Società Medico Chirurgica di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

Gestione clinica delle epatiti croniche virali

Sabato 2 marzo 2013
Nuovo Ospedale di Cona
Aula Magna
Azienda Ospedaliero Universitaria di Ferrara

Il Segretario
Dott. V.Giancarlo Matarese

Il Presidente
Dott. Sergio Gullini

E' stata inoltrata richiesta di crediti formativi ECM per Medici, Biologi, Farmacisti e Infermieri

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Gestione multidisciplinare del paziente

Endocrinologo

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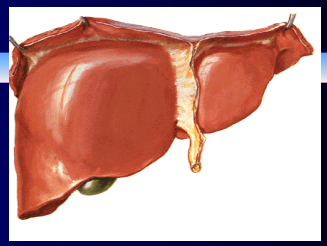


VIRUS EPATOTROPI

Maggiori	Altri Virus	Minori
HBV (1965 Blumberg)	HGV	CMV
HAV (1973 Feinstone)	TTV	EBV
HDV (1977 Rizzetto)	SEN-V	Coxackiae
HCV (1989 Hugtone)		Herpes
HEV (1990 Reyes)		Parotite Rosolia

Gestione clinica delle epatiti croniche virali

Hepatitis C Virus Infection

Antiviral Therapy

Extrahepatic Manifestations

including

- Hematologic diseases such as cryoglobulinemia and lymphoma
- Autoimmune disorders such as thyroiditis
- Renal disease
- Dermatologic conditions such as lichen planus and porphyria cutanea tarda

Gestione clinica delle epatiti croniche virali

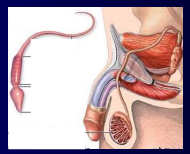
Epatite virale C

Manifestationi extraepatiche

TIREOPATIA AUTOIMMUNE

INSULINO RESISTENZA / DIABETE MELLITO

ALTERAZIONE FUNZIONE IPOFISARIA / IPOFISITE



ALTERAZIONI DEL SISTEMA RIPRODUTIVO

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Gestione clinica delle epatiti croniche virali

Extrahepatic manifestations of hepatitis C virus infection

Thyroid disease

- Thyroid disorders are common in patients with chronic hepatitis C virus (HCV) infection, particularly women
- Antithyroid antibodies ➔ 5 - 17 % of patients infected with HCV
- Thyroid disease (primarily hypothyroidism) ➔ 2 - 13 %
- The highest prevalence of both thyroid antibodies and thyroid disease is found in older women

Tran A et al. Hepatolgy.1993;18:253 Antonelli A et al. Am J Med. 2004;117:10
Roti E et al. Am J Med. 1996;101:482 Marazuela M et al. Clin Endocrinol.1996;44:635

Gestione clinica delle epatiti croniche virali

Thyroid Disorders in Chronic Hepatitis C

Thyroid Status in Hepatitis C Virus- and Hepatitis B Virus-Infected Patients, and Control Subjects from Iodine-Deficient and Iodine-Sufficient Areas

Characteristic	Control Subjects from an Iodine-Deficient Area (n = 389)	Control Subjects from an Iodine-Sufficient Area (n = 268)	Hepatitis B Virus–Infected Patients (n = 86)	Hepatitis C Virus–Infected Patients (n = 630)	*P* Value
	Number (%) or Mean ± SD				
TSH (μIU/mL)	1.5 ± 3.1	1.3 ± 1.1	1.7 ± 1.3	3.2 ± 9.8*	0.001
Free thyroxine (ng/L)	9.6 ± 2.9	9.3 ± 2.1	9.1 ± 2.9	8.0 ± 5.2*	0.001
Free triiodothyronine (ng/L)	3.7 ± 0.9	3.7 ± 0.6	3.8 ± 0.9	3.1 ± 1.3*	0.0001
Anti-thyroid peroxidase antibody (U/mL)	42 ± 127	47 ± 144	51 ± 114	127 ± 467*	0.0007
Antithyroglobulin antibody (U/mL)	38 ± 187	41 ± 186	37 ± 85	124 ± 560*	0.01
Anti-thyroid peroxidase antibody positive	47 (12)	27 (10)	11 (13)	132 (21)*	0.0001
Anti-thyroglobulin antibody positive	39 (10)	24 (9)	9 (10)	108 (17)*	0.01
Either antibody positive	66 (17)	40 (15)	14 (16)	158 (25)*	0.0002
Both antibody positive	16 (4)	11 (4)	5 (6)	57 (9)*	0.006
Hypothyroidism (TSH >4 μIU/mL)	12 (3)	13 (5)	3 (4)	82 (13)*	0.0001
Hyperthyroidism (TSH <0.3 μIU/mL)	39 (10)	19 (7)	3 (4)	63 (10)	0.1

* $P \leq 0.05$ vs. all other groups.
TSH = thyroid-stimulating hormone.

Antonelli A et al. Am J Med. 2004;117:10

Gestione clinica delle epatiti croniche virali

Extrahepatic manifestations of hepatitis C virus infection

Thyroid disease

TAKE HOME MESSAGE

Thyroid function tests should be checked when a patient is first diagnosed with HCV

Patients found to be hypothyroid should receive thyroid hormone replacement

Tran A et al. Hepatolgy.1993;18:253 Antonelli A et al. Am J Med. 2004;117:10
Roti E et al. Am J Med. 1996;101:482 Marazuela M et al. Clin Endocrinol.1996;44:635

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Interferon therapy in liver disease and thyroid disease

Interferon-alfa

development of antithyroid antibodies without clinical disease 5-40 %

~ 5 to 10 % of patients develop clinical thyroid disease, including

- Painless thyroiditis
- Hashimoto's thyroiditis
- Graves' disease
- Graves' ophthalmopathy

Tong MJ et al Hepatology. 1997;26:747
Deutsch M et al. Hepatology 1997;26:206
Mandac JC et al Hepatology 2006;43:661
Bini EJ et al Arch Intern Med 2004;164:2371

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Development of clinical thyroid disease during interferon therapy

Risk factors

- antithyroid peroxidase antibodies before treatment
- female gender
- older age
- presence of other autoantibodies (ANA, anti-DNA ...)
  liver-kidney microsomal antibodies in one report

TAKE HOME MESSAGE

Women with chronic hepatitis C and high antithyroid peroxidase antibody titers are at particular risk

Marazuela M et al. Clin Endocrinol.1996;44:635
Muratori L et al. Clin Gastroenterol Hepatol 2005;3:595

Gestione clinica delle epatiti croniche virali

Extrahepatic manifestations of hepatitis C virus infection

The development of thyroid disorders during interferon treatment of chronic hepatitis C is associated with an increased likelihood of a sustained virological response

Tran H A et al. BMC Endocr Disord.2011;11:10

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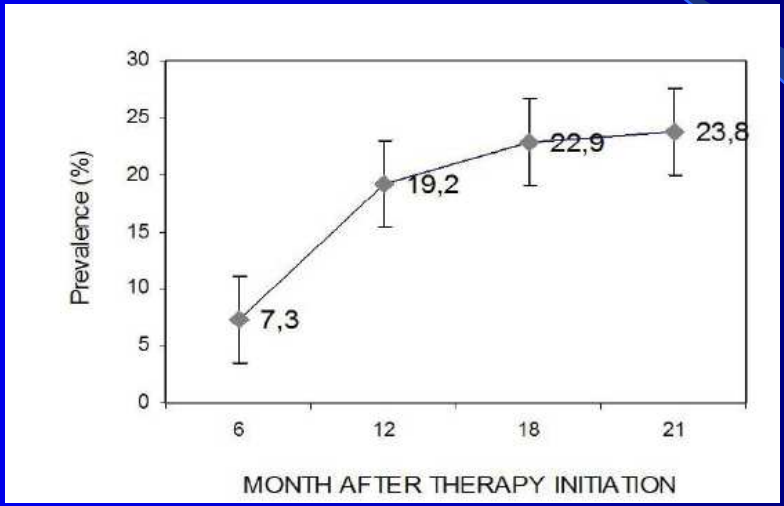
Development of clinical thyroid disease during interferon therapy

Prevalence (%) of thyroid disorders
after therapy initiation



Themistoklis V et al. Ann Acad Med Singapore 2011;40:394-400

The changes in thyroid function usually appear after three months of therapy, but can occur as long as IFN-alfa is given

Rare patients develop thyroid autoantibodies after interferon-alfa treatment has been completed

Carella C et al.Horm Res.1995;44:110

Gestione clinica delle epatiti croniche virali

Development of clinical thyroid disease during interferon therapy

Monitoring of thyroid disease

WHO? WHEN? HOW?

All patients receiving IFN alfa should be monitored for thyroid disease, particularly women and patients with preexisting antithyroid antibodies

It's suggested measuring TSH and antithyroid antibodies

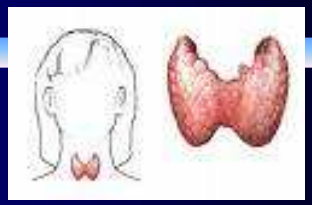
before treatment and every 12 weeks during treatment

Gestione clinica delle epatiti croniche virali

Development of clinical thyroid disease during interferon therapy

The addition of ribaverin to interferon therapy does not alter the thyroid autoantibody pattern but increases the risk of developing hypothyroidism

Gestione clinica delle epatiti croniche virali



Management of the side effects of peginterferon and ribavirin being used for treatment of chronic hepatitis C virus infection

Thyroid dysfunction

TAKE HOME MESSAGE

IFN therapy can usually be continued while hypothyroidism is being treated

Asymptomatic biochemical hyperthyroidism due to Graves' disease or painless thyroiditis can be observed closely and, if symptoms are minimal, low dose Propranolol can be instituted

Clinically apparent hyperthyroidism requires to stop stop PEG-IFN/RBV and endocrinologist management

Before a new round of therapy with IFN +RBV is necessary to definitively cure the hyperthyroidism to avoid the risk of recurrence

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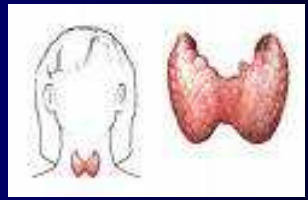
Gestione clinica delle epatiti croniche virali

Thyroid Disorders in Chronic Hepatitis C



Thyroid cancer

An increased prevalence (2.2%) of papillary thyroid cancer has been reported in HCV-positive patients with thyroid autoimmunity

AITD might represent a predisposing condition for papillary thyroid cancer in HCV-positive individuals

Antonelli A et al.Nat Clin Prac Endocrinol Endocrinol & Metabol. 2009; 5:26

HCV infection and Insulin Resistance

HCV infection is associated with the development of IR and T2DM

HCV can be considered a metabolic disease

T2DM may be an extrahepatic manifestation of HCV infection

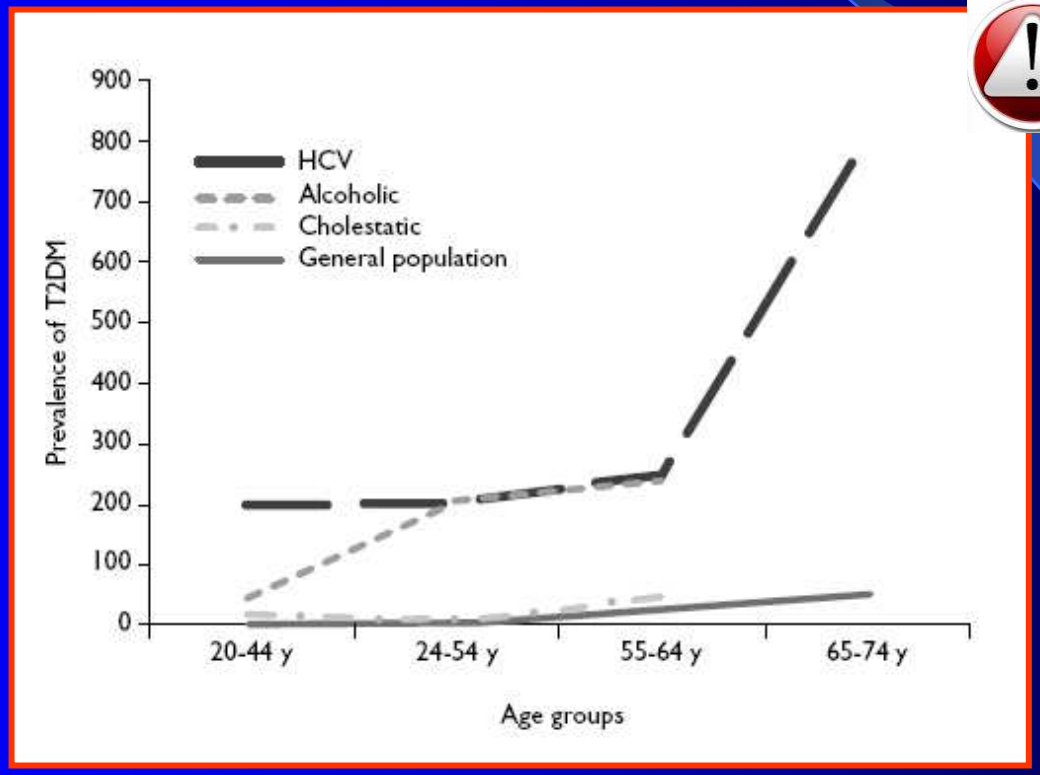
A meta-analysis of 34 studies estimated that the risk of T2DM was increased by almost 70 % in HCV-infected patients compared with non-infected controls (OR 1.7)

The risk was also increased compared with patients who had chronic HBV infection

Machado MV et al. Ann Hepatol 2009;8:S67
Chen HF et al J Chin Med Assoc 2006;69:146
Gutiérrez-Grobe Y et al Salud Publica Mex 2011;53 supl 1:S46

Gestione clinica delle epatiti croniche virali

Prevalence of T2DM in patients with liver cirrhosis caused by diverse etiologies. Notice the higher prevalence among HCV-infected patients



HCV: hepatitis C virus

Gutiérrez-Grobe Y et al Salud Publica Mex 2011;53 supl 1:S46

Chronic Hepatitis and Insulin Resistance

Prevalence rates of T2DM

in HCV infection is 22-33%

in HBV infection is of 12-17 %

Risk factors for DM in HCV infected patients

- Older age
- Obesity
- Severe liver fibrosis
- A family history of diabetes mellitus

Gutiérrez-Grobe Y et al Salud Publica Mex 2011;53 supl 1:S46

Chronic Hepatitis and Insulin Resistance

The presence of IR itself predicts

a faster progression to fibrosis

particularly with HCV genotypes 1 and 4 and with high serum RNA levels

cirrhosis

liver failure

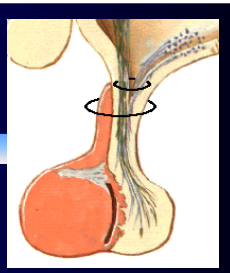
hepatocellular carcinoma

a poor response to antiviral therapy against HCV

Successful HCV treatment may decrease the risk of diabetes mellitus

Gutiérrez-Grobe Y et al Salud Publica Mex 2011;53 supl 1:S46

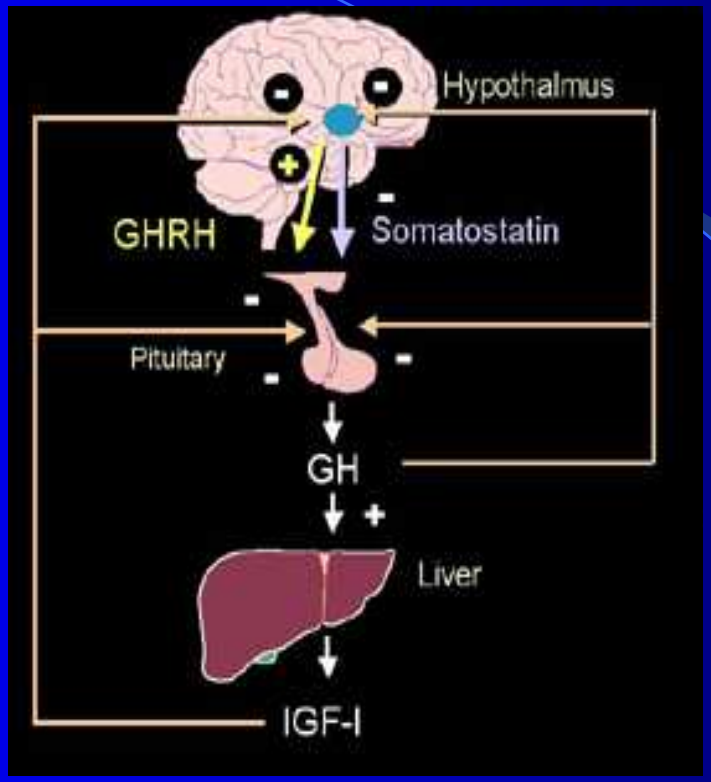
Gestione clinica delle epatiti croniche virali



Stress, inflammation, or infection
induce
integrated bidirectional neuroendocrine
immune responses

Cytokine-mediated modulation of the
ACTH/cortisol or GH/IGF-1 system occurs
during inflammation and chronic illness

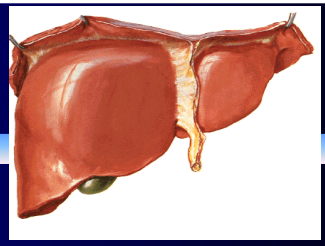
Gestione clinica delle epatiti croniche virali



Liver is the central organ of GH/IGF-1 axis

IGF-1 might be considered an early marker
of functional reserve or hepatocellular functional capacity

Gestione clinica delle epatiti croniche virali



Chronic Hepatitis and Insulin Like Growth Factor 1

Child-Pugh staging with IGF-1 measurement could predict disease severity more accurately than Child-Pugh staging alone

CHILD-PUGH CLASSIFICATION OF CIRRHOSIS

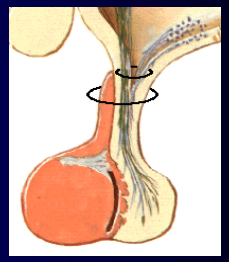
Factor	Units	1	2	3
Serum bilirubin	µmol/L mg/dL	<34 <2.0	34–51 2.0–3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30–35 3.0–3.5	<30 <3.0
Prothrombin time	Seconds prolonged INR	0–4 <1.7	4–6 1.7–2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

Note: The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5–15. Child-Pugh class is either A (a score of 5–6), B (7–9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (class B). This level has been the accepted criterion for listing for liver transplantation.

Ghada F. Helaly et al Transl Res 2011; 158:155

Gestione clinica delle epatiti croniche virali

Hepatitis-C Patients Have Reduced Growth Hormone (GH) Secretion Which Improves During Long-Term Therapy With Pegylated Interferon-*a*



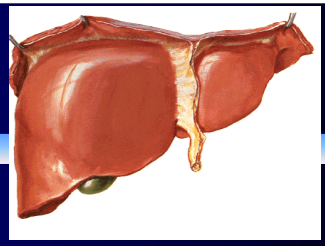
Patients with chronic HCV infection have impaired GH secretion

During antiviral therapy basal and stimulated GH secretion increases and may even be normalized

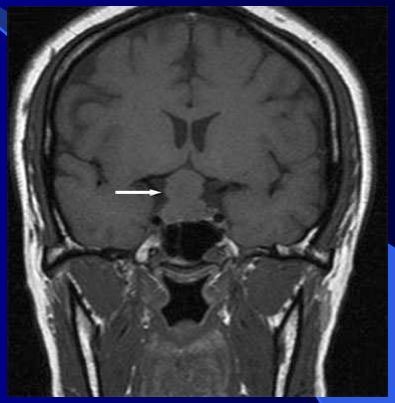
HCV infection reduces basal and stimulated GH secretion directly at the pituitary

Plöckinger U et al. Am J Gastroenterol 2007;102:2724

Gestione clinica delle epatiti croniche virali



During treatment of chronic hepatitis C with interferon alpha e ribaverin

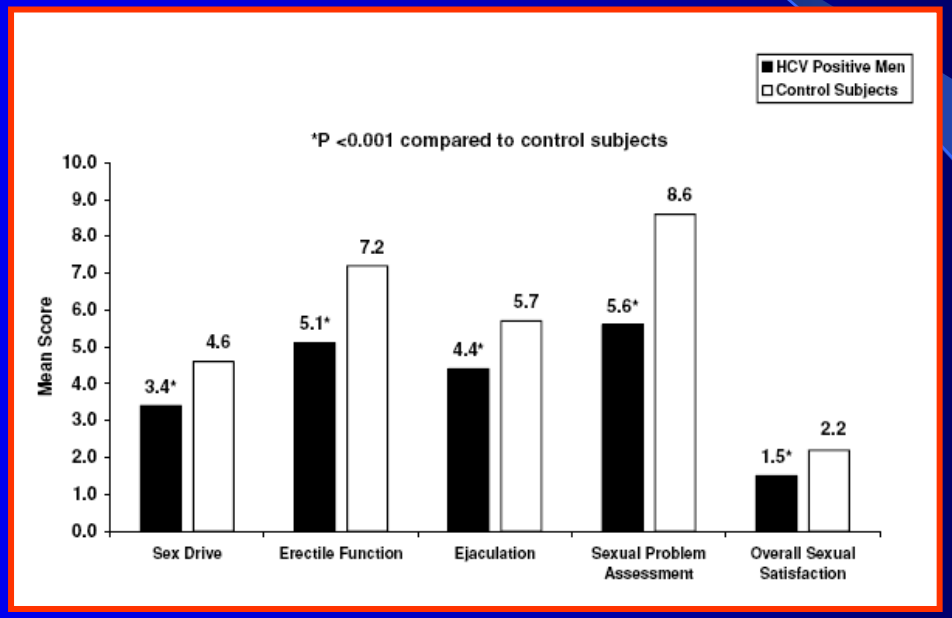


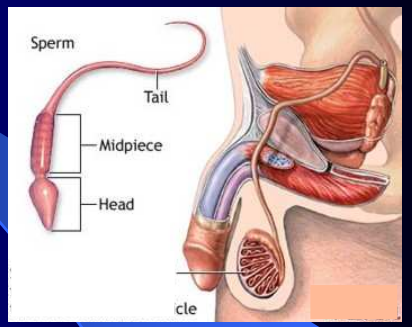
Hypophysitis

Central Hypothyroidism

Gestione clinica delle epatiti croniche virali

Sexual Dysfunction is Highly Prevalent Among Men with Chronic Hepatitis C Virus Infection and Negatively Impacts Health-Related Quality of Life





Sexual dysfunction is highly prevalent in men with chronic HCV infection, is independent of depression, and is associated with a marked reduction in HRQOL

Dannof A et al Am J Gastroenterol 2006;101:1235

Gestione clinica delle epatiti croniche virali

Elevated Sex Hormone Binding Globulin Levels May Contribute to Sexual Dysfunction in Men With Chronic Hepatitis C Virus Infection

Laboratory Data of the 75 Study Subjects

Rao J et al J Clin Gastroenterol.2009;43:94

Gestione clinica delle epatiti croniche virali

Chronic hepatitis C infection and sex hormone levels: effect of disease severity

	Men with fibrosis score 0–2 (*n* = 20)	Men with fibrosis score 3–6 (*n* = 15)	Reference range
Age (years)	42.0 ± 7.3	37.1 ± 8.5	
ALT (U/L)†	36.0 (13–90)	63.0 (11–306)*	<50
Albumin (g/L)	42.0 (39–46)	42.0 (36–48)	35–50
INR	1.0 (0.8–1.1)	1.0 (0.9–1.1)	0.9–1.2
Activity score	5 (2–10)	8 (3–14)*	
Total HAI	6.5 (4–11)	12 (6–18)**	
Testosterone (nmol/L)	19.2 ± 6.0	19.6 ± 10.4	(8–35)
Free T (pmol/L)	380.4 ± 102.0	255.9 ± 83.0*	(See text)
SHBG (nmol/L)	38.0 ± 13.2	66.7 ± 43.3**	(20–120)
Oestradiol (pmol/L)	73.1 ± 25.0	76.8 ± 25.0	(<100)

*$P < 0.05$, **$P < 0.001$.

†Data reported as median and range.

ALT, alanine aminotransferase; HAI, Knodell histological activity index; INR, international normalized ratio; SHBG, sex hormone-binding globulin T, testosterone.

Liver biopsies were scored according to the modified Knodell histological activity index comprising a 20-point Activity Index assessing disease activity and a 6-point Fibrosis Score grading severity of liver fibrosis

Nguyen H V et al. Inter Med J.2006;36 : 362

Gestione clinica delle epatiti croniche virali

Chronic hepatitis C infection and sex hormone levels: effect of recombinant interferon-a therapy

Effect of 6 months of IFN-a treatment on liver function and sex hormone levels in men with hepatitis C infection

	Initial visit	Within 6 months (nadir values)	Post-treatment
ALT (U/L)	119.1 ± 35.5	57.7 ± 33.7*	44.7 ± 39.9*
Total T (nmol/L)	24.4 ± 8.4	18.7 ± 3.5*	22.0 ± 4.5
Free T (nmol/L)	0.34 ± 0.11	0.29 ± 0.08	0.40 ± 0.12
SHBG (nmol/L)	63.1 ± 23.1	52.7 ± 17.3**	45.9 ± 16.4*

*Paired *t*-tests comparing nadir and post-treatment to baseline values with a significant two-tailed $P < 0.025$, **$P = 0.026$.
ALT, alanine aminotransferase; IFN-α, interferon-α; SHBG, sex hormone-binding globulin; T, testosterone.

Nguyen H V et al. Inter Med J.2006;36 : 362

Gestione clinica delle epatiti croniche virali

Seminal and hormonal parameters in responders and non responders before, during and after treatment (mean ± SD)

	Month 0	Month 6	Month 12	Month 0	Month 6	Month 12
	Non responders			Responders		
Sperm concentration (*n*/mL)	84.2 ± 56.6	69.0 ± 35.5	66.6 ± 36.1	86.9 ± 76.6	35.2 ± 25.8	76.8 ± 75.3
Normal motility (%)	45.2 ± 7.0	51.4 ± 13.9	46.0 ± 7.4	46.2 ± 10.7	37.0 ± 17.8	43.8 ± 24.3
Normal morphology (%)	34.8 ± 7.6	24.6 ± 11.3	26.0 ± 6.8	21.4 ± 6.0	14.4 ± 9.2	21.6 ± 12.8
Inhibin B (pg/mL)	98.0 ± 49.2	166.4 ± 30.3[b]	95.4 ± 55.6	105.3 ± 50.1[a]	157.4 ± 72.7	143.4 ± 46.1
Free Testosterone (pg/mL)	16.2 ± 1.6	16.4 ± 2.0	16.9 ± 3.4	14.2 ± 2.5	14.6 ± 2.8	17.1 ± 2.6[c]
Total testosterone (μg/L)	7.4 ± 2.0	7.9 ± 0.9[d]	6.6 ± 1.0	6.0 ± 2.0	7.3 ± 2.1	6.9 ± 1.0
PRL (μg/L)	7.0 ± 3.8	7.9 ± 1.8	8.9 ± 3.3	9.4 ± 6.3	7.4 ± 3.9	6.5 ± 2.8
LH (mU/mL)	4.2 ± 2.1	3.6 ± 1.8	3.0 ± 1.2	3.8 ± 2.6	4.5 ± 2.5	3.6 ± 0.7
FSH (mU/mL)	4.8 ± 1.7	4.9 ± 1.0	5.7 ± 1.6	4.8 ± 2.1	5.2 ± 0.8	5.1 ± 0.9
17-βE (pg/mL)	19.4 ± 5.3[e]	14.6 ± 5.1	20.2 ± 6.8	20.0 ± 7.9	12.7 ± 5.2	14.5 ± 2.8

[a]$P = 0.039$ (0 *vs* 12 mo); [b]$P < 0.01$ (6 *vs* 12 mo); [c]$P < 0.05$ (0 *vs* 12 mo); [d]$P < 0.05$ (6 *vs* 12 mo); [e]$P < 0.01$ (0 *vs* 6 mo).

The combined antiviral therapy could cause a further alteration in spermatic morphology
On the other hand, its antiviral activity could improve spermatogenesis, as demonstrated by the increased inhibin B levels after six and twelve months of therapy in responders

Durazzo M et alWorld J Gastroenterol 2006 May 21; 12: 3073

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Gestione clinica delle epatiti croniche virali

Risk factor/Cause

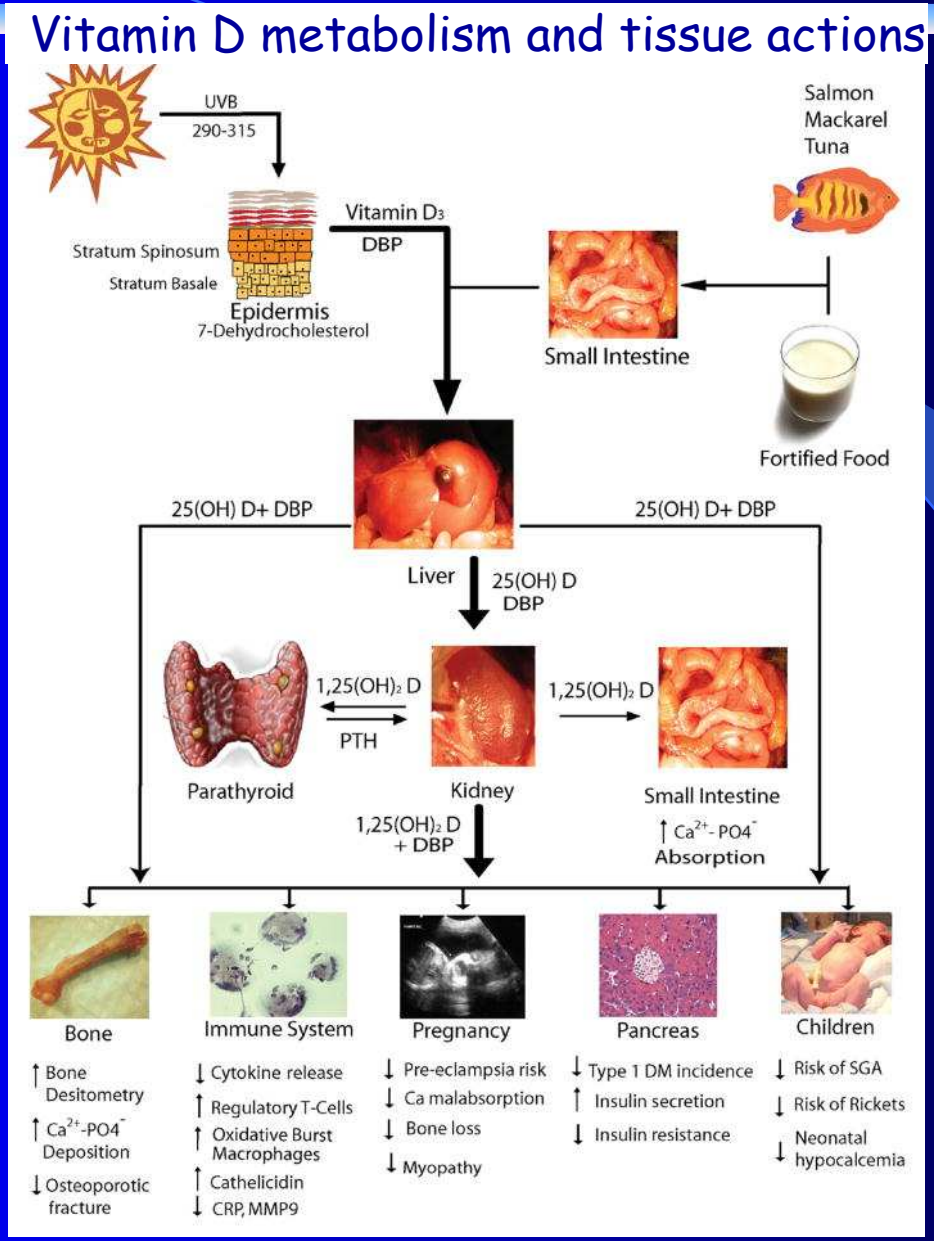
Vitamin D deficiency

Chronic liver disease

Effect

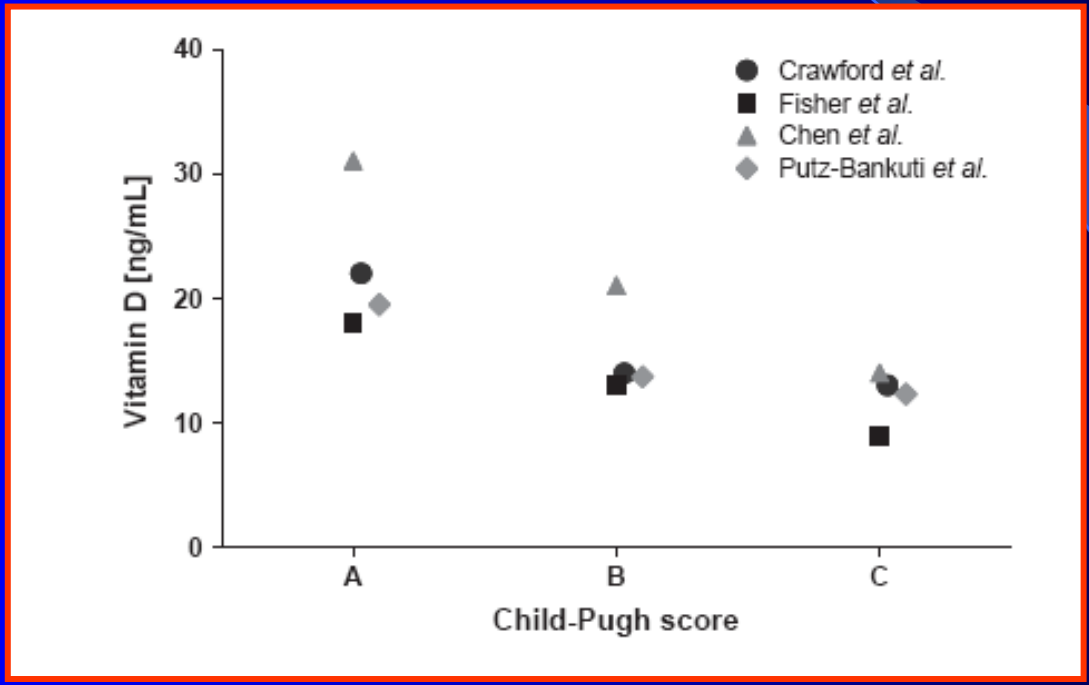
Gestione clinica delle epatiti croniche virali

Vitamin D metabolism and tissue actions



Vitamin D in chronic liver disease (CLD)

The prevalence of vitamin D levels < 20 ng/ml in CLD has been reported to range from 64 to 92% and is commonly inversely related to disease progression



Serum 25-hydroxyvitamin D concentrations (ng/ml) in patients with cirrhosis, stratified by Child-Pugh score

Stokes CS et al. Liver International. 2013;33.338

Vitamin D in chronic hepatitis C

TAKE HOME MESSAGE

Vitamin D deficiency has been linked to a
low rate of sustained virological response in
HCV patients undergoing interferon-based therapy
and
to more severe liver fibrosis

Stokes CS et al. Liver International. 2013;33.338

Vitamin D in chronic hepatitis C

TAKE HOME MESSAGE

Vitamin D supplements
improve treatment response
in patients with chronic hepatitis C
and
increase the likelihood of
achieving sustained virological response

Stokes CS et al. Liver International. 2013;33.338

Gestione clinica delle epatiti croniche virali

Vitamin D in chronic hepatitis C

Is reasonable

Monitoring

of serum 25(OH)D

and

vitamin D supplementation

Stokes CS et al. Liver International. 2013;33.338

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Hepatic Osteodystrophy

specific cronic liver disease (CLD) associated bone disease
and
related metabolism abnormalities
with both osteopenia and osteoporosis

- incidence of bone disease ➔ 11 - 48% in patients with CLD

↪ osteoporotic fracture rate is double that of age-matched controls

↪ prevalence of osteoporosis is between 20% and 60%
with the variance dependent on diagnostic criteria and patient selection

Stokes CS et al. Liver International. 2013;33.338

Gestione clinica delle epatiti croniche virali

Hepatic Osteodystrophy

pathogenesis is multifactorial and only partially understood

↓ concentrations of insulin-like growth factor 1

↑ cytokine concentrations

(IL-1, IL-6 and tumour necrosis factor)

↓ Vitamin D levels

risk factors

- increased alcohol intake
- low BMI
- hypogonadism
- corticosteroid use

Stokes CS et al. Liver International. 2013;33.338

Grazie per l'attenzione

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Trasforini Giorgio
Zatelli Maria Chiara

Tagliati Federico
Buratto Mattia
Bruni Stefania
Gentilin Erica

Calabrò Veronica
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