶, Paolo Onori⁴, Eugenio Gaudio^{4*}

1 Unit of Liver Research, Bambino Gesù Children's Hospital, Rome, Italy, **2** Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome, Italy, **3** Unit of Pathology, Bambino Gesù Children's Hospital, Rome, Italy, **4** Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Rome, Italy, **5** Eleonora Lonillard Spencer-Cenci Foundation, Rome, Italy, **6** Department of Medicine, Scott & White and Texas A&M Health Science Center College of Medicine, Temple, Texas, United States of America

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Conclusions: DHA could modulate hepatic progenitor cell activation, hepatocyte survival and macrophage polarization through the interaction with GPR120 and NF- κ B repression. In this scenario, the modulation of GPR120 exploits a novel crucial role in the regulation of the cell-to-cell cross-talk that drives inflammatory response, hepatic progenitor cell activation and hepatocyte survival.

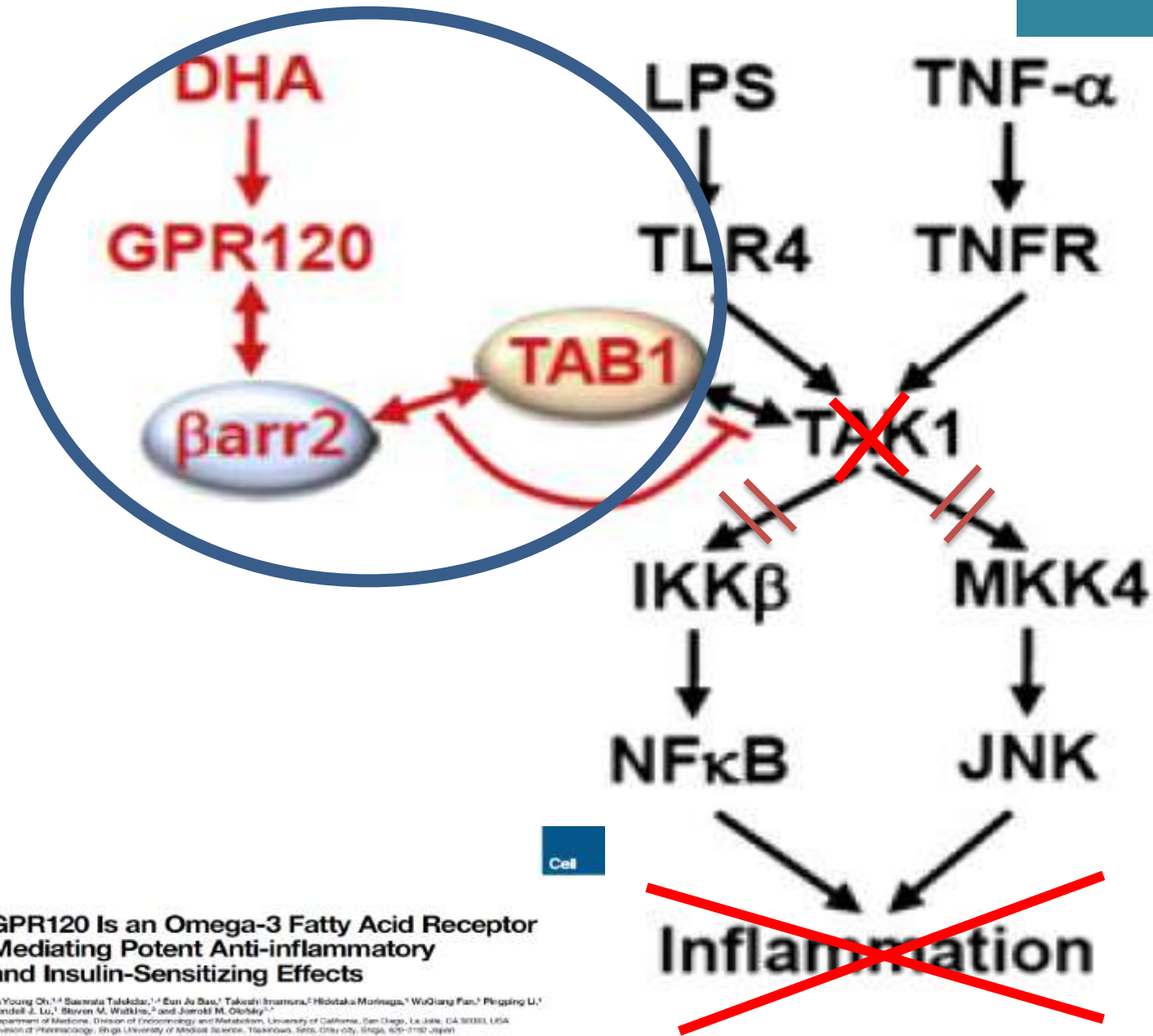


Cell

GPR120 Is an Omega-3 Fatty Acid Receptor Mediating Potent Anti-inflammatory and Insulin-Sensitizing Effects

Da Young Oh,^{1,4} Saewon Takahara,^{1,4} Eun Ju Bae,¹ Takashi Inamura,² Hirotaka Morinaga,¹ WuQiang Fan,³ Pingping Li,¹ Wendell J. Li,¹ Steven M. Watkins,² and Jerome M. Olefsky^{1,4}

¹Department of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, La Jolla, CA 92038, USA
²Division of Pharmacology, Shiga University of Medical Science, Tokinaka 3, Seta, Otsu City, Shiga, 520-7192, Japan
³Farnam Biociences, 3490 Industrial Boulevard, Suite 100, West Sacramento, CA 95691, USA
⁴These authors contributed equally to this work
 *Correspondence: olefsj@ucsd.edu
 DOI: 10.1016/j.cel.2013.07.041

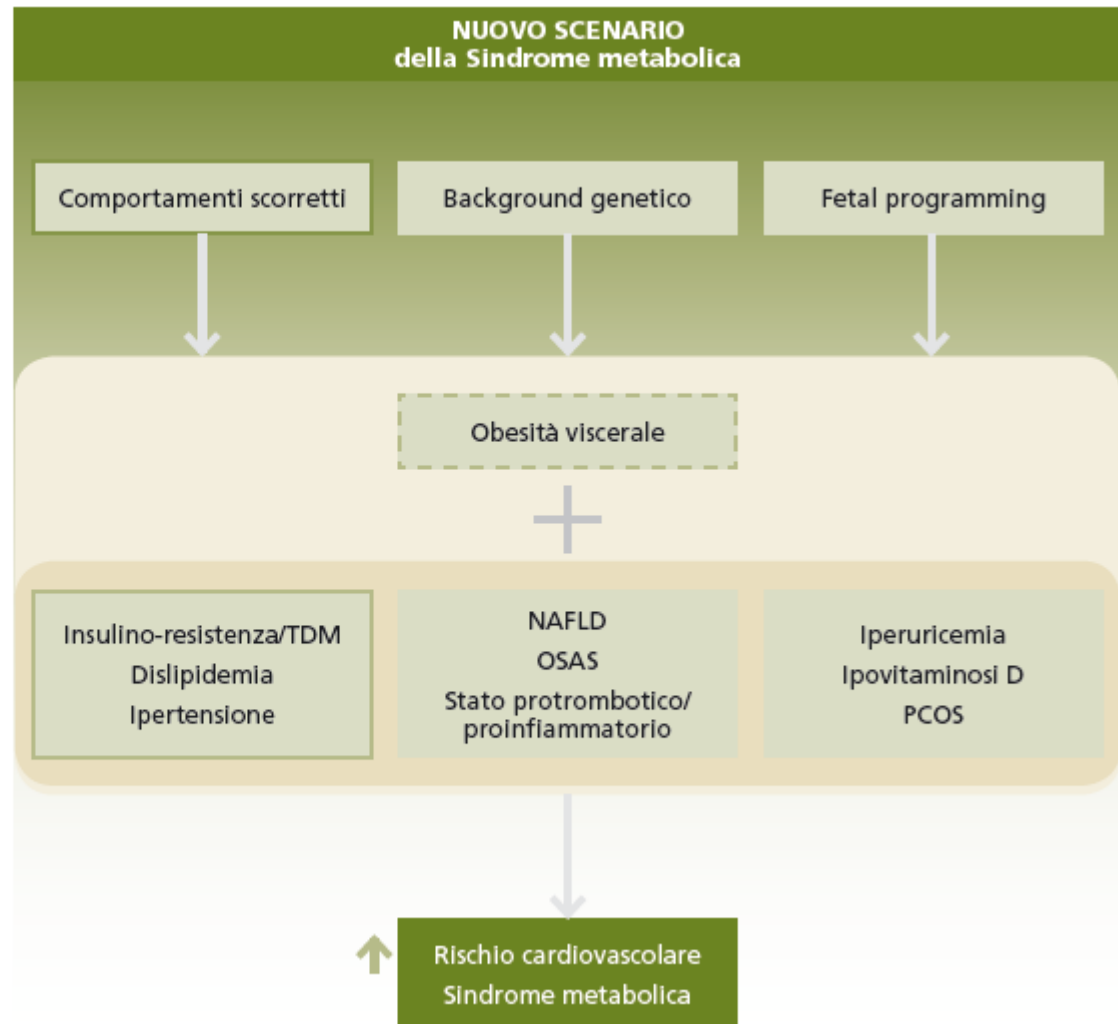
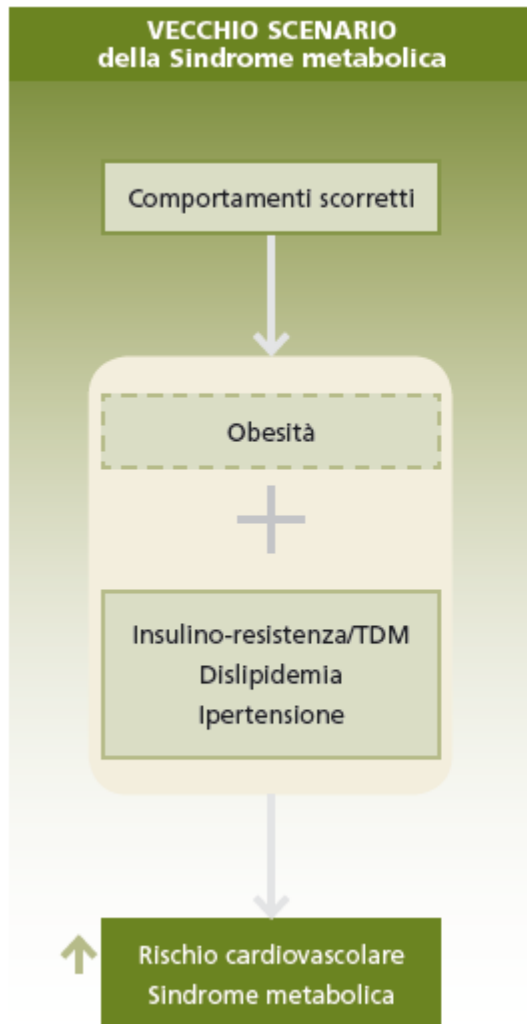


GPR120 Is an Omega-3 Fatty Acid Receptor Mediating Potent Anti-inflammatory and Insulin-Sensitizing Effects

Da Young Oh,^{1,4} Saesara Talekar,^{1,4} Eun Ju Bae,¹ Takashi Inamura,² Hirotaka Morinaga,¹ WuQiang Fan,³ Pingping Li,¹ Wendell J. Li,¹ Barry M. Wudlinski,² and Jerome M. Olefsky^{1,4}
¹Department of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego, La Jolla, CA 92038, USA
²Division of Pharmacology, Shiga University of Medical Science, Tokushima, Seta, Okay City, Shiga, 520-8501 Japan
³Farnam Biosciences, 3490 Industrial Boulevard, Suite 100, West Sacramento, CA 95691, USA
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*Correspondence: olefsky@ucsd.edu
DOI: 10.1016/j.cell.2013.07.041



Conclusioni



La sindrome metabolica in età pediatrica:
è tempo di ripensare i criteri diagnostici?



- ✓ Rilevare stati di sovrappeso/obesità
- ✓ Sospettare la Sindrome Metabolica
- ✓ Indagare il paziente
- ✓ Trattare



- ✓ Rilevare stati di sovrappeso/obesità
- ✓ Sospettare la Sindrome Metabolica
- ✓ Indagare il paziente
- ✓ Trattare

Tabella 1. Criteri per la diagnosi di sindrome metabolica in età pediatrica

<i>Parametri</i>	<i>Criteri diagnostici per SM</i>			
	<i>International Diabetes Foundation (IDF)*</i>	<i>Spesso precoce</i>	<i>National Cholesterol Education Program/Adult Trial Panel III^o</i>	<i>American Heart Association (AHA)[^]</i>
Età	10 – 16 anni	> 16 anni	12–19 anni	12–19 anni
Circonferenza addominale	≥ 90° percentile	Nei caucasici ≥ 90 cm	≥ 90° percentile per età e sesso	≥ 90° percentile per età, sesso ed etnia
Trigliceridi	≥ 150 mg/dl (≥ 1,7 mmol/l)	≥ 150 mg/dL (1.7 mmol/L) o terapia con farmaci ipolipemizzanti	> 110 mg/dl (1.24 mmol/L)	≥ 110 mg/dl (1.24 mmol/L)
HDL-colesterolo	< 40 mg/dl (≤1,3 mmol/l)	< 40 mg/dL (1.03 mmol/L) nei maschi < 50 mg/dL (1.29 mmol/L) nelle femmine o terapia con farmaci ipolipemizzanti	< 40 mg/dL (1.03 mmol/L)	≤ 10° percentile per sesso ed etnia
Glicemia a digiuno	> 100 mg/dl (5.6 mmol/L)	> 100 mg/dl (5.6 mmol/L) o DM2	> 110 mg/dl (6.1 mmol/L)	≥ 100 mg/dl (5.6 mmol/L)
Pressione arteriosa (PA)	PA sistolica ≥ 130 mmHg PA diastolica ≥ 85 mmHg	PA sistolica ≥ 130 or PA diastolica ≥ 85 mm Hg o trattamento per una ipertensione precedentemente diagnosticata	PA sistolica o diastolica > 90° percentile (specifico per età, sesso ed altezza)	≥ 90 percentile per età, sesso ed altezza

Note:
HDL – lipoproteine ad alta densità
DM2 – diabete mellito tipo 2

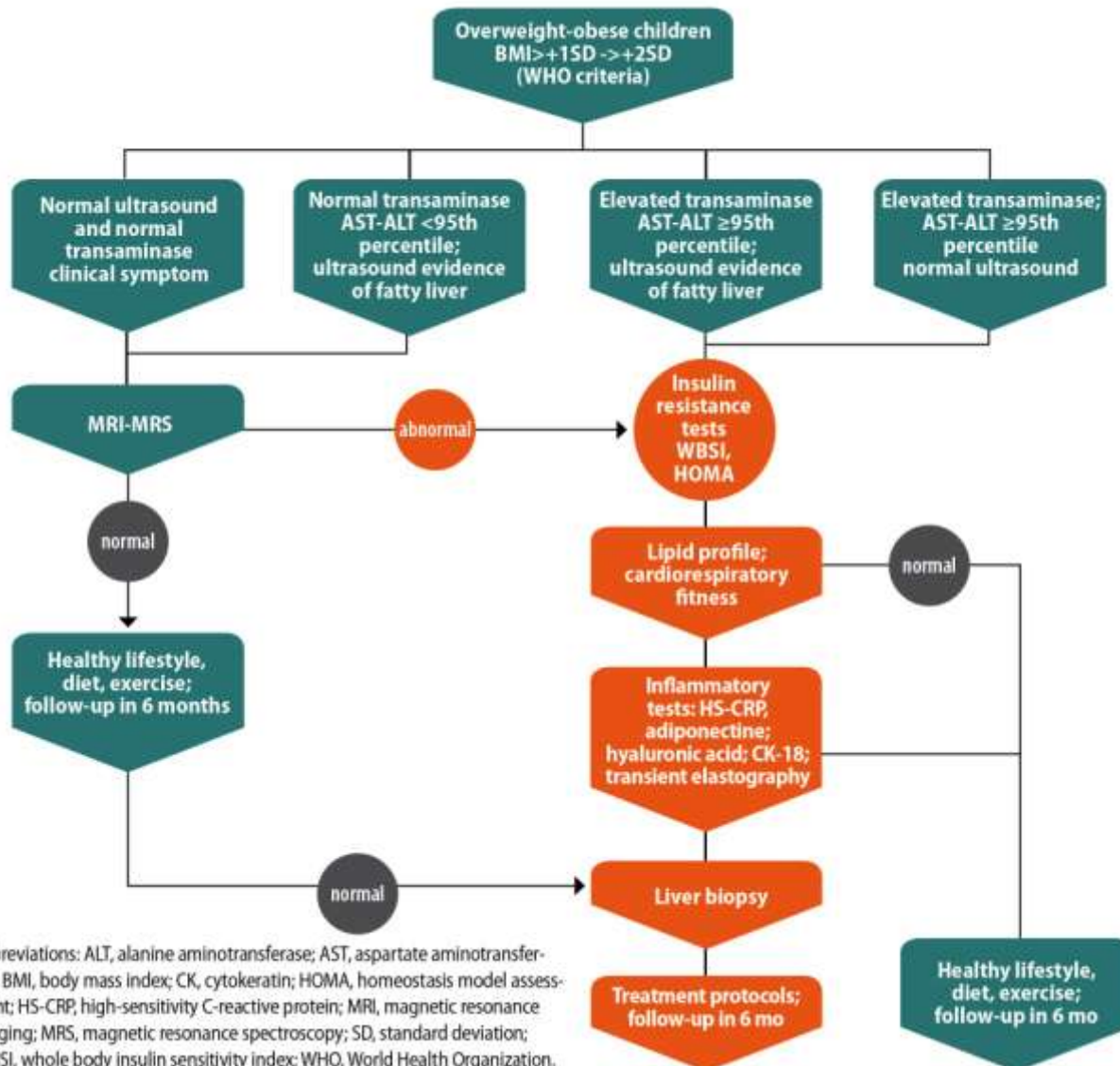
* Per la diagnosi di SM, 3 dei 5 criteri devono essere presenti
[^] Per la diagnosi di SM, devono essere presenti l'obesità viscerale e 2 dei 4 criteri
^o Per la diagnosi di SM devono essere presenti almeno 3 criteri.

La sindrome metabolica in età pediatrica: è tempo di ripensare i criteri diagnostici?

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 Ospedale Pediatrico
 "Bambino Gesù", Roma

FIGURE Algorithm for diagnosis of nonalcoholic fatty liver disease



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK, cytochrome; HOMA, homeostasis model assessment; HS-CRP, high-sensitivity C-reactive protein; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; SD, standard deviation; WBSI, whole body insulin sensitivity index; WHO, World Health Organization. Adapted from Widhalm K, et al.¹

[Contemporary Pediatrics/PediatricsDiagnosticsLog.in](http://ContemporaryPediatricsPediatricsDiagnosticsLog.in) is to save to my locker

Pediatric nonalcoholic fatty liver disease

The growing obesity epidemic is believed to be a main driver of the rising prevalence of nonalcoholic fatty liver disease (NAFLD) in children and adolescents. This review article provides an overview of pediatric NAFLD's unique pathophysiology and tools for diagnosis and treatment.

September 01, 2013
By Mary Beth Narangatten, MD

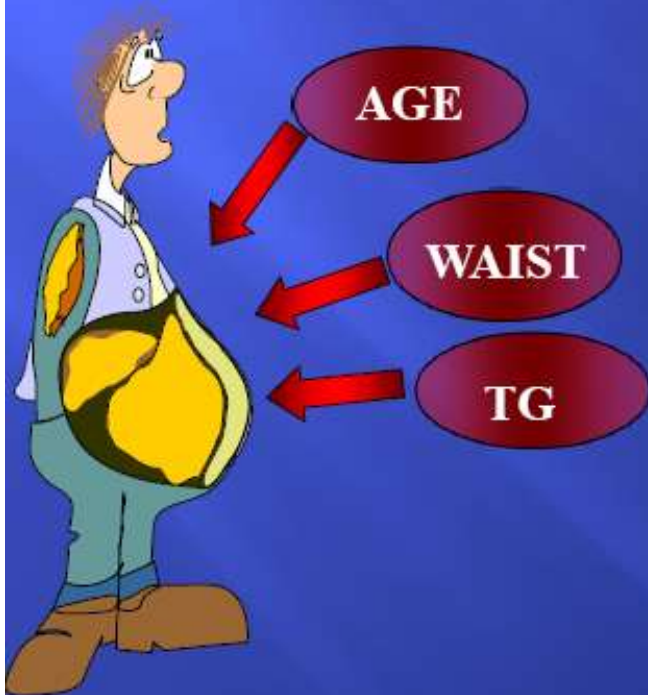
Table 1 Laboratory work up in suspected pediatric NAFLD

Laboratory workup	What to rule out
Basic profile: Full blood count, Liver function tests, fasting glucose and insulin, urea and electrolytes, coagulation, INR, iron, ferritin, uric acid	
Lipid profile	Dyslipidemia/Familial hypercholesterolemia/ Cholesterol ester storage disease
Lipoproteins	Abetalipoproteinemia
Glucose tolerance test (OGTT), glycosylated hemoglobin	Insulin resistance/Type 2 Diabetes Mellitus (DM2)
Thyroid function tests	Hypothyroidism
Ceruloplasmin level	Wilson Disease
Viral hepatitis panel	Viral - hepatitis (HBV, HCV)
C-Reactive-Protein + consider EBV, CMV immune state profile	Acute systemic disease
Sweat test	Cystic Fibrosis
Anti-Transglutaminase IgA and total IgA	Coeliac disease
CPK	Muscular Dystrophy
Alpha-1-antitrypsin serum level	Alpha-1-antitrypsin deficiency
Serum lactate +/- amino and organic acids +/- plasma-free fatty acids +/- acyl carnitine profile	Metabolic diseases (Galactosaemia -in infants-, hereditary fructose intolerance, glycogen storage disease (Type VI and IX), others
Serum Immunoglobulin, Liver autoantibodies	Autoimmune hepatitis
Specific tests as suggested by history, consider:	Drug toxicity, Parenteral Nutrition, Protein malnutrition, others

Laboratory tests in suspected pediatric NAFLD, and correspondent ruled out diseases of other etiology.

Pediatric NAFLD Fibrosis Index

• The index uses an algorithm based on **age, waist circumference, and triglycerides** with an accuracy of 0.84 (95%CI 0.81–0.87) in detecting fibrosis into the liver.



Nobili et al, BMC Medicine, 2009

Thanks to Dr. Valerio Nobili

The best
Is yet
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