The Immune Response of Prolactin and the Induction of Tumor Necrosis Factor (TNF) in Iraqi Patients Infected with Hepatitis C Virus.

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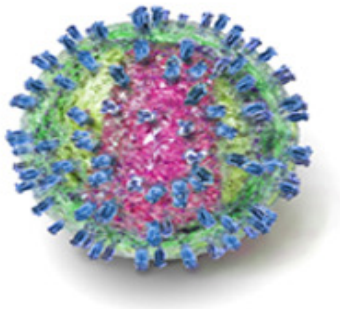
7/23/2016

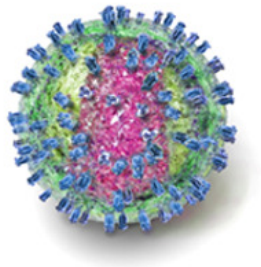
Prof. Dr. Hedef Dhafir El-Yassin 2016
Berlin/ Germany



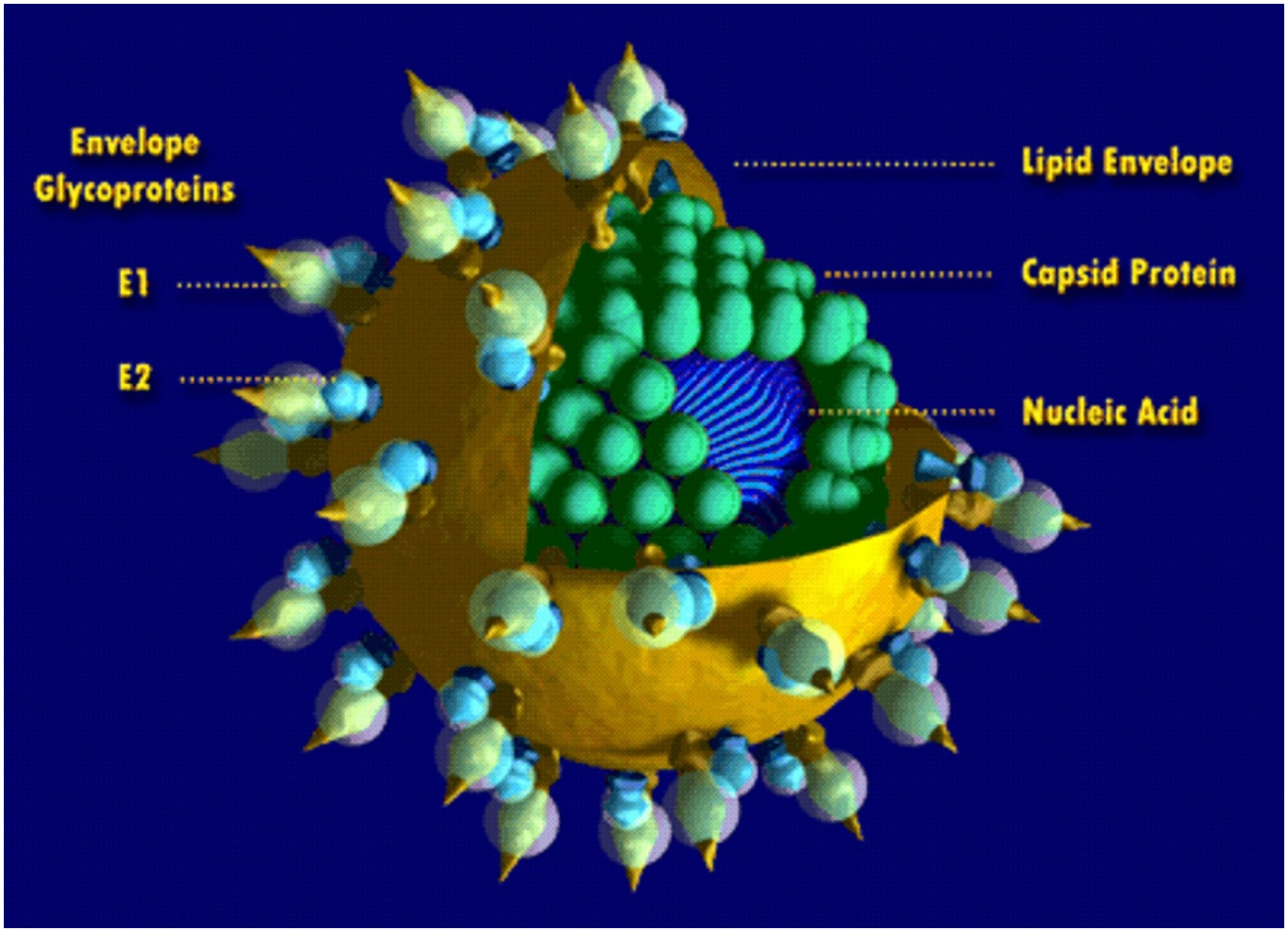
- Viral Hepatitis Type C is a serious public health challenge throughout the world and remain to be the major causes of chronic hepatitis.

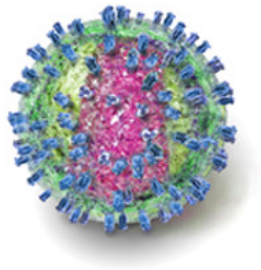
- During the 80s, Iraq had low endemicity among blood donors.

- However its prevalence is now increased with high rate of mortality.

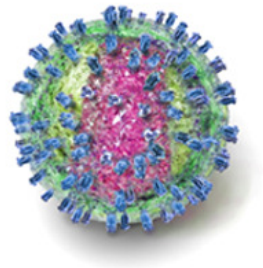


- Hepatitis C is a contagious viral disease caused by hepatitis C virus.





- Brett D. Lindenbach and charles M. Rice described a hypothesis for the detailed molecular mechanism of HCV infection in an article entitled :" The ins and outs of hepatitis C virus entry and assembly", published in *Nature Reviews Microbiology* : Volume: 11, Pages:688–700 :(2013)



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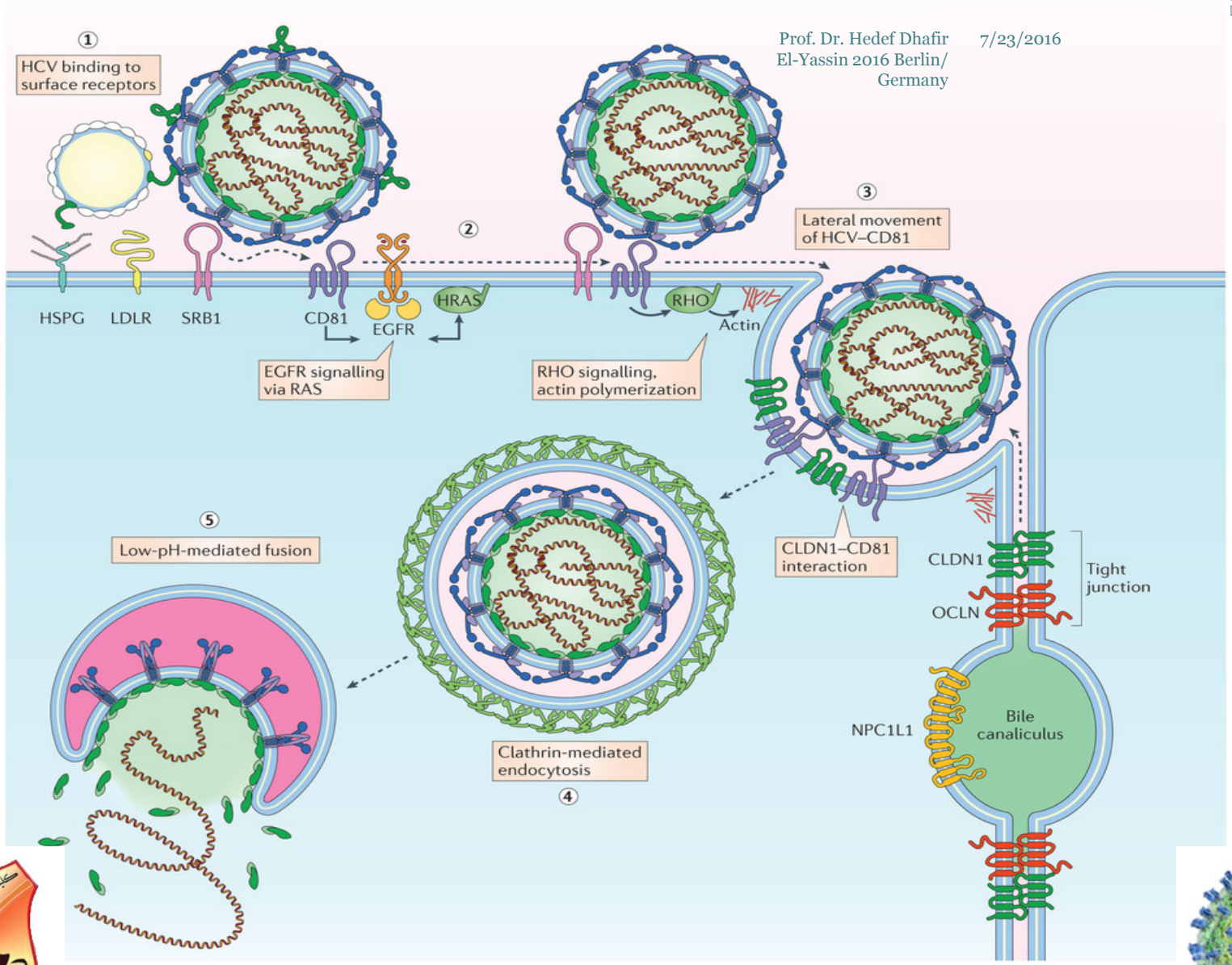
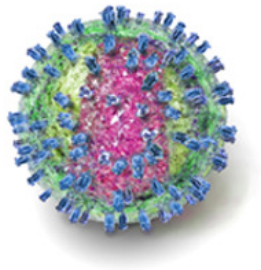
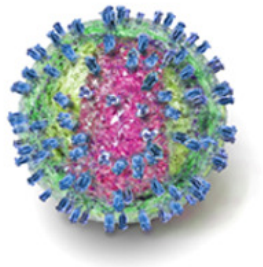


Nature Reviews | Microb



(step 1)

- Hepatitis C virus (HCV) lipoviral particles (LVPs) attach to the cell surface by interacting with:
  - heparan sulphate proteoglycans (HSPGs),
  - low-density-lipoprotein receptor (LDLR) and
  - scavenger receptor class B member 1 (SRB1).
- SRB1 might delipidate HCV-associated lipoproteins and induces conformational changes in the E2 glycoprotein, exposing the CD81-binding site

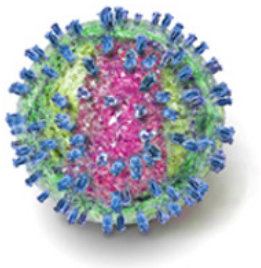


(step 2)

- Interaction of E2 with CD81 then activates signal transduction through epidermal growth factor receptor (EGFR) and HRAS, as well as through RHO GTPases.

(step 3)

- These signaling events promote lateral movement of HCV– CD81 complexes to sites of cell–cell contact.

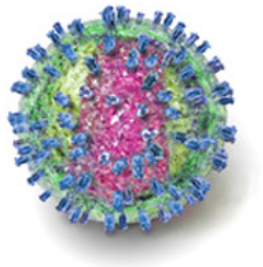


(step 4)

- Interaction of CD81 with claudin 1 (CLDN1), and HCV internalization via clathrin-mediated endocytosis.

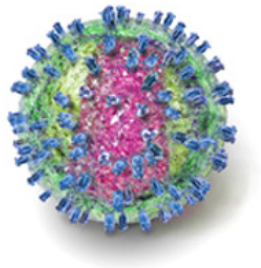
(step 5)

- The low pH of the endosomal compartment induces HCV fusion.

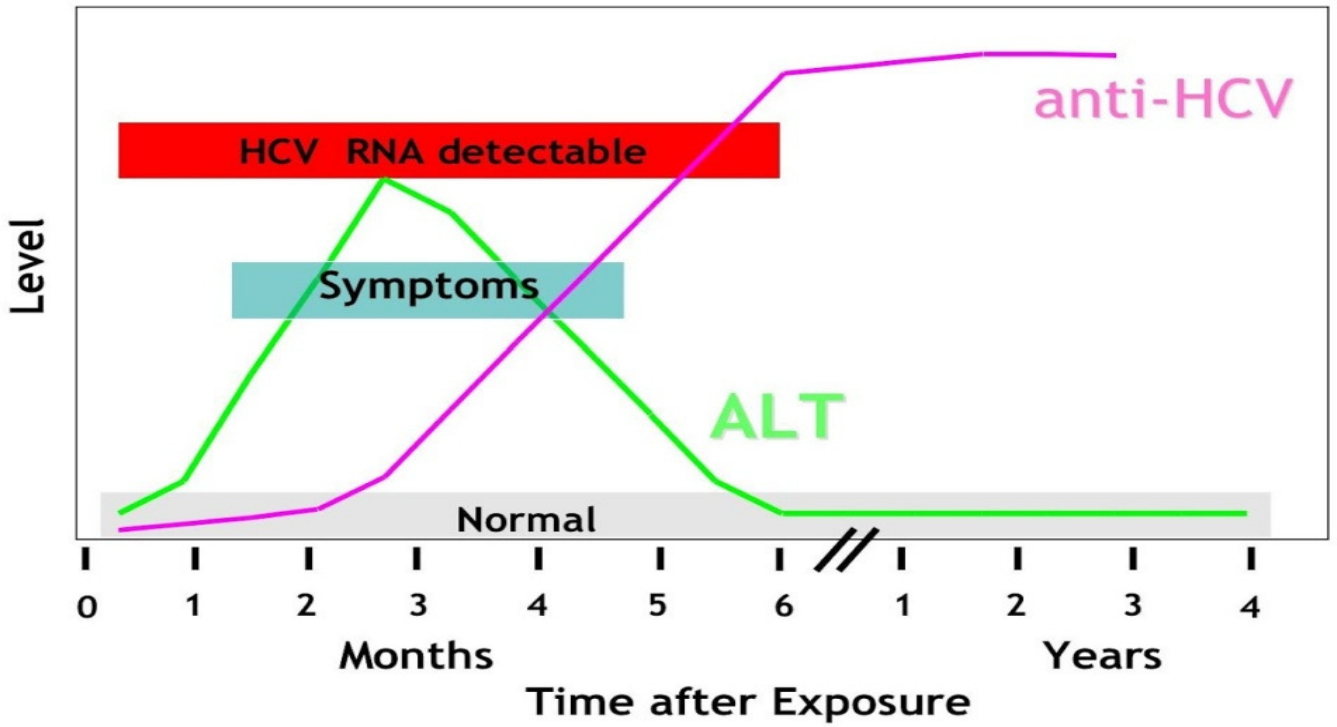


- Many cases (two –third) could go through undiagnosed because they might be asymptomatic.

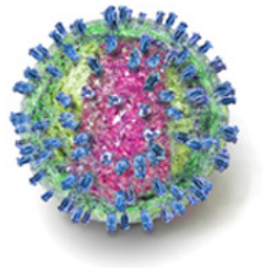
- However the rest one-third of people initially infected with hepatitis C develop symptoms and are more likely to be treatment efficiently with antiviral drugs.



Acute HCV Infection with Recovery

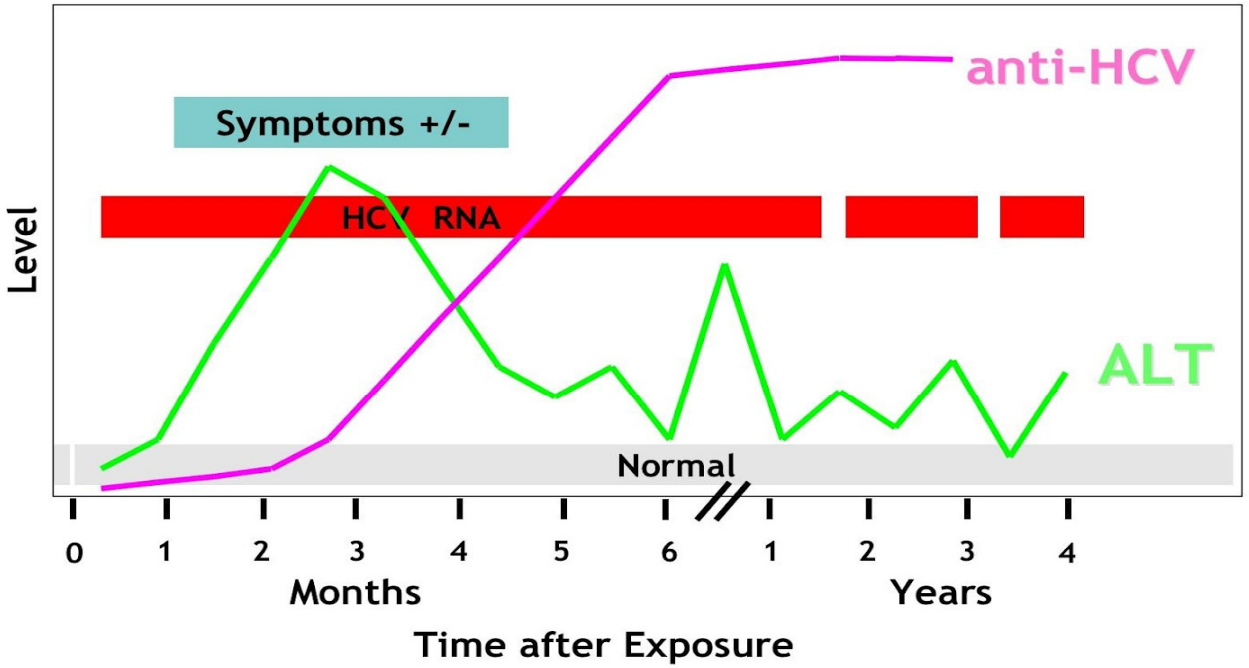


Source: Adapted from MMWR 1998; 47(No. RR19)

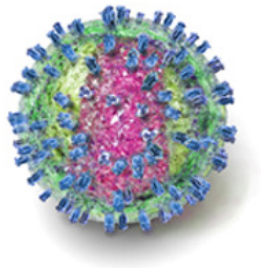


- Those infected but asymptomatic will develop to chronic HCV and will initiate a broad-based immune response. (adaptive and innate immune response).

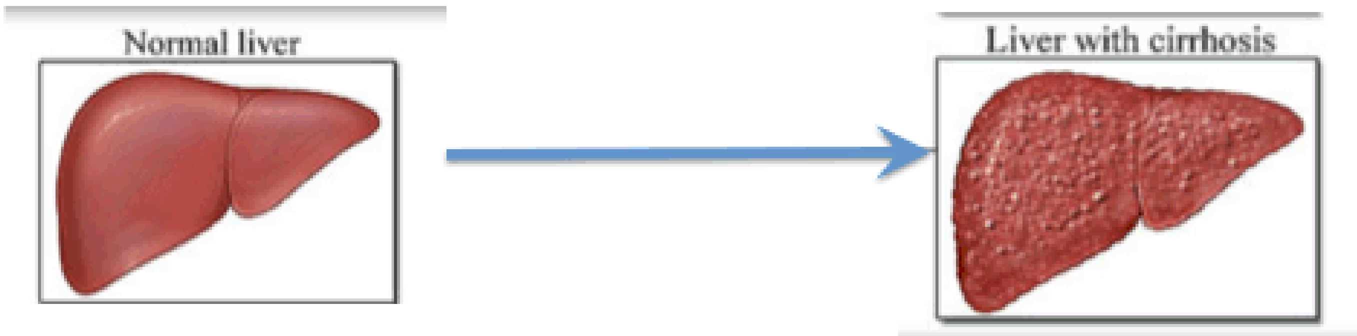
Acute HCV Infection Evolving to Chronic Infection



:e: Adapted from MMWR 1998; 47(No. RR19)



Risk Factors Associated with Faster Fibrosis Progression in Chronic HCV



Disease State Factors

- Fibrosis stage
- HCV onset after 40 years of age
- Persistently elevated ALT

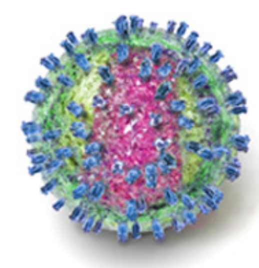
Host Factors

- Male gender
- Age
- Obesity
- Diabetes
- HIV, HBV coinfection
- Immune system compromise
- Steatosis
- Iron overload

Lifestyle Factors

- Heavy alcohol consumption
- Cannabis use
- Tobacco use

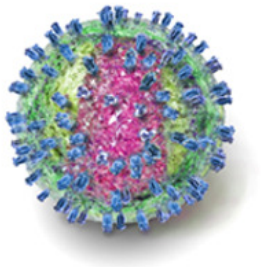
Antivir Ther. 2010;15:281-91.
al. *Lancet* .1997;349:825-32.



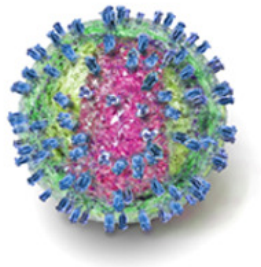
- It is clinically important

1. to differentiate :
   - incident HCV infections

   from
   - chronic infections
2. and to identify
   - primary infections that are asymptomatic.

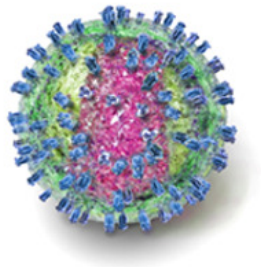


- Occasional occurrences of acute exacerbation in chronic infection, will complicate decisions regarding whom to treat with the suitable treatment.(1)

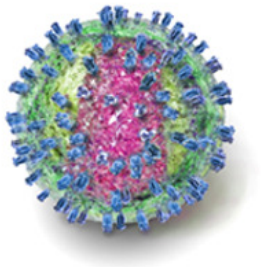


Hepatitis C virus-related chronic hepatitis is associated with various immunological disorders example:

- Immuno-endocrine
- Cytokines
- Anti-tissue antibodies



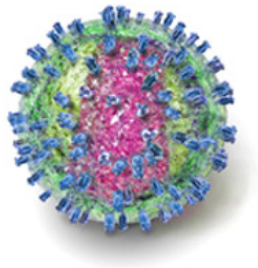
- Interaction of these molecules might trigger a cascade of reaction that will be involved in the progression of the disease.
- And/or might influence the effect of drug of choice that is used for the management of the disease.

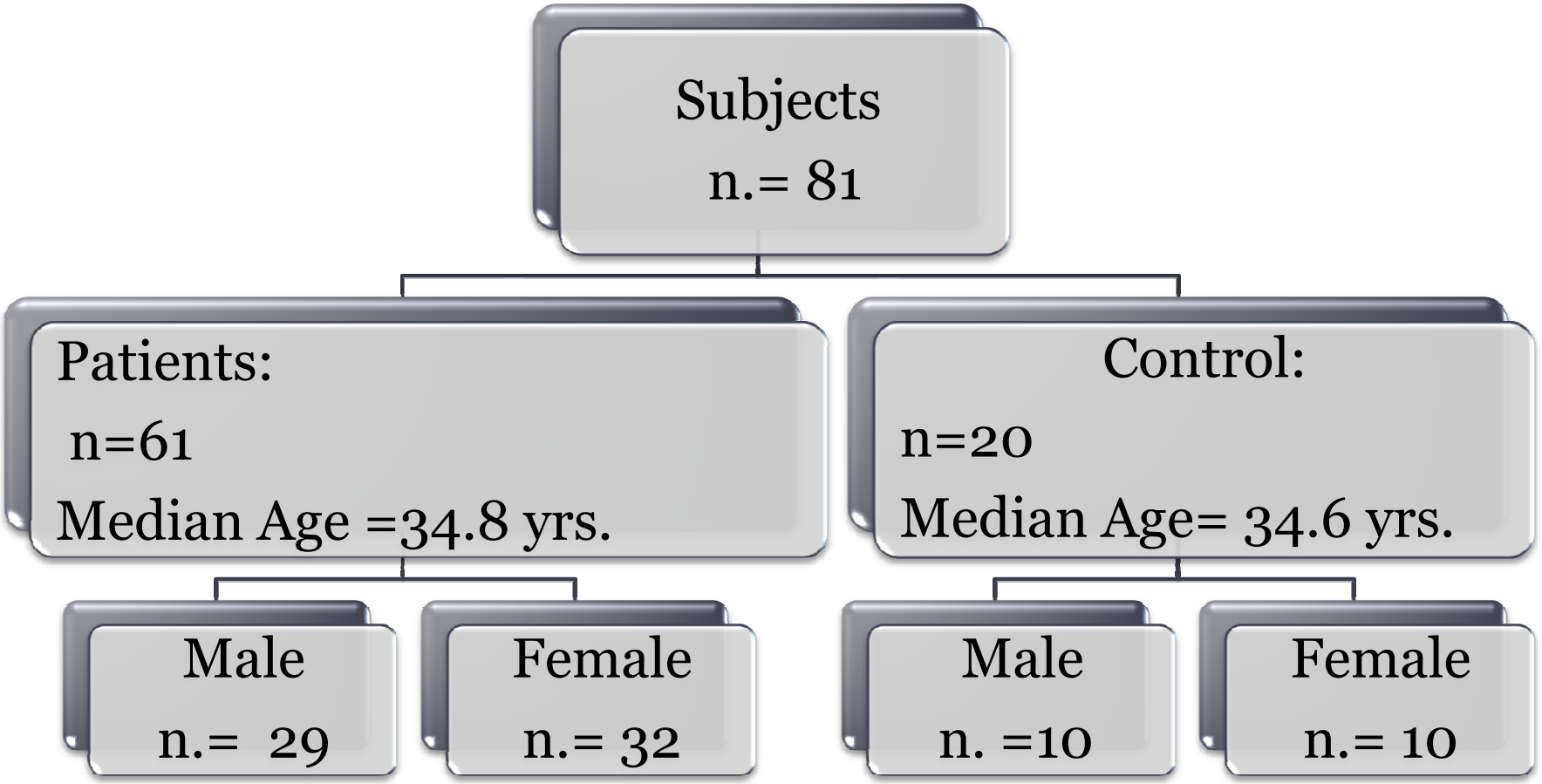


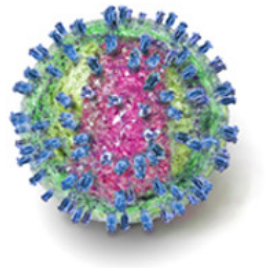
Aim of the study:

To evaluate the role of the immunoendocrine system in the pathogenesis of chronic hepatitis c, by measuring serum prolactin and tumor necrosis factor-alpha.

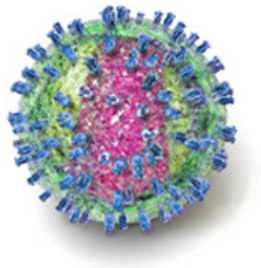
- Subjects involved in the study were selected from Gastrointestinal Hospital in Baghdad, Iraq .
- During the period from July 2014 to September 2014.
- A written consent was taken from each.



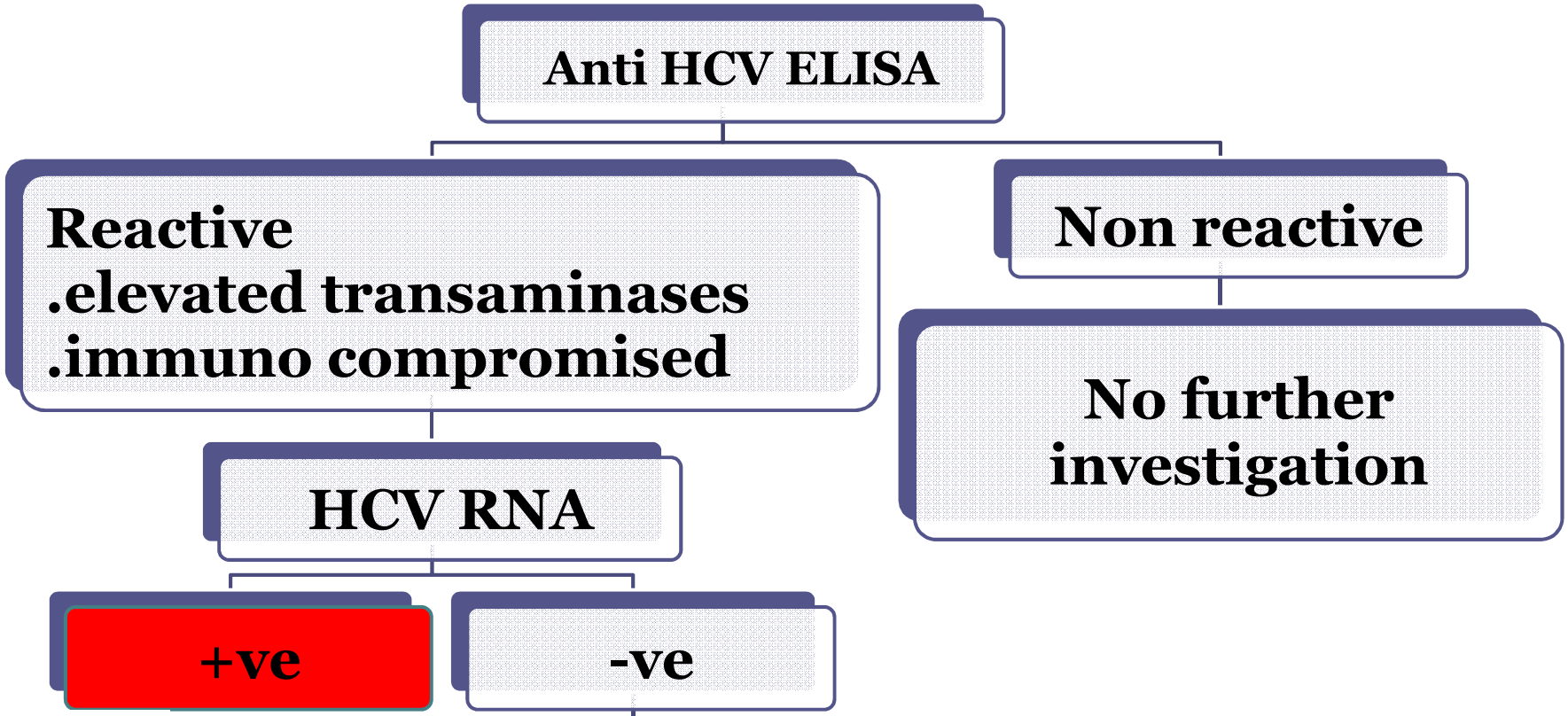

Subjects
n.= 81
Patients:
n=61
Median Age =34.8 yrs.
Control:
n=20
Median Age= 34.6 yrs.
Male
n.= 29
Female
n.= 32
Male
n. =10
Female
n.= 10

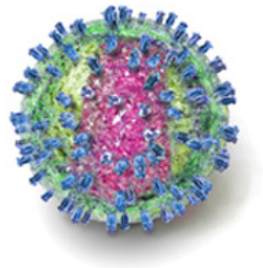


- All patients had chronic hepatitis C virus and were on interferon alpha therapy.
- All of them were positive for HCV RNA by means of polymerase chain reaction.

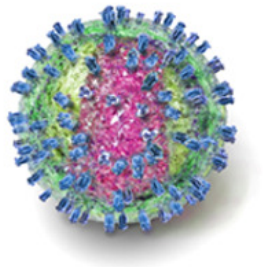


Diagnostic algorithm for hepatitis C

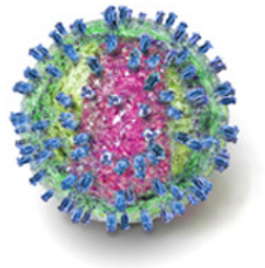




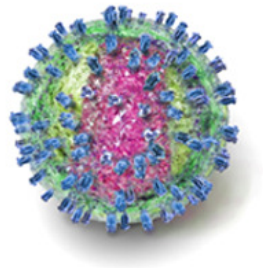
- Blood samples were collected between (9.00a.m-12.00p.m).
- The blood was allowed to clot in plain tube for 30-45 minutes at room temperature.
- Sera were obtained by centrifugation of the collected blood and then stored in plain tubes at -20 c.
- ELISA technique was used to measure (TNF and Prolactin)



Parameter	Serum prolactin (ng/ml)	
Groups	Patients	Controls
Mean ± SEM	12.54	2.9	11.50	2.7

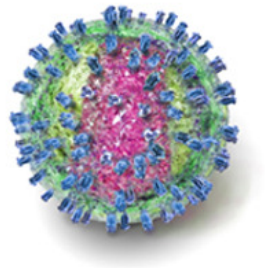


- The role of PRL in the immune reactions is stimulating; its presence significantly increases the ability of the immune cells to proliferate and produce cytokines such as TNF-alpha(2)

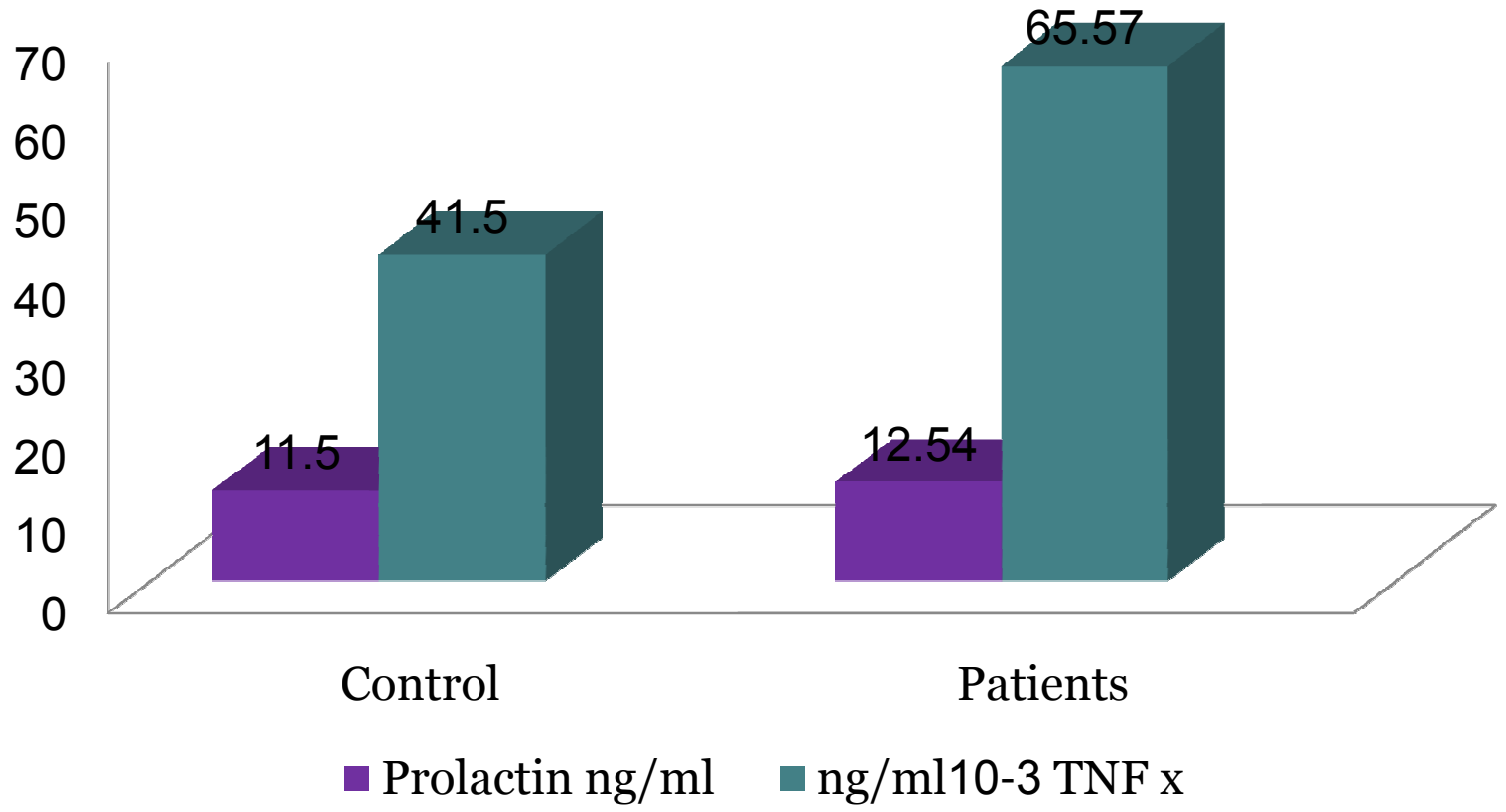


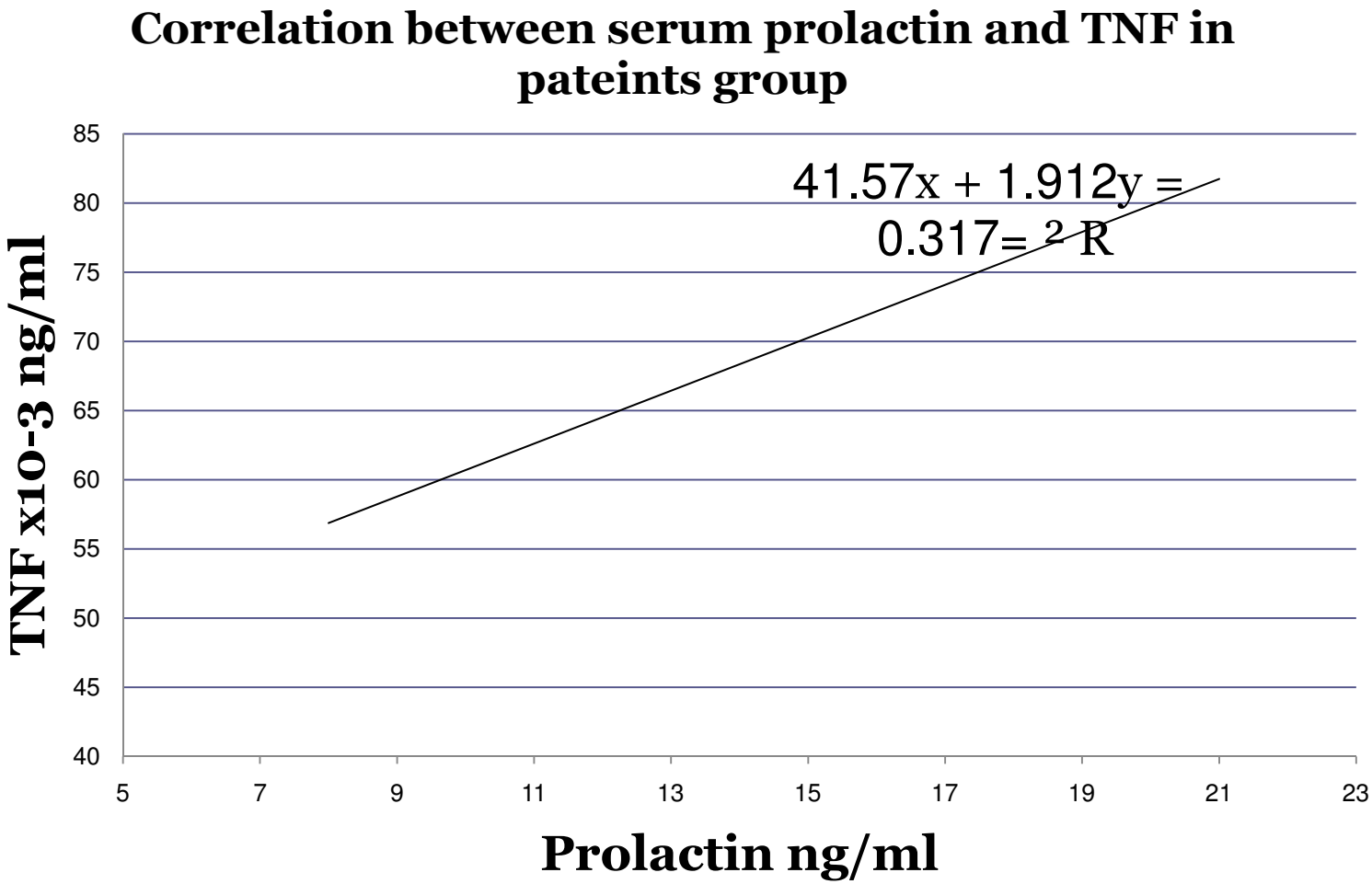
- Recent studies suggest that prolactin is important both for normal liver growth and for regenerating the liver after part of it is removed, with extra prolactin providing a boost for repair mechanisms. Consequently, enhancing prolactin levels could provide a way to improve regeneration when the liver becomes damaged or diseased with viruses, or after surgery.(3)

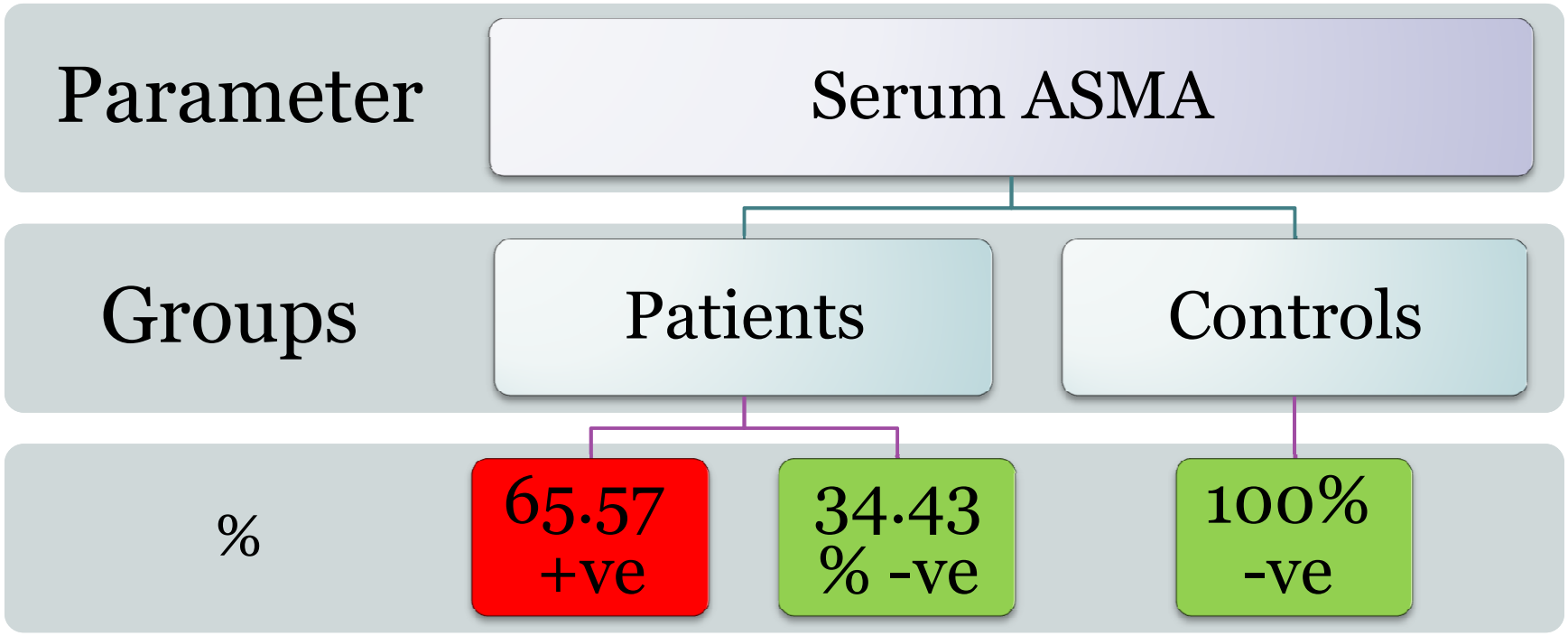
Parameter	Serum TNF-alpha (ng/ml)	
Groups	Patients	Controls
Mean ± SEM	65.57 x10^{-3}	7.03x 10^{-3}
	41.52 x10^{-3}	1.86x 10^{-3}



- HCV infection enhances TNF-α-induced cell death by suppressing nuclear factor NF-κB activation through the action of core, (non structural HCV) NS4B, and NS5B. This mechanism may contribute to immune-mediated liver injury in HCV infection. (4)


70
60
50
40
30
20
10
0
11.5
41.5
12.54
65.57
Control
Patients
Prolactin ng/ml
ng/ml10-3 TNF x


Correlation between serum prolactin and TNF in pateints group
41.57x + 1.912y =
0.317= ² R
TNF x10-3 ng/ml
85
80
75
70
65
60
55
50
45
40
5
7
9
11
13
15
17
19
21
23
Prolactin ng/ml


Parameter
Serum ASMA
Groups
Patients
Controls
%
65.57
+ve
34.43
% -ve
100%
-ve

- The result agrees with Clifford et al in their study they reviewed the presence of autoimmune markers in sera of chronic hepatitis C patients.

- Their study showed that treatment with interferon alfa (IFN-alpha) will exacerbate autoimmune hepatitis. (5)

- The pathogenesis of autoimmune hepatitis due to medications is not clear.

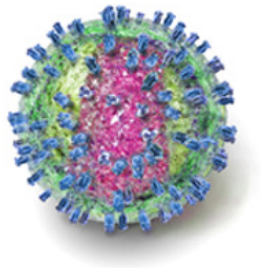
Recommendations from an expert panel

- Aiming for treatment optimization by filling some of the gaps of the current guidelines, a group of Italian experts, experienced on treatment of HCV infection, met in Stresa in February 2016.
- The summary of all the considerations arising from this two-day meeting and the final statements are reported in *Digestive and Liver Disease Journal June* 2016 [Epub ahead of print]

- "Treatment of chronic HCV (CHC) has been revolutionized in the last few years by the introduction of highly effective and well tolerated direct acting antiviral agents (DAAs) able to achieve >90% rates of sustained virological response (SVR) in many groups of patients, including those previously excluded from interferon-based regimens.
- For such reason interferon-free regimens are now the treatments of choice for all patients.
- Successful anti-HCV treatment can stop liver disease progression and can solve the HCV-related extra hepatic manifestations, eventually reducing both liver-related and overall mortality."

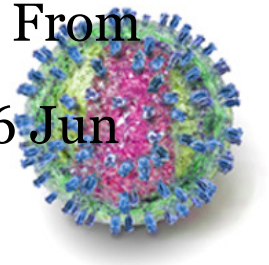
Conclusions:

- Chronic hepatitis C is associated with an immunological abnormality mainly represented by tumor necrosis factor-alpha and prolactine.
- This might shed a light of the type of therapy and drug of choice when managing the disease.



References:

1. C.H. Chen, and C.-S. Changchien. Is it possible to diagnose acute hepatitis C virus (HCV) infection by a rising anti-HCV titer rather than by seroconversion? J. Viral Hepat. 11:563–570, 2004
2. Fojtíková M[1], Cerná M, Pavelka K. A review of the effects of prolactin hormone and cytokine on the development and pathogenesis of autoimmune diseases.Vnitr Lek.56(5):402-13, .2010 [Article in Czech].
3. CarmenC, Moreno B, Maite G. Prolactin promotes normal liver growth survival and regeneration in rodents. American Physiological Society; 10:1152, 2012.
4. Park J, Kang W, Ryu SW.Hepatitis C virus infection enhances TNFα-induced cell death via suppression of NF-Kb.Journal of Hepatology; 56(3):831-40, 2012
5. Clifford BD,Donahue D,Smith L.High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Journal of Hepatology; 21(3):613, 1995
6. Craxì A, Perno CF, Viganò M, Ceccherini-Silberstein F, Petta S; AdHoc (Advancing Hepatitis C for the Optimization of Cure) From current status to optimization of HCV treatment: Recommendations from an expert panel. Dig Liver Dis. 2016 Jun



Any questions?

Thank You