Metabolik Hastalıklar ve Hepatitis C

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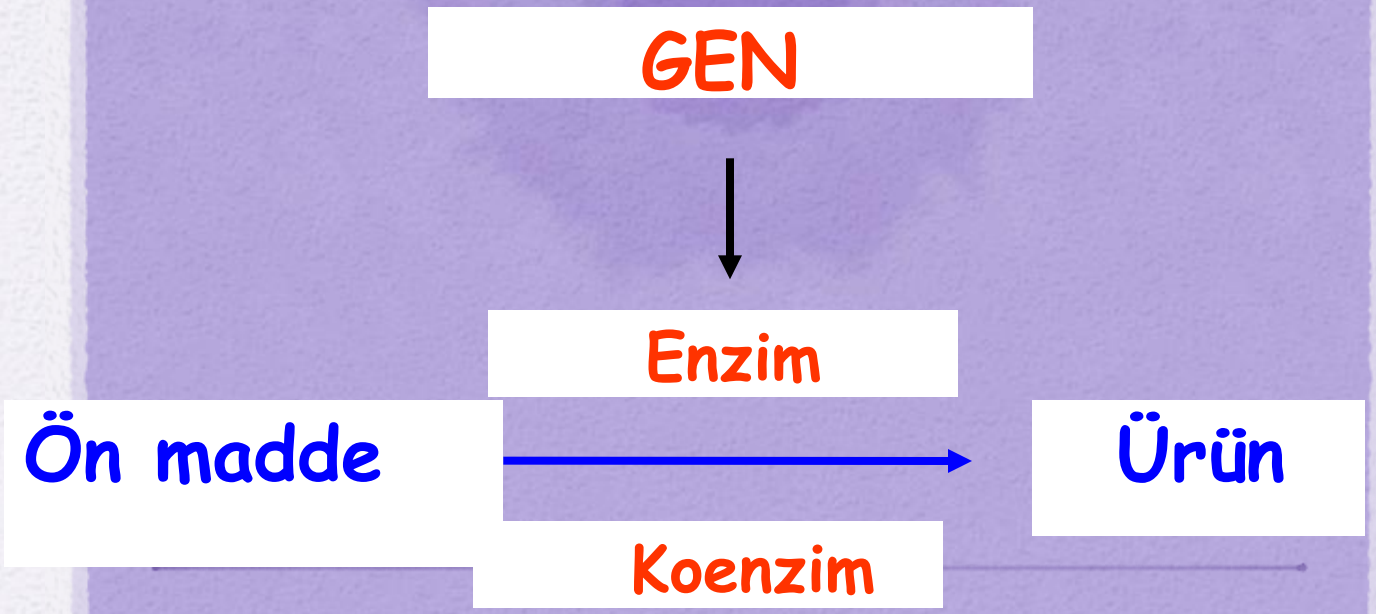
Metabolizma

- Metabolizma sağlam olan organizma, diferansiye organ, hücre ve hücre altı organeldeki entegre biyokimyasal süreçlere verilen kollektif isimdir.

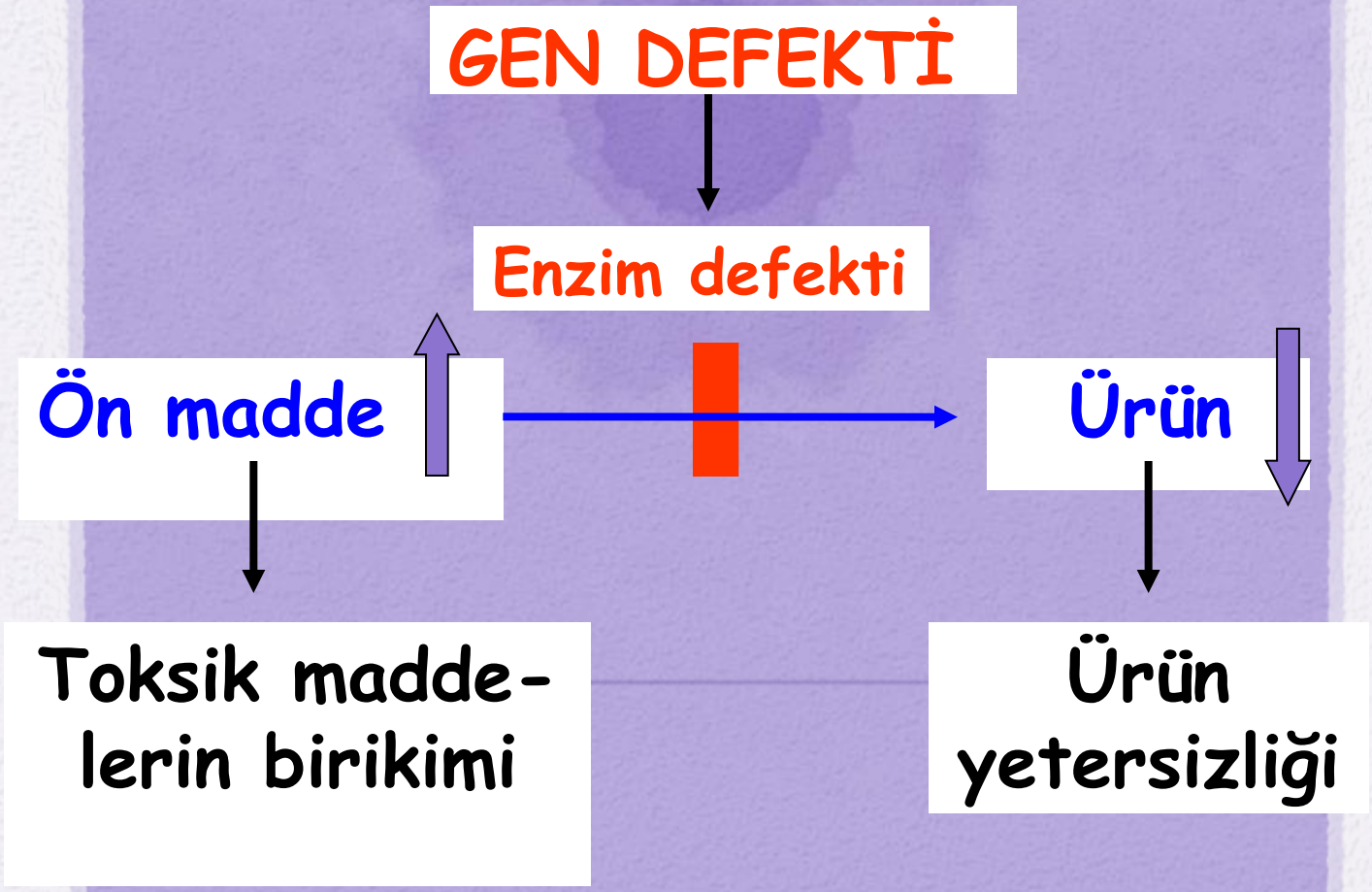
- İlk kez 1908 de Garrod doğumsal metabolizma hastalıklarını tanımlamış ve dört hastalığı tanımlamıştır. Alkaptonüri, albinizm, sistinüri ve pentozüri

- Metabolik hastalıklar protein, karbohidrat ve yağ asitlerinin sentezi ya da katabolizması ile ilgili olaylar sonucu gelişen patolojik tablolardır.
- Metabolik hastalıklar tek tek düşünüldüklerinde nadirdir, ancak çok çeşitli oldukları düşünülürse toplamda daha sık akla gelmesi gerekir.
- Çoğu otozomal resesif kalıtılan bu hastalıklar akraba evliliğinin sık olduğu ülkemizde daha da sık akla gelmelidir.

Genler enzimleri yaparlar, enzimler ise biyokimyasal reaksiyonları hızlandırırlar



Kalıtsal metabolizma hastalıklarının fizyopatolojisi



1) Entoksikasyon tipi küçük molekül hastalığı

- **Amino asidopatiler** (MSUD, tirozinemi, nonketotik hiperglisinemi)
- **Organik asidemiler** (piruvik, izovalerik, metilmalonik asidemiler, biotinidaz yetersizliği)
- **Üre siklusu defektleri** (OTC yetersizliği, sitrullinemi vb)
- **Şeker entoleransı** (galaktozemi, früktozemi vb)

2) Enerji yetersizliği tipi küçük molekül hastalığı

- **Glükoneogenez defektleri** (G-6-Paz, PC, F-1, 6-diP, PEP karboksikinaz yetersizlikleri)
- **Glikojenoliz defektleri** (GSD III, GSD V, ve GSD VI)
- **Glikojenez defektleri** (GSD 0, GSD IV)
- **Laktik asidemiler** (PDH yetersizliği, elektron-transfer zinciri hastalıkları)
- **Yağ asidi oksiasyonu defektleri** (MCAD, SCAD yetersizlikleri vb)

Kalıtsal Metabolizma Hastalıkları

- Genetik bozukluklar sonucu gelişir, etyolojide genetik bozukluklar sorumludur.
- İnfeksiyon ancak daha sonra gelişen metabolik hastalıkların etyolojisinde vardır.

Hepatit C ve Metabolik hastalıklar

- Hipolipidemi
- IR
- Hepatosteatoz
- Obezite
- İskemik kalp hastalığı, kalp yetmezliği

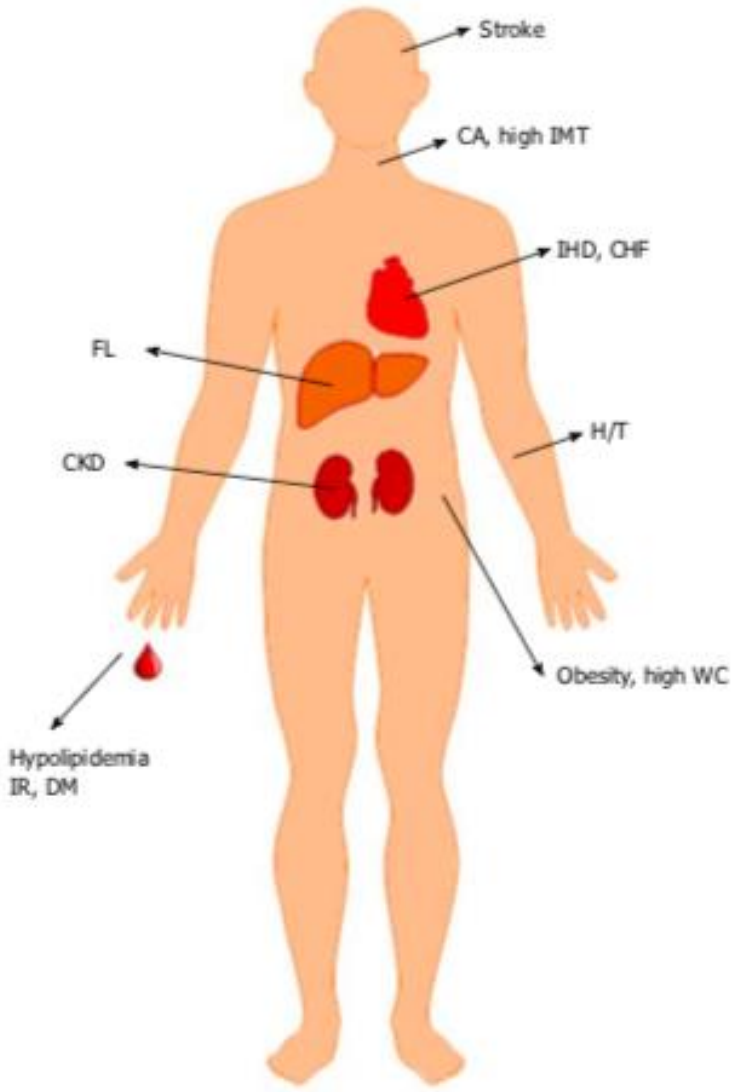


Figure 4 Hepatitis C virus-associated metabolic alterations and cardiovascular events, data from human studies. CA: Carotid atherosclerosis; IMT: Intima-media thickness; IHD: Ischemic heart disease; CHF: Congestive heart failure; FL: Fatty liver; H/T: Hypertension; WC: Waist circumference; IR: Insulin resistance; DM: Diabetes; CKD: Chronic kidney disease.

Prevalence of clinical extrahepatic manifestations in 321 patients with chronic HCV infection

	N (percent)
Skin involvement	
Purpura	21 (7)
Raynaud phenomenon	21 (7)
Cutaneous vasculitis	19 (6)
Pruritus	20 (6)
Psoriasis	6 (20)
Porphyria cutanea tarda	3 (1)
Lichen planus	3 (1)
At least one skin manifestation	55 (17)
Rheumatologic involvement	
Arthralgia	60 (19)
Arthritis	6 (2)
Myalgia	31 (2)
Neurologic involvement	
Sensory neuropathy	28 (9)
Motor neuropathy	15 (5)
Miscellaneous	
Sicca syndrome (mouth)	40 (12)
Sicca syndrome (eye)	32 (10)
Hypertension	32 (10)
Uveitis	2 (1)
Overall	
At least one extrahepatic clinical manifestation	122 (38)

Data from: Cacoub P, Renou C, Rosenthal E, et al. Medicine 2000; 79:47.

HCV ve otoimmün hastalıklar

- Otoantikor yapımı
- Tiroid hastalığı
- Sialadenit
- ITP

HCV ve tiroid

- HCV li hastaların %5-17 sinde tiroid otoantikorları
- %2 ila 13 ünde Tiroid hastalığı saptanmış

Hepatol Int. 2018 Mar;12(2):143-148. doi: 10.1007/s12072-018-9845-2. Epub 2018 Feb 14.

9.

High prevalence of HCV (GT4)-related TSH abnormality among 13402 Egyptian patients treated with direct acting antiviral therapy.

Eletreby R[1], Said M[2], Abdellatif Z[2], Saad Y[2], ElSerafy M[2], Dabes H[3], ElSaeed K[4], El-Shazly Y[4], Doss W[2].

Author information

Abstract

BACKGROUND: HCV is associated with several extra hepatic diseases including thyroid dysfunction. This study aims at evaluating prevalence of thyroid dysfunction and its possible predictors in a large cohort of HCV GT4-infected patients, and the role of thyroid dysfunction as a predictor of response in the setting of direct acting antivirals (DAAs).

METHODS: Patients registered on the web-based registry system to receive therapy for chronic HCV in Beheira governorate viral hepatitis specialized treatment center affiliated to the National committee for control of viral hepatitis (NCCVH), Ministry of health, Egypt in the period from January 2015 to October 2016. Their data were exported and analyzed for the prevalence of thyroid dysfunction and its associated variables.

RESULTS: Out of 13,402 patients, 2833 (21.1%) had elevated TSH level > 4.5 mIU/l (hypothyroidism). Female gender (62.7%), older age, higher FIB4, AST, and BMI and lower albumin were significantly associated with elevated TSH level on univariate analysis, while liver stiffness measured by fibroscan was not significantly associated. On the other hand, 466 patients (3.5%) showed low TSH level < 0.4 mIU/l (hyperthyroidism). Older age (median 52 years) and male gender (51.5%) were the only significantly associated variables. No association was found between SVR and baseline TSH level. Follow-up of 236 patients after SVR revealed improvement in TSH level in 80% of them.

CONCLUSION: Hypothyroidism is prevalent in patients with chronic HCV GT4, and is influenced by patient gender and age. Pretreatment TSH does not affect SVR after DAAs. Despite limited data SVR achievement after DAAs improves thyroid dysfunction.

KEYWORDS: Genotype IV; HCV; Thyroid dysfunction

Przegl Epidemiol. 2017;71(4):555-569.

12. ## Long-term outcomes of thyroid dysfunction in patients with chronić hepatitis C treated with pegylated interferon alpha and ribavirin

Kozielewicz D[1], Wietlicka-Piszcz M[2], Halota W[1].

Author information

Abstract

INTRODUCTION: Thyroid dysfunctions (TDs) are associated with pegylated interferon and ribavirin (PegIFN-α/RBV) therapy in patients with chronic hepatitis C (CHC) and are considered as possible extrahepatic manifestation of HCV infection

OBJECTIVES: This study aimed to assess the long-term outcomes of TDs in patients with CHC treated with PegIFN-α/RBV

METHODS: A total of 1,047 treatment-naïve patients with CHC were treated with PegIFN-α/RBV. TSH and FT4 were assessed at baseline, every 3 months during therapy and 6, 12 and 24 months after the end of therapy. Analysis was performed for two groups of patients depending on the absence (group A, n=77) or presence (group B, n=39) of TDs at baseline

RESULTS: At baseline, TDs' prevalence was 3.7%; 53.8% hypothyroidism, 38.5% goiters, and 7.7% hyperthyroidism. 77 (7.4%) out of 1,008 euthyroid patients developed TDs; 45.5% hypothyroidism, 33.8% hyperthyroidism, 19.5% destructive thyroiditis, and 1.3% goiters. TDs' remission (TDR) was achieved in 59/116 (50.9%) of treated patients; 64.9% in group A and 23.1% in group B ($p<0.001$). Hyperthyroidism as compared to hypothyroidism increases the odds of TDR (OR=4.87 (1.65-14.35), p=0.004), whereas preexisting TDs and higher baseline viral load tend to decrease the probability of TDR (OR=0.21 (0.07-0.58), p=0.003 and OR=0.4 (0.22-0.73), p=0.003, respectively)

CONCLUSIONS: The prevalence of TDs was low but over one-third of patients in whom TDs developed under PegIFN-α/RBV therapy did not recover. In one-fourth of patients with preexisting TDs remissions were observed. Treatment with PegIFN-α in the past must be taken into account as a potential cause of TDs

Clin Liver Dis. 2017 Aug;21(3):543-554. doi: 10.1016/j.cld.2017.03.009. Epub 2017 Apr 22.

33. # Hepatitis C and Risk of Nonhepatic Malignancies.

Balakrishnan M[1], Glover MT[2], Kanwal F[3].

Author information

Abstract

Epidemiologic studies show an increased risk of mortality among hepatitis C virus (HCV)-infected individuals compared with uninfected individuals from hepatic and nonhepatic causes. This article reviews the biologic plausibility of and epidemiologic evidence for the association between HCV and five extrahepatic malignancies: cholangiocarcinoma (CCA), pancreatic adenocarcinoma, papillary thyroid cancer, oral squamous cell cancer, and renal/kidney cancer. There is sufficient evidence to suggest that HCV is associated with intrahepatic CCA. The evidence for the link between HCV and pancreatic adenocarcinoma, oral squamous cell cancer, and renal/kidney cancer is compelling but requires further study. Based on available studies, there is no significant association between HCV, extrahepatic CCA, and papillary thyroid cancer.

KEYWORDS: Cholangiocarcinoma; Hepatitis C virus; Oral squamous cell cancer; Pancreatic adenocarcinoma; Papillary thyroid cancer; Renal/kidney cancer

HCV ve DM

- HCV li hastalarda DM riski artmış

İnterferon tedavisi glukoz toleransını düzeltebilir

type

terol Hepatol. 2018 Oct 30. doi: 10.1097/MEG.0000000000001292. [Epub ahead

cting antiviral hepatitis C virus treatment perturb
bolic milieu.

Galanakis C[2], Doyle MA[1], Cooper CL[1].

nformation

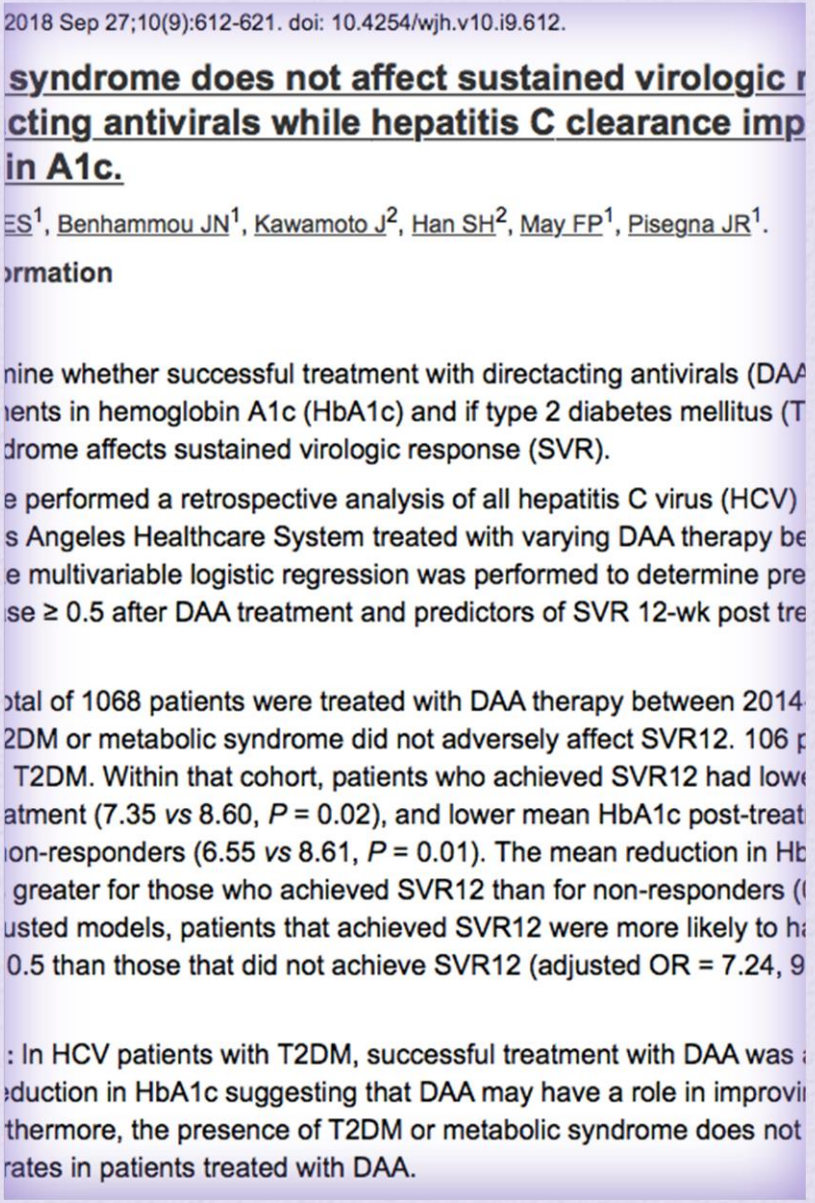
: Hepatitis C virus (HCV), cirrhosis, and HCV medications including
AAs) ±ribavirin may all influence the metabolic milieu. While interfe
prove glucose tolerance, evidence is limited on DAAs. Cases of ele
ly been reported in patients treated with DAAs, and lactic acidosis is
n of antivirals used to treat hepatitis B virus and HIV.

ND METHODS: Measures were evaluated at baseline, week 4, end
veeks after treatment. Mixed-effects modeling was used to determin
glucose and lactate over time.

n total, 442 patients were treated (mean age 56, 65% male, 72% ge
lucose did not change on or after DAA treatment from baseline (P=(
ntreated diabetes, which declined (P=0.02). Overall, there was a de
CV treatment (mean 2.4-2.1 mmol/l; P<0.001). Lactate initially increa
nd then decreased after treatment completion in male patients treat
was not observed in other groups. There was no evidence of lactic
tide use.

ON: Distinct glucose and lactate trajectories were identified without e
xicity. HCV treatment does not improve random glucose levels asid
diabetic patients.

Direkt etkili antiviral kullanımı ile HA1c düşüyor



2018 Sep 27;10(9):612-621. doi: 10.4254/wjh.v10.i9.612.

syndrome does not affect sustained virologic r
cting antivirals while hepatitis C clearance imp
in A1c.

ES[1], Benhammou JN[1], Kawamoto J[2], Han SH[2], May FP[1], Pisegna JR[1].

rmation

nine whether successful treatment with directacting antivirals (DAA
ents in hemoglobin A1c (HbA1c) and if type 2 diabetes mellitus (T
drome affects sustained virologic response (SVR).

e performed a retrospective analysis of all hepatitis C virus (HCV)
s Angeles Healthcare System treated with varying DAA therapy be
e multivariable logistic regression was performed to determine pre
se ≥ 0.5 after DAA treatment and predictors of SVR 12-wk post tre

otal of 1068 patients were treated with DAA therapy between 2014
2DM or metabolic syndrome did not adversely affect SVR12. 106 p
T2DM. Within that cohort, patients who achieved SVR12 had lowe
atment (7.35 *vs* 8.60, *P* = 0.02), and lower mean HbA1c post-treat
on-responders (6.55 *vs* 8.61, *P* = 0.01). The mean reduction in Hb
greater for those who achieved SVR12 than for non-responders (
usted models, patients that achieved SVR12 were more likely to ha
0.5 than those that did not achieve SVR12 (adjusted OR = 7.24, 9

: In HCV patients with T2DM, successful treatment with DAA was a
eduction in HbA1c suggesting that DAA may have a role in improvi
thermore, the presence of T2DM or metabolic syndrome does not
rates in patients treated with DAA.

ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld.2014.1121.273.daa

Impact of Direct Acting Antiviral (DAA) Treatment on Glucose Metabolism and Reduction of Pre-diabetes in Patients with Chronic Hepatitis C

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ABSTRACT

Background & Aim: With the development of direct acting antiviral agents (DAA) chronic hepatitis C virus (HCV) infection has become curable in most patients. Since HCV infection is known to have direct and/or indirect effects on glucose metabolism, successful HCV treatment may have an impact in reducing glucose level, pre-diabetes, the need of treatment for diabetes, and ultimately diabetes-associated morbidity. We investigated the association of DAA treatment and glucose metabolism in the context of development or resolution of hepatic fibrosis in a large cohort of HCV- infected patients.

Methods: In this retrospective single-center observational study, we investigated 281 patients receiving all-oral DAA therapy for fasting plasma glucose, HbA1c, liver enzymes and general clinical chemistry, measured during a 52-week follow-up. In addition, elastography, FIB-4- and APRI-calculation were used to assess hepatic fibrosis non-invasively.

Results: Successful elimination of HCV through DAA treatment was associated with a significant drop in fasting glucose level and a reduced rate of impaired fasting plasma glucose (FPG). Interestingly, this metabolic change was BMI-independent. In addition, long-term glucose levels also decreased after successful DAA treatment. A significant APRI-score reduction was associated with a persistent improvement of FPG. However, DAA did not have an impact on glucose metabolism in patients suffering from liver cirrhosis.

Conclusion: This study highlights the beneficial impact of successful HCV therapy on glucose metabolism and identifies patients with liver cirrhosis as a collective in need of intensified surveillance with regard to diabetes progression despite HCV eradication.

28. **Endotoxinemia contributes to steatosis, insulin resistance and atherosclerosis in chronic hepatitis C: the role of pro-inflammatory cytokines and oxidative stress.**

Zampino R[1], Marrone A[1], Rinaldi L[1], Guerrera B[1], Nevola R[1], Boemio A[1], Iuliano N[1], Giordano M[1], Passariello N[1], Sasso FC[1], Albano E[2], Adinolfi LE[3].

Author information

Abstract

PURPOSE: Endotoxin is a component of the outer membrane of gram-negative bacteria that live in the intestine. Endotoxinemia is reported in non-alcoholic fatty liver disease and in cirrhotic patients, causing various biological and clinical effects in the host. It is not known whether endotoxinemia occurs in chronic hepatitis C patients (CHC), therefore we evaluated the occurrence of endotoxinemia and its effect on inflammation, liver damage, insulin resistance (IR) and atherosclerosis.

METHODS: Consecutive CHC patients assessed by liver biopsy were enrolled. Endotoxinemia was evaluated by LAL test. IR was estimated by HOMA-IR. Serum TNF-α, IL-8, adiponectin and MCP-1 were measured with ELISA tests. Oxidative stress was estimated by circulating IgG against malondialdehyde adducts with human serum albumin (MDA-HAS). Carotid atherosclerosis was assessed by ultrasonography.

RESULTS: Endotoxinemia was found in 60% of the 126 patients enrolled. A serum level-dependent association between endotoxinemia, steatosis ($p < 0.001$) and HOMA-IR ($p < 0.006$) was observed. Patients with endotoxinemia showed significant increase in TNF-α and IL8 levels. TNF-α correlated with steatosis ($p < 0.001$) and HOMA-IR ($p < 0.03$), whereas IL8 correlated with steatosis ($p = <0.001$), TNF-α ($p < 0.04$) and atherosclerosis ($p < 0.01$). The highest levels of endotoxinemia were associated with oxidative stress and a higher prevalence of carotid atherosclerosis. Multivariate logistic regression analysis showed that the independent factors associated with endotoxinemia were hepatic steatosis, HOMA-IR, IL8 and MDA-HAS.

CONCLUSIONS: Endotoxinemia occurs with high frequency in CHC patients and contributes to the development of hepatic steatosis, IR and atherosclerosis through increased pro-inflammatory cytokines and oxidative stress. Anti-endotoxin treatment could be of clinical relevance.

- HCV nin başarılı bir şekilde antivirallerle tedavisi açlık kan şekerinde düşmeye neden olur

Table 1 The reversibility of hepatitis C virus-associated cardiometabolic diseases after viral clearance

HCV-associated cardiometabolic diseases	Reversible after viral clearance	Ref.
Hypolipidemia	Yes	[3,110,140-142]
Hepatic steatosis	Yes	[140]
Obesity	No	[110]
Glucose intolerance, insulin resistance and diabetes	No	[110,143]
	Yes	[145-148]
Cardiovascular events	No	[152]
	Yes	[153-155]

HCV: Hepatitis C virus.

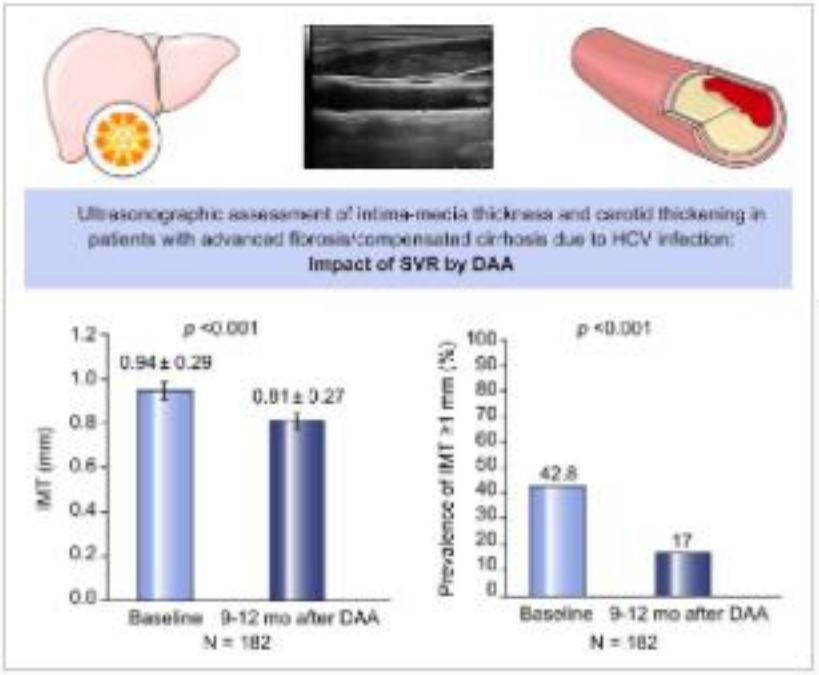
Results

All patients achieved a 12-week sustained virological response. IMT significantly decreased from baseline to follow-up (0.94±0.29mm *vs.* 0.81±0.27, $p<0.001$). Consistently, a significant reduction in the prevalence of patients with carotid thickening from baseline to follow-up was observed (42.8% *vs.* 17%, $p<0.001$), while no changes were reported for carotid plaques (42.8% *vs.* 47.8%, $p=0.34$). These results were confirmed in subgroups of patients stratified for cardiovascular risk factors and liver disease severity.

Conclusion

HCV eradication by DAA improves carotid atherosclerosis in patients with severe fibrosis with or without additional metabolic risk factors. The impact of this improvement in the atherosclerotic burden in terms of reduction of major cardiovascular outcomes is worth investigating in the long term.

Graphical abstract



Open Access Research

BMJ Open

Association between visceral obesity and hepatitis C infection stratified by gender: a cross-sectional study in Taiwan

Yu-Chung Tsao,[1,2,3,4] Jau-Yuan Chen,[3,4] Wei-Chung Yeh,[3,4] Yun-Shing Peng,[4,5] Wen-Cheng Li[6,7]

To cite: Tsao Y-C, Chen J-Y, Yeh W-C, *et al*. Association between visceral obesity and hepatitis C infection stratified by gender: a cross-sectional

ABSTRACT

Objectives The global prevalence of hepatitis C virus (HCV) is approximately 2%–3%, and the prevalence of the positive anti-HCV antibody has been increasing. Several

Strengths and limitations of this study

- Hepatitis C virus (HCV) infection is endemic to Taiwan, and we designed the study to determine

older and have lower total cholesterol levels and higher alanine aminotransferase (ALT) levels ($p<0.001$). Women with HCV infection tended to be older and have higher levels of fasting glucose and ALT ($p<0.001$). After adjusting for confounding factors, body fat percentage, fat-free mass/body weight (BW) and muscle mass/BW were found to be the independent determinants of visceral obesity in patients without HCV infection ($p<0.001$). However, the trend was not such obvious in patients with HCV infection, though still statistically significant ($p<0.05$). Furthermore, the trend was less significant in men with HCV infection.
Conclusions The findings suggested that HCV modulates host lipid metabolism and distribution to some extent, and a gender difference was also noted.

INTRODUCTION

The global prevalence of human hepatitis C virus (HCV) is approximately 2%–3%, and the prevalence of the positive anti-HCV antibody increased from 2.3% to 2.8% between 1990 and 2005.[1] HCV infection leads to chronic hepatitis in 60%–80% of infected individuals,[2] and it is associated with liver steatosis, fibrosis, cirrhosis and hepatocellular carcinoma.[3] According to data from the Liver Disease Prevention and Treatment Research Foundation, HCV prevalence in Taiwan has been estimated to be 4.4% in adults aged more than 20 years, with significant geographical variation.[4]

Abnormal fat accumulation in the liver (steatosis) is commonly observed in patients with HCV infection.[5] The two main types of steatosis in patients with HCV infection are metabolic steatosis and viral steatosis.[6] Metabolic steatosis is found in patients infected with genotype 1 and is associated with metabolic syndrome. By contrast, viral steatosis is reported in patients infected with genotype 3a but without other known steatogenic cofactors, and this type of steatosis is directly linked to the cytopathic effect of the virus. Similarly, chronic HCV infection can also induce insulin resistance.[7]

Digestion. 2017 Oct 30;96(4):228-230. doi: 10.1159/000484237. [Epub ahead of print]

104. # Hepatitis C Treatment with Sofosbuvir and Ledipasvir Accompanied by Immediate Improvement in Hemoglobin A1c.

Ikeda A[1], Ikeda K[2], Takai A[3], Takahashi K[3], Ueda Y[3], Marusawa H[3], Seno H[3], Inagaki N[2], Kokuryu H[1].

Author information

Abstract

BACKGROUND/AIMS: Direct-acting antiviral agents (DAAs) have increased the sustained viral response rate with minimal adverse effects and short treatment duration. In addition, recent data suggest the possibility that hepatitis C virus (HCV) clearance results in rapid improvement in metabolic pathways. The aim of the present study was to evaluate whether the DAA treatment without ribavirin lowers hemoglobin A1c (HbA1c) at 12 weeks after therapy completion.

METHODS: We performed an observational study to assess the effect of sofosbuvir and ledipasvir (SOF/LED) treatment on glycemic control. We compared HbA1c levels before and after treatment with SOF/LED, considering that anemia is not a side effect of these drugs.

RESULTS: In the 36 patients with HCV eradication, HbA1c levels decreased significantly after treatment (pre-treatment 5.85% vs. post-treatment 5.65%, $p < 0.01$).

CONCLUSION: This pilot study shows the possibility that HCV eradication by SOF/LED was accompanied by an improvement of glucose metabolism in the population with or without diabetes, and suggests further investigation.

Infect Dis Ther. 2017 Dec;6(4):515-529. doi: 10.1007/s40121-017-0171-0. Epub 2017 Sep 22.

121. # Effect of Hepatitis C Treatment with Ombitasvir/Paritaprevir/R + Dasabuvir on Renal, Cardiovascular and Metabolic Extrahepatic Manifestations: A Post-Hoc Analysis of Phase 3 Clinical Trials.

Mehta DA[1,2], Cohen E[3], Charafeddine M[3], Cohen DE[3], Bao Y[4], Sanchez Gonzalez Y[4], Tran TT[5].

Author information

Abstract

INTRODUCTION: We analyzed phase 3 trial data of ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) ± ribavirin (RBV) in genotype 1 chronic hepatitis C patients to investigate the impact of 3D ± RBV on renal, cardiovascular and metabolic extrahepatic manifestations (EHMs), including persistency 52 weeks post treatment and differential impact by EHM disease severity.

METHODS: Estimated glomerular filtration rate (eGFR), fasting triglyceride and fasting glucose values from clinical trials were used to assess renal, cardiovascular and metabolic EHMs, respectively. Two placebo-controlled trials were used to study the effect of treatment, while the pooled sample of treated patients was used to study the persistency and differential effect of treatment by baseline EHM disease severity, as defined by baseline values of respective EHM biomarkers. Changes in EHM outcomes from baseline were assessed with mixed models adjusting for patient baseline demographic and clinical characteristics.

RESULTS: Treatment with 3D ± RBV resulted in statistically significant declines from baseline of triglycerides and glucose and no statistical change in eGFR. By 52 weeks post treatment patients with elevated triglycerides (-35.3 mg/dl), pre-diabetes (-4.4 mg/dl), diabetes (-34.2 mg/dl) and CKD stage 3 (+1.6 ml/min/1.73 m^2) at baseline experienced a statistically significant improvement in their respective EHM values. Patients with CKD stages 2, 4 and 5 experienced no statistically significant change in eGFR from baseline.

CONCLUSION: Treatment with 3D ± RBV resulted in improvement or no worsening of cardiovascular, metabolic and renal EHM markers, especially in patients with severe EHMs at baseline, which persisted until 52 weeks post treatment.

World J Gastroenterol. 2017 Aug 21;23(31):5645-5649. doi: 10.3748/wjg.v23.i31.5645.

129. # Direct-acting antiviral agents against hepatitis C virus and lipid metabolism.

Kanda T[1], Moriyama M[2].

Author information

Abstract

Hepatitis C virus (HCV) infection induces steatosis and is accompanied by multiple metabolic alterations including hyperuricemia, reversible hypocholesterolemia and insulin resistance. Total cholesterol, low-density lipoprotein-cholesterol and triglyceride levels are increased by peginterferon and ribavirin combination therapy when a sustained virologic response (SVR) is achieved in patients with HCV. Steatosis is significantly more common in patients with HCV genotype 3 but interferon-free regimens are not always effective for treating HCV genotype 3 infections. HCV infection increases fatty acid synthase levels, resulting in the accumulation of fatty acids in hepatocytes. Of note, low-density lipoprotein receptor, scavenger receptor class B type I and Niemann-Pick C1-like 1 proteins are candidate receptors that may be involved in HCV. They are also required for the uptake of cholesterol from the external environment of hepatocytes. Among HCV-infected patients with or without human immunodeficiency virus infection, changes in serum lipid profiles are observed during interferon-free treatment and after the achievement of an SVR. It is evident that HCV affects cholesterol metabolism during interferon-free regimens. Although higher SVR rates were achieved with interferon-free treatment of HCV, special attention must also be paid to unexpected adverse events based on host metabolic changes including hyperlipidemia.

KEYWORDS: Cholesterol; Hepatitis C virus; Interferon-free; Lipid metabolism

CONCLUSION

HCV infection induces steatosis and is accompanied by multiple metabolic alterations, such as hyperuricemia, reversible hypocholesterolemia, insulin resistance, arterial hypertension and visceral adipose tissue

expansion[32-34]. Eradication of HCV with interferon-free regimens increases total cholesterol levels. Because of the worsening nutritional status as an adverse event of interferon-based regimens, it is difficult to examine the effects of HCV on serum lipid profiles[6]. It is evident that HCV affects cholesterol metabolism during interferon-free regimens because these regimens have no influence on the nutritional status of the host[6]. The increase in cholesterol levels during treatment was much greater in the sofosbuvir plus ledipasvir-SVR group than in the daclatasvir plus asunaprevir-SVR group[6,29]. Although higher SVR rates were achieved with interferon-free treatment of HCV, special attention must also be paid to unexpected adverse events based on host metabolic changes.

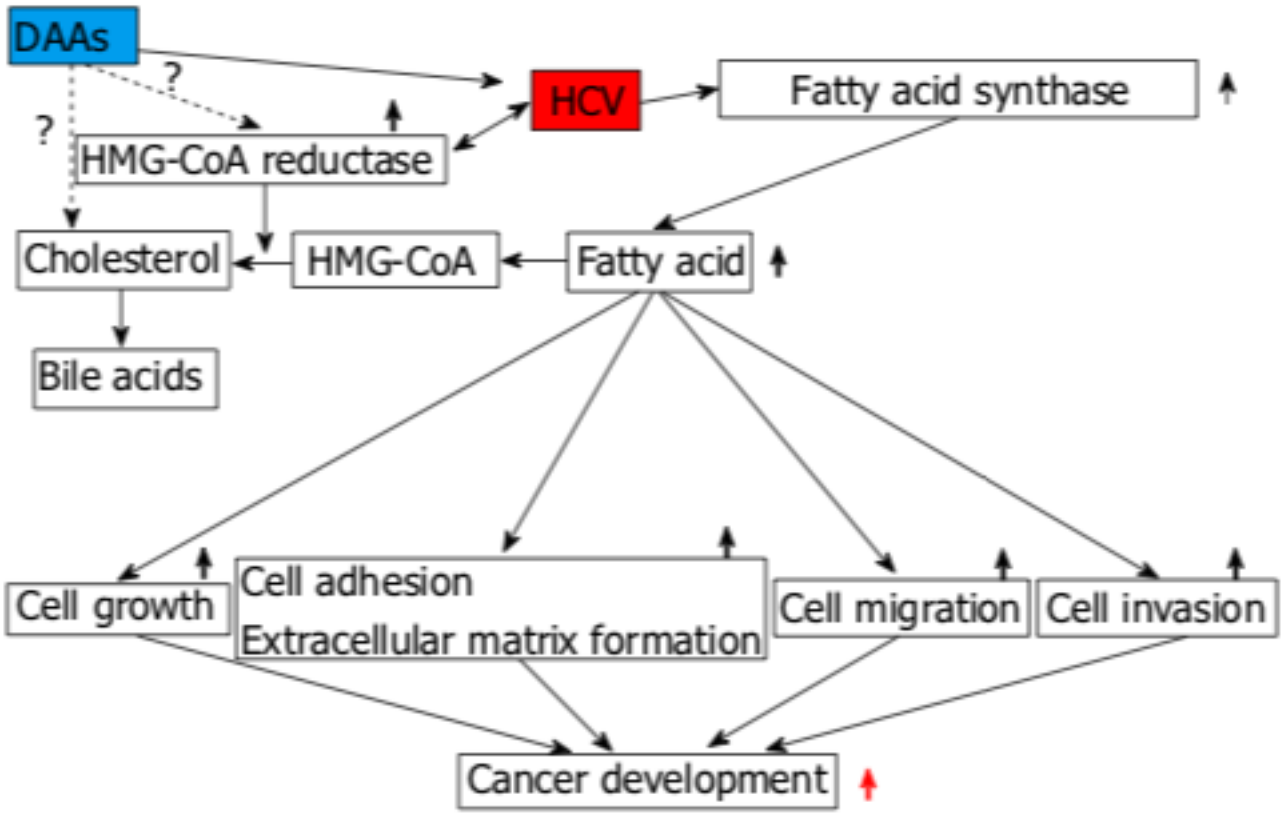


Figure 1 Hepatitis C virus and fatty acid synthesis. DAAs: Direct-acting antiviral agents; HCV: Hepatitis C virus; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

HMG-CoA reductase inhibitors, fluvastatin is an anti-HCV reagent that is used in combination with interferons[8]. Steatosis and abnormal lipid metabolism caused by HCV infection may enhance lipid droplet formation in hepatocytes[9-11]. Lipid droplets, which store neutral lipids, are required for the formation of infectious HCV particles[11].

death due to these liver diseases.

Associations of HCV with host lipoproteins have been reported[2]. Hepatocytes take up low-density lipoproteins (LDLs) and very low-density lipoproteins through LDL receptors. Antibodies to the HCV envelope may disrupt the HCV lipid-containing envelope[3]. These antibodies could provide an efficient mode of viral entry into liver cells[2]. HCV core protein colocalizes with apolipoprotein AII at the surface of lipid droplets, suggesting a relationship between the expression of HCV core protein and cellular lipid metabolism[4]. HCV infection or core protein expression also increases the expression of sterol regulatory element binding protein 1c and its target, fatty acid synthase (FASN), which are both involved in lipid synthesis[5].