Meditsiini UPDATE 2019

Gastroenteroloogia

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5. detsember 2019
Swissôtel Tallinn konverentsikeskus

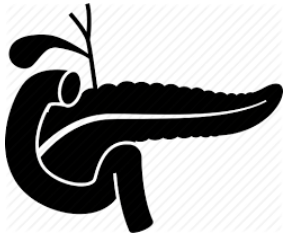
Uudised gastroenteroloogiast

- Helicobacter pylori infektsiooni uued rahvusvahelised ravijuhised
  - Management of Helicobacter pylori infection – the MaastrichtV/Florence Consensus Report; Gut 2017

- Kroonilised põletikulised soolehaigused:
  - Uued bioloogilised ravimid: vedolizumab, tofatsitinib
  - Effektiivsus endiselt < 50%

- Mikrobioom

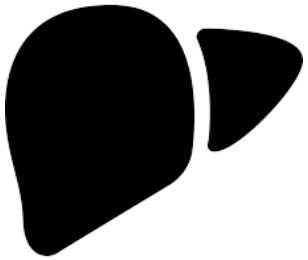
Uudised gastroenteroloogiast



- ??

- Fookus kvaliteedile
- Protseduurid muutuvad invasiivsemaks

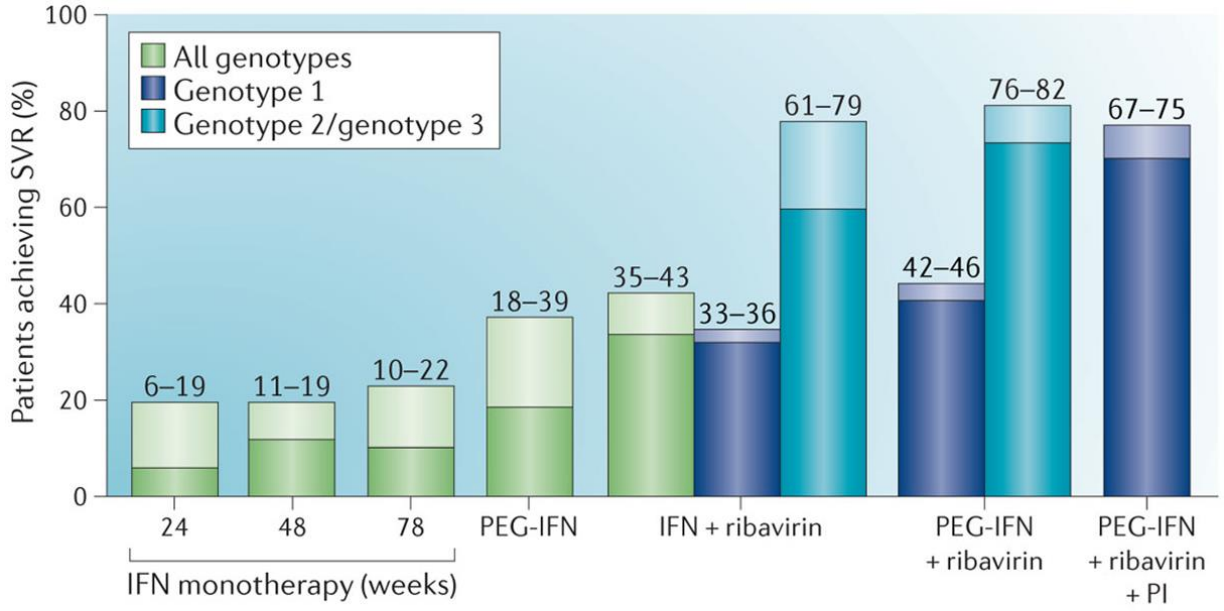
Uudised gastroenteroloogiast



- Hepatoloogia on hetkel kõige kiiremini arenev ala gastroenteroloogias
- Krooniline C – viirus hepatiit
- Mittealkohoolne maksasteatoos/steatohepatiit

Krooniline C – viirus hepatiit

- Eestis umbes 20.000 nakatunut
- 20% patsientidest tekib maksatsirros, 3% tsirroosihaigetest aastas haigestub maksavähki
- Ravi kuni aastani 2014:
  - Pikk
  - Väikese efektiivsusega
  - Tugevad kõrvaltoimed



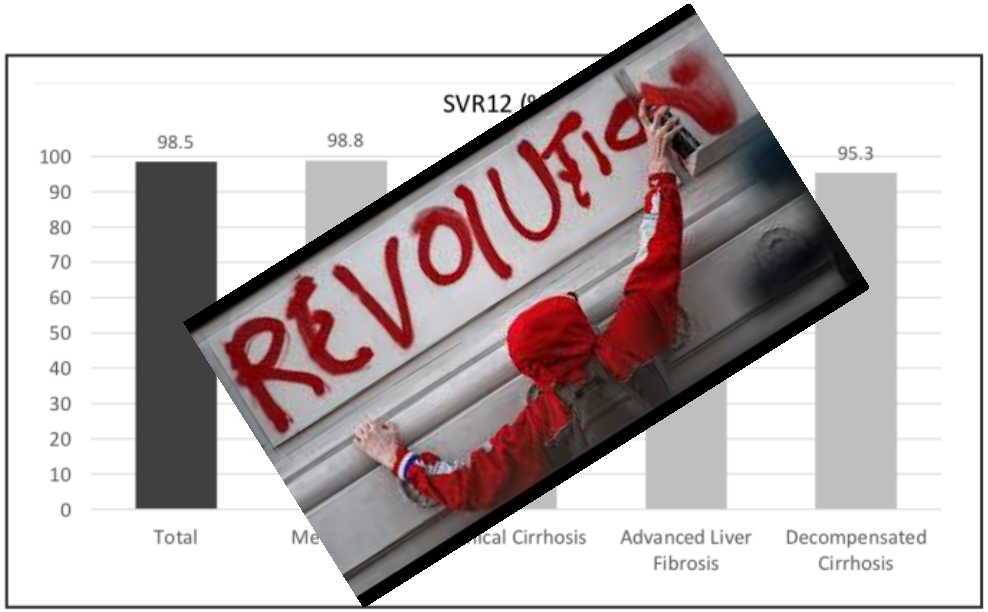
Nature Reviews | Drug Discovery

Chen SL, Int J Med Sci 2006; Manns P Nature Reviews Drug Discovery 2013

Krooniline C – viirus hepatiit

- Uued otsesed antiviraalsed ravimid (DAA)
- Ravi lühike (8 – 12 nädalat)
- Efektiivsus suur: > 95%
- Kõrvaltoimeid väga harva, kerged

- 100% kompensatsioon ≥ fibroos F2
- Hind langenud: ca. 7500€



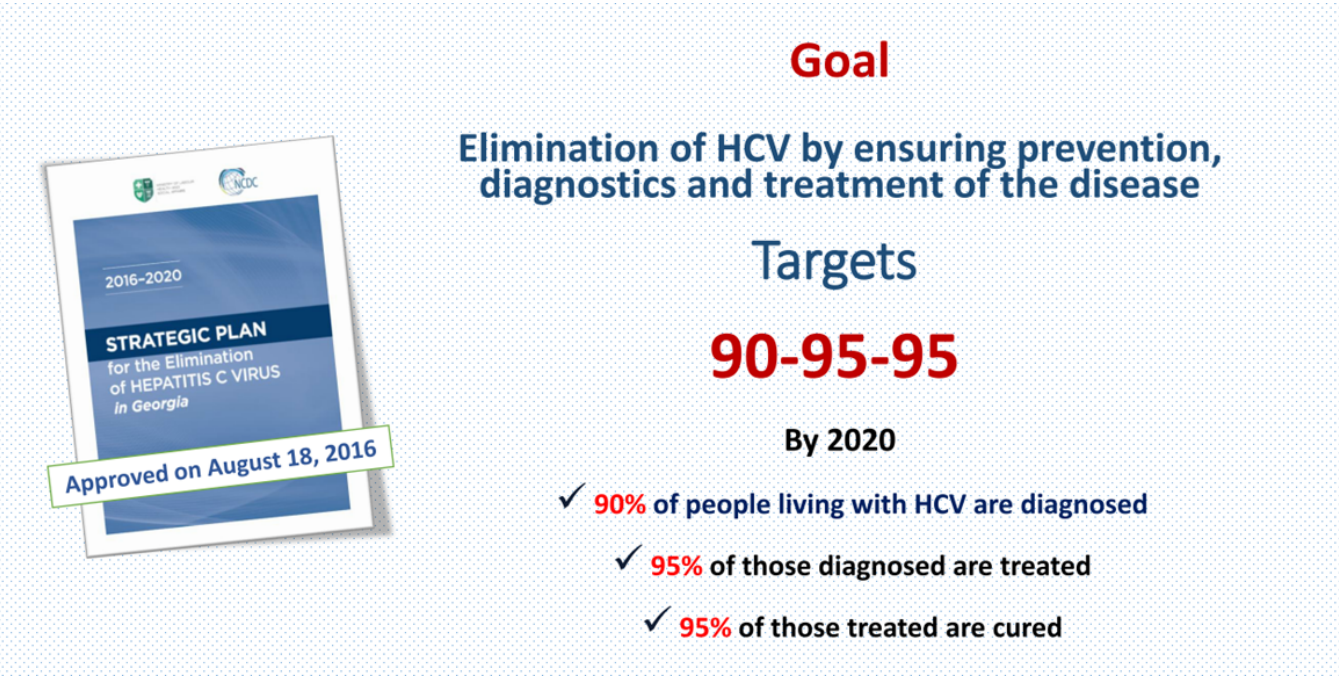
- Itaalia „real life“ kohort, 953 patsienti, GT 1-6
- 1. põlvakonna ravimid, ravi 2015 - 2018

Gentile I et al. Efficacy of the “first wave” Direct Acting antivirals against HCV infection: results from the Italian LINA (Liver Network Activity) cohort New Microbiologica , 42, 2, 94-100, 2019

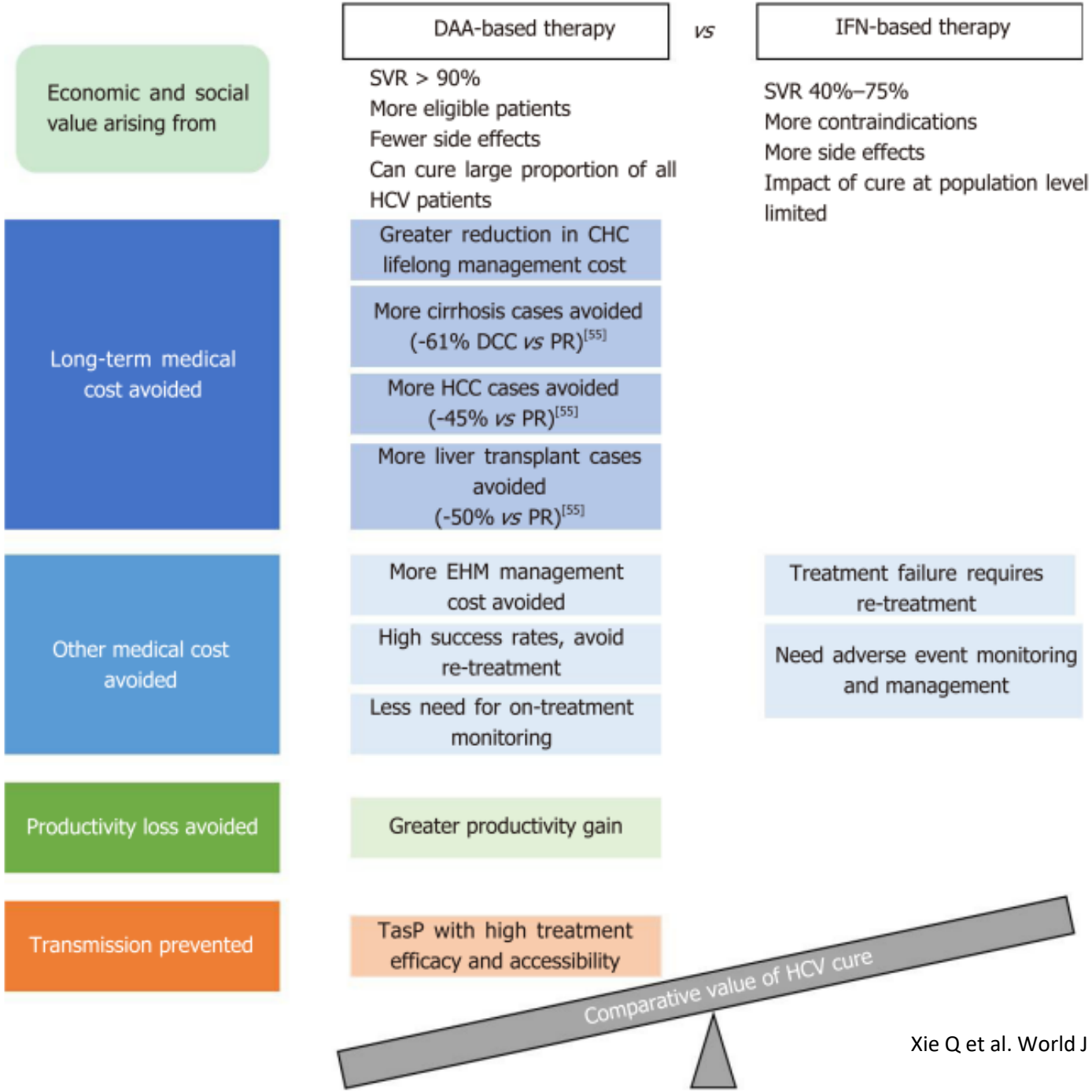
Krooniline C-viirus hepatiit

- Maailma tervise organisatsioon (WHO) eesmärk: HCV eliminatsioon aastaks 2030!

- Gruusia HCV eliminatsiooni programm
- Koostöö CDCga ja Gileadiga



- C-hepatiidi epideemia likvideerimis-strateegia eesmärgid ja tegevusplaan Eestis aastaks 2018–2030. Eesti Gastroenteroloogide Seltsi ja Eesti Infektsioonhaiguste Seltsi visioon Eesti Arst 2017; 96(4):192–193. HCV skriinig eemaldatud järgmisest tervishoiu strateegia kavast

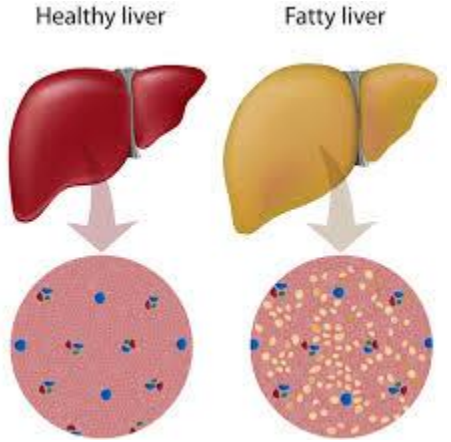


Xie Q et al. World J Hepatol 2019 May 27; 11(5): 412-488

Krooniline C – viirus hepatiit

- Probleem ei ole enam raviefektiivsuses, vaid patsientide identifitseerimises ja ravi kättesaadavuses riskirühmades (narkomaanid, kindlustamata patsiendid…)
- Skriinig: Anti HCV IgG
  - Transaminaasi tõus
  - Vereülekanne enne 1994
  - Tätoveering/piercing
  - Püsiv/varasem i/v narkootikumide tarvitamine
  - Seksuaalsed riskirühmad: homoseksuaalsed mehed

Mittealkohoolne maksasteatoos/steatohepatiit



Miks?

- Patsientide arv suur ka/eriti perearstikeskustes
- Osal patsientidest tõsine prognoos
- Hetkel puudub efektiivne ravi, ravimifirmade huvi on suur -> palju uuringuid, kiire areng

Class	Drug	Latest phase of development in NAFLD	Pre-clinical data	Clinical data
Incretin based therapy	Liraglutide (GLP-1 analogue)	Proof of concept phase IIb trial completed (approved for use in type 2 diabetes)	Improved steatosis, ALT, and insulin sensitivity; hypertension and cardiac hypertrophy also reduced [27]	Histology: NASH resolution[a] [28,32] Nonhistological: weight loss, improved diabetic control
	Exenatide (Synthetic exendin-4)	Proof of concept phase IIb trial completed in patients with NASH and diabetes (approved for use in type 2 diabetes)	Improved steatosis [26,121]	Results from phase IIb trial not published Nonhistological: Improved insulin resistance and weight loss (diabetics)[29,30]
	Sitagliptin (DDP-4 inhibitor)	Phase IIa trial in NAFLD completed Approved for use in type 2 diabetes	Improved steatosis and insulin sensitivity [122]	Histology: improved hepatocyte ballooning and reduction in NAS scores in diabetic subjects with NASH.[35] (Nonhistological studies have shown mixed results for steatosis)[36,38] and no improvement in serum markers [37,38]
SGLT-2 inhibitor	Canagliflozin Ipragliflozin Luseogliflozin	Ipragliflozin: Rodent studies completed. Luseogliflozin: Rodent studies completed (all approved for use in type 2 diabetes)	Ipragliflozin: improved steatosis, apoptosis and fibrosis [43-45] Luseogliflozin: improved steatosis and fibrosis[42]	Nonhistological: weight loss [39] and improved ALT/FLI demonstrated in trials for T2DM (Canagliflozin, Ipragliflozin) [47,48,50]
PPAR agonists	Pioglitazone (PPARγ agonist)	Phase IIb trial completed Approved for use in type 2 diabetes	Improved inflammation and fibrosis[123]	Histology: improved hepatic steatosis, inflammation, ballooning and fibrosis [57,59] Nonhistological: reduction in death, myocardial infarction and stroke in patients with T2DM
	Elafibranor (Dual PPARα/δ agonist)	Phase IIb trial in NASH completed. Global phase III trial recruiting	Improved steatosis, inflammation and fibrosis [67]	Histology: NASH resolution in those with NAS≥4[b] [69,70]
	Saroglitazar (Dual PPARα/γ agonist)	Phase IIa trial in NASH and diabetes completed. Approved for treatment of dyslipidaemia in diabetics	Reduced steatosis, NASH and fibrosis[64]	Nonhistological: improved ALT, HBA1c and serum triglycerides, improved steatosis on USS [65,66]
	MSDC -0602 (PPARγ sparing TZD)	Phase IIb	Reduced transaminases, histological NASH, and stellate cell activation [73]	Nonhistological: Improved fasting glucose and HBA1c in patients with diabetes[72]
FXR-bile acid axis	Obeticholic acid (Synthetic bile acid)	Phase IIb trial in NAFLD completed in US, Global phase III trial recruiting Approved for use in PBC in the US	Improved steatosis[124]	Histology: improved NAS scores and fibrosis[82]
	GS-9674 (Selective Farnesoid X receptor agonist)	Phase IIa recruiting	Reduce serum transaminases, hepatic steatosis and fibrosis in NASH[86]	–
	INT-767 (Dual FXR/ TGFR agonist)	Phase I trial anticipated	Improved histological NASH in mice[125]	–
	Volixibat ASBT inhibitor	Phase IIa trial in NASH recruiting	Improved glycaemic control in rats[78]; improved glucose tolerance, reduced hepatic triglyceride and total cholesterol concentrations, and improved NAFLD activity scores in mice[84]	–
	Sevelamer (Bile acid sequestrant)	Animal studies only	Reduced steatosis and lobular inflammation in mice [79]	–
Hormone signalling	BMS-986036 (Fibroblast growth factor 21 analogue)	Phase IIa trial evaluating effect on hepatic fat content measured by MRS in NASH registered but not yet recruiting	Improved insulin sensitivity, reduced hepatic fat content, and de novo lipogenesis in rats[91]	–
	NGM-282 (Recombinant FGF-19 variant)	Phase IIa trial in NASH recruiting	Reduction of hepatic fat, ALT, and improved NAS scores[93]	–
De novo lipogenesis/ lipid	Aramchol (arachidic and cholic acid conjugate)	Phase IIa complete. Phase IIb trial recruiting	Reduced *de novo* lipogenesis[104,105]	Nonhistological: reduction in liver fat content by MRS at higher dose[106]
	NDI-010796 (Acetyl Co–A carboxylase inhibitor)	Phase I trial completed. Phase II recruiting	Increased fatty acid oxidation, reduced lipogenesis and hepatic fat content, and improved insulin sensitivity in rats[107]	Nonhistological: reduced de novo lipogenesis in obese adults[108]
	MGL-3196 (thyroid hormone receptor beta (THR-β) agonist)	Phase 1 complete. Phase IIa trial recruiting	Reduced hepatic steatosis as well as reduced plasma FFA and triglycerides[110]	Reductions in LDL cholesterol of up to 30%, and trend to reduce triglycerides[109]
Antioxidant	Vitamin E	Phase IIb trials completed	Reduced steatohepatitis [126] and fibrosis[127]	Histology: reduced steatosis and improved NAS scores[c] Nonhistological: reduced ALT [59,75]
	Cysteamine (Aminothiol)	Proof of concept phase IIb trial in children with NAFLD completed	–	Results of proof of concept phase IIb trial not published Nonhistological: reduced AST, ALT and CK-18 fragment levels (children)[128]
Targeting apoptosis	Emricasan (Caspase inhibitor)	Phase IIb in NASH and NASH cirrhosis recruiting	Improved NAS score and fibrosis[101]	Nonhistological: reduced ALT and markers of apoptosis[102]
	Selonsertib (ASK-1 inhibitor)	Phase IIb trial in NASH and fibrosis and cirrhosis recruiting	Reduced hepatic fibrosis, steatosis, and insulin resistance in mice[98]	Histology: improved fibrosis demonstrated in phase IIb trial using selonsertib in combination with simtuzumab (with no additional benefit of simtuzumab)[99]
Anti-inflammatory	Cenicriviroc (C-C chemokine receptor types 2/5 antagonist)	Phase IIb trial completed. Phase III trial opening soon.	–	Histology: Did not meet primary endpoint of 2 point reduction in NAS, but reduced fibrosis (secondary endpoint)[96]
	BTT1023 (Anti-VAP antibody)	Phase IIa trial in NAFLD open	Animal data: reduced inflammatory cell recruitment and fibrosis (mice)[100]	–
Gut microbiome	IMM-124e (IgG-rich extract of bovine colostrum)	Phase IIa trial in NASH ongoing	Improved ALT and glucose tolerance[111]	–
Anti-fibrotic	Simtuzumab (LOXL2 antibody)	Phase IIb trial terminated	Reduced collagen cross linking in fibrosis models only[129]	Results of phase IIb trial in NASH and fibrosis not published Histology: no benefit from the addition of simtuzimab to selomsertib in phase IIb combination trial[99]
	GR-MD-02 (Galectin inhibitor)	Phase IIa trial completed, further proof of concept phase IIb in NASH related cirrhosis and portal hypertension ongoing	Reduced hyaluronic acid in mice[116]	Results of phase IIa trial not published

Townsend SA: Aliment Pharmacol Ther. 2017;46:494 – 507.

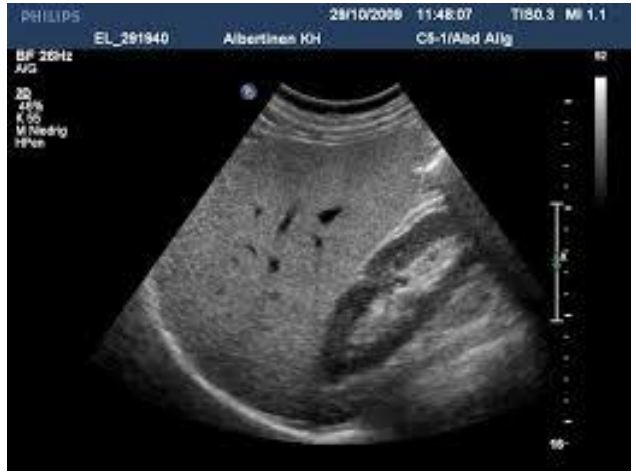
Mittealkohoolne maksasteatoos/steatohepatiit

Definitsioon:

- Rasvasisaldus maksakoes > 5% (ultraheli sensitiivsus rasvmaksale ületab 50% alates 30% rasvumisest!)

- „Signifikantne“ alkoholitarvitamine välistatud: (♂: 30g/p, ♀: 20g/p)

- Sekundaarne maksasteatoosi põhjus välistatud



Most common concurrent diseases

- AFLD-Alcoholic fatty liver disease
- Drug-induced fatty liver disease
- Hepatitis C virus-associated fatty liver (genotype 3)
- Others
  - Haemochromatosis
  - Autoimmune hepatitis
  - Coeliac disease
  - Wilson’s disease

Mittealkohoolne maksasteatoos/steatohepatiit

Mittealkohoolne rasvmaks (NAFLD)

	Maksasteatoos	Steatohepatiit (NASH)	Maksatsirroos
	- Steatoos	- Steatoos - Põletik - „Ballooning“ -±Fibroos - Maksavähk	- Tüsistused - Maksavähk
Esinemissagedus:	- 25%	- 3% (10% maksasteatoosist)	- 0,3 – 0,5% (10-25% NASHist)
Patsiente Eestis:	- 250.000	- 30.000	- 3000 - 7500

Chalasani N et al: The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases HEPATOLOGY, Vol. 67, No. 1, 2018

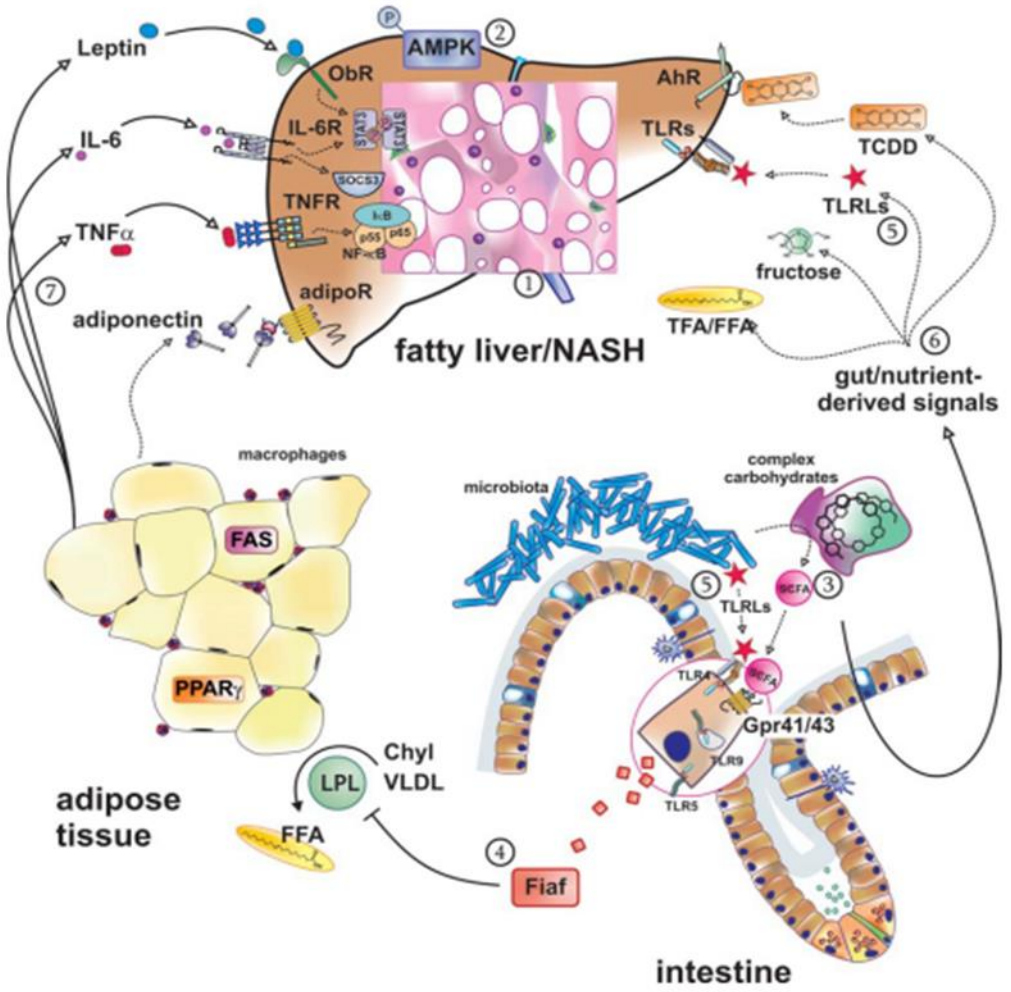
Patofüsioloogia

Maksasteatoos:

- positiivne energiabilanss -> triglütseriidide ladestumine maksarakkudesse
- Insuliinresistentsus -> vähendatud lipolüüs

Steatohepatiit (NASH):

- Proinflammatoorsed signaalid rasvkoest ja soolest
- Fruktoos
- Mikrobioom

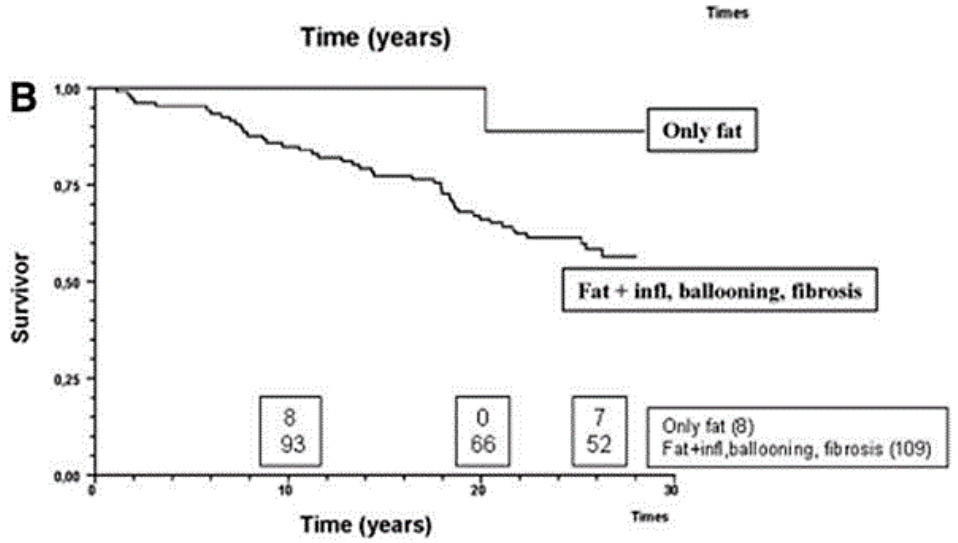


Tilg et al. Hepatology 2010

Mittealkohoolne maksasteatoos/steatohepatiit

Söder C et al. Hepatology 2010:

- 118 rasvmaksa patsienti : 28 aastat jälgimine
- NASHi patsientidel oluliselt halvem prognoos



Surmapõhjused:

1. Kardiovaskulaarsed haigused
2. Ekstrahepaatilised malignoomid
3. Maksaga seotud haigused

(üldpopulatsioonis 12. kohal!)

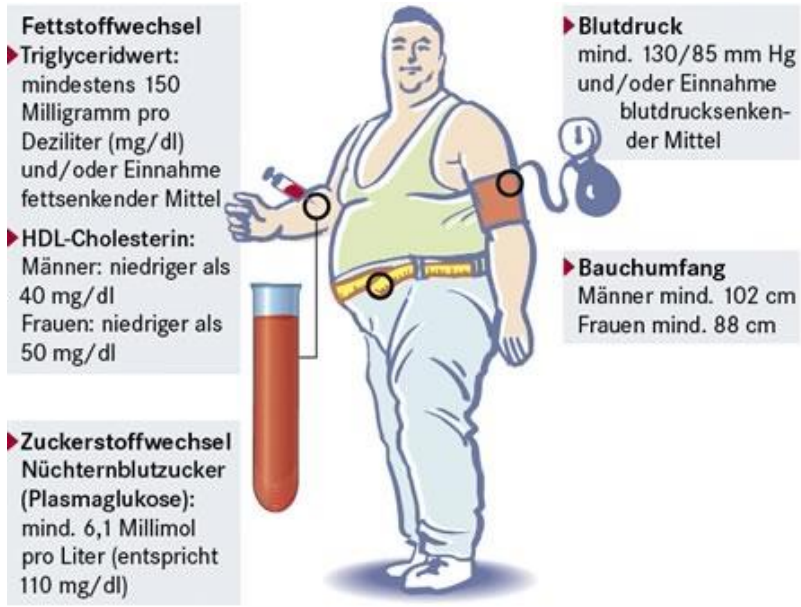
Table 5. The Cause of Death in the Deceased Patients with NAFLD

	Stage of Fibrosis					
Cause of Death	1	2	3	4	0	Missing
Cirrhosis			2	1		1
Perforation of intestine	1					
Liver cancer	1		1	3		
Extrahepatic cancer	2	6	1	2	1	
Diabetes		2			1	
Cardiovascular	4	6	3	1	1	
Alcohol abuse	1					
Poisoning/accident	1			1	1	

The number of patients with fibrosis stage 0–4 is given for each group of patients with a specific cause of death.

Maksasteatoos – metaboolne sündroom

- Marchesini et al. 2003, Hepatology
  - Metaboolse sündroomi esinemissagedus :
    - Tavapopulatsioonis: 22%
    - Maksasteatoosi haigetel (N: 43): 53%
    - NASH haigetel (N: 120): 88%
  - Maksasteatoos pluss metaboolne sündroom
    - → suurenenud NASHi risk (OR 3,2)
    - → suurenenud risk raskele fibroosile (OR 3,5)



Maksasteatoos – kardiovaskulaarsed haigused

- 2839 patsienti II. tüübi diabeediga
  - Maksasteatoos 69,5% patsientidest
- Maksasteatoosi olemasolu on sõltumatu arteroskleroosi riskifaktor

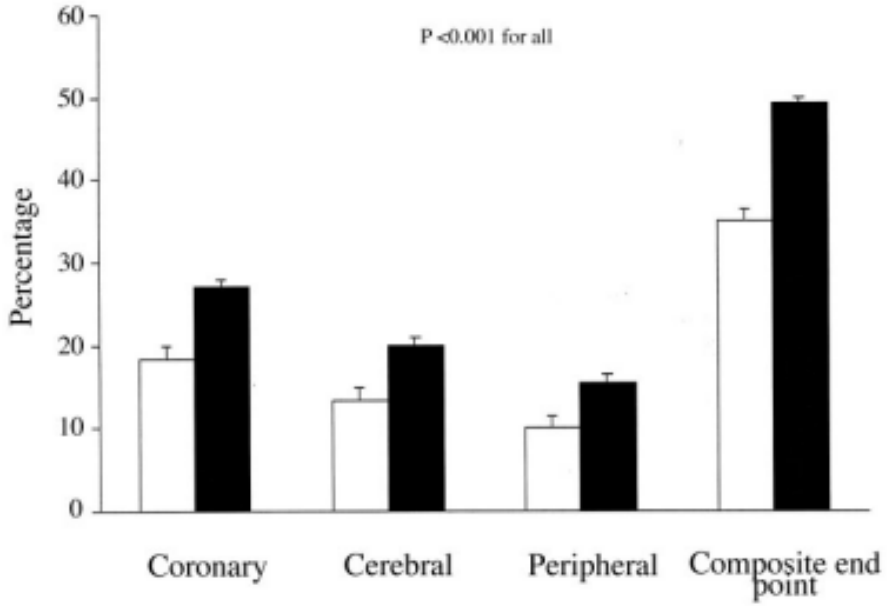


Figure 2—*Age- and sex-adjusted prevalence of CVD in type 2 diabetic adults with (■) and without (□) NAFLD. Data are expressed as percentages ± SE. P < 0.001 for differences between the groups.*

Targher G et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007 May;30(5):1212-8

Steatohepatiit – maksahaiguse progressioon

- Fibroosi progressioon on seotud
- Metaboolse sündroomi olemasoluga
- Vanusega

- Steatohepatiit põhjustab > 50% „krüptogeensetest“ tsirroosidest

- Steatohepatiit: kõrge maksavähirisk ka patsientidel, kellel tsirroosi ei ole!

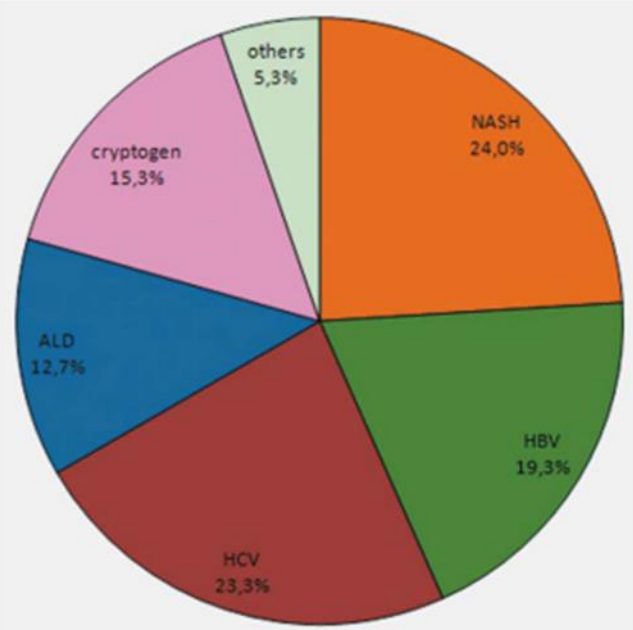


Figure 2. Etiologies of underlying liver disease for hepatocellular carcinoma (HCC). HCCs were most commonly associated with chronic viral hepatitides. The second leading cause for HCC was non-alcoholic steatohepatitis (NASH) (24%), while only 13% had alcoholic steatohepatitis.

- 162 HCC patsienti, NASH 2. kõige sagedasem põhjus
- 42% NASHi haigetest ilma tsirroosita

Ertle J et al. International Journal of Cancer 2010

Steatohepatiit – maksasiirdamine

- NASH on USAs juba 3. kõige sagedasem maksasiirdamise näidustus
- Kõige kiiremini kasvav maksasiirdamise näidustus

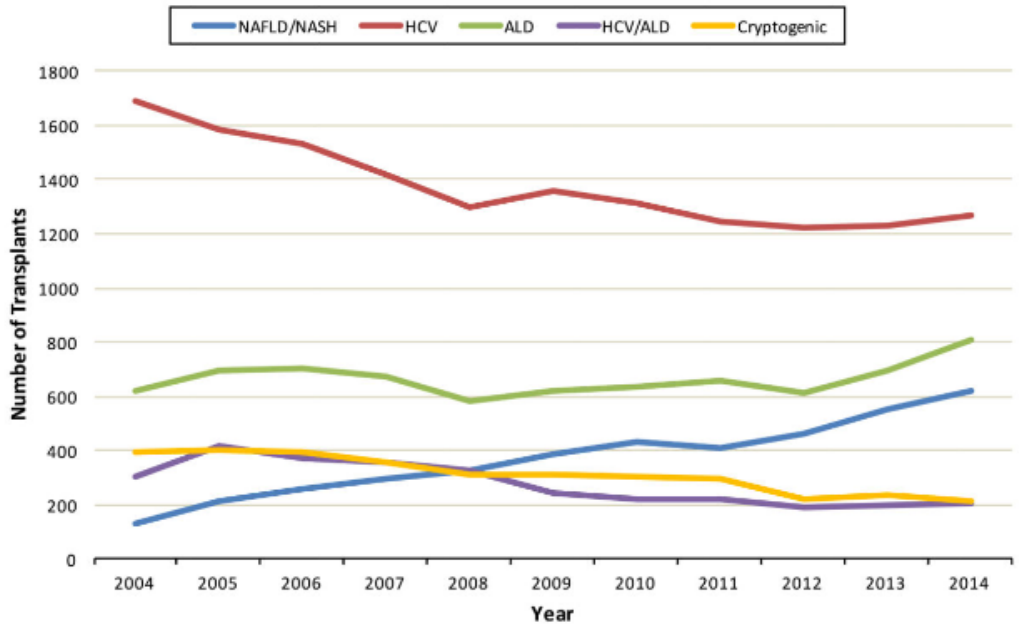


Fig. 1.
Annual trends in the number of adult liver transplants performed in the USA between 2004 and 2014 by etiology. Based on Organ Procurement and Transplantation Network (OPTN) data as of October 5, 2015. Data for hepatocellular carcinoma are not included

Patel J et al. Nonalcoholic Fatty Liver Disease: Key Considerations Before and After Liver Transplantation. Dig Dis Sci. 2016 May ; 61(5): 1406–1416

Mittealkohoolne maksasteatoos/steatohepatiit

- Vahekokkuvõte:
  - Maksasteatoos väga sage probleem (25% elanikest)
  - Eriti steatohepatiidi (NASHi) haigetel on suurem kardiovaskulaarne ja maksaga seotud haigestumus ja suremus (10% maksasteatoosi haigetest)

- Küsimused:
  - Kas otsida (skriinida) maksasteatoosi ülekaalulistel patsientidel, diabeetikutel?
  - Kuidas diagnoosida steatohepatiiti (histoloogiline diagnoos)? Igalt patsiendilt maksabiopsia?
  - Kuidas/kui tihti jälgida maksahaigust? Maksavähi skriining?
  - Ravi?

Mittealkohoolne maksasteatoos - ravijuhised

Clinical Practice Guidelines

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Journal of Hepatology **2016** vol. 64 | 1388–1402

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Naga Chalasani,[1] Zobair Younossi,[2] Joel E. Lavine,[3] Michael Charlton,[4] Kenneth Cusi,[5] Mary Rinella,[6] Stephen A. Harrison,[7] Elizabeth M. Brunt,[8] and Arun J. Sanyal[9]

Mittealkohoolne maksasteatoos/steatohepatiit

- Metaboolse sündroomi skriining kõikidel maksasteatoosi haigetel
- Püsiva maksanäitajate tõusuga patsientidel otsida põhjust , s.h. välistada maksasteatoos
- Maksasteatoosi skriining ülekaalulistel ja metaboolse sündroomiga patsientidel: ALT, AST, GGT, ultraheli

Maksasteatoos - diagnostika

- Baasprogramm
  - Anamnees
  - ALT, AST, GGT
  - B-/C-hepatiidi seroloogia
  - Ultraheli maksast
- Selle alusel tihti juba maksasteatoosi kahtlus
- Kinnitamiseks ja fibroosi/NASHi välistamiseks suunata gastroenteroloogi vv-le

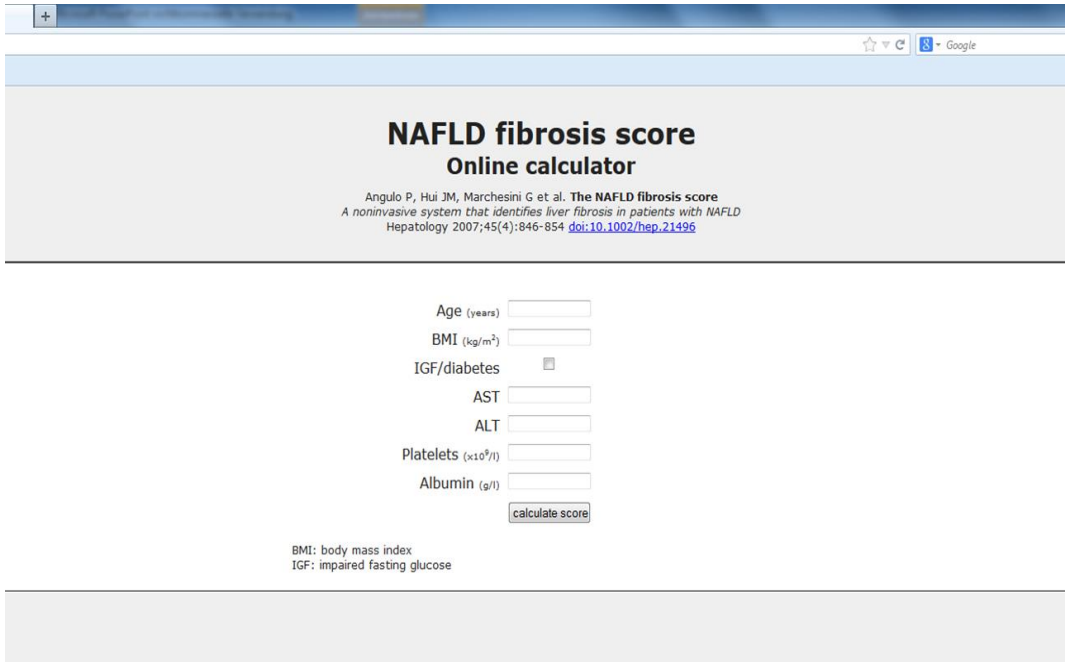
Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

Level		Variable
Initial	1.	Alcohol intake: <20 g/day (women), <30 g/day (men)
	2.	Personal and family history of diabetes, hypertension and CVD
	3.	BMI, waist circumference, change in body weight
	4.	Hepatitis B/Hepatitis C virus infection
	5.	History of steatosis-associated drugs
	6.	Liver enzymes (aspartate and alanine transaminases (γ-glutamyl-trans-peptidase))
	7.	Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR])
	8.	Complete blood count
	9.	Serum total and HDL-cholesterol, triacylglycerol, uric acid
	10.	Ultrasonography (if suspected for raised liver enzymes)
Extended *	1.	Ferritin and transferrin saturation
	2.	Tests for coeliac and thyroid diseases, polycystic ovary syndrome
	3.	Tests for rare liver diseases (Wilson, autoimmune disease, α1-antitrypsin deficiency)

*According to a priori probability or clinical evaluation.

Steatohepatiidi (NASH) diagnoos

- NASH on histoloogiline diagnoos, aga me ei saa 25% elanikest teha maksabiopsiat
- Head mitteinvasiivsed markerid puuduvad
- Kaudne marker: fibroos!
- Elastograafia:



- Fibroosi ei ole: < - 1,455 NPV: 88-93%
- Raske fibroos: > 0,676 PPV: 82-90%

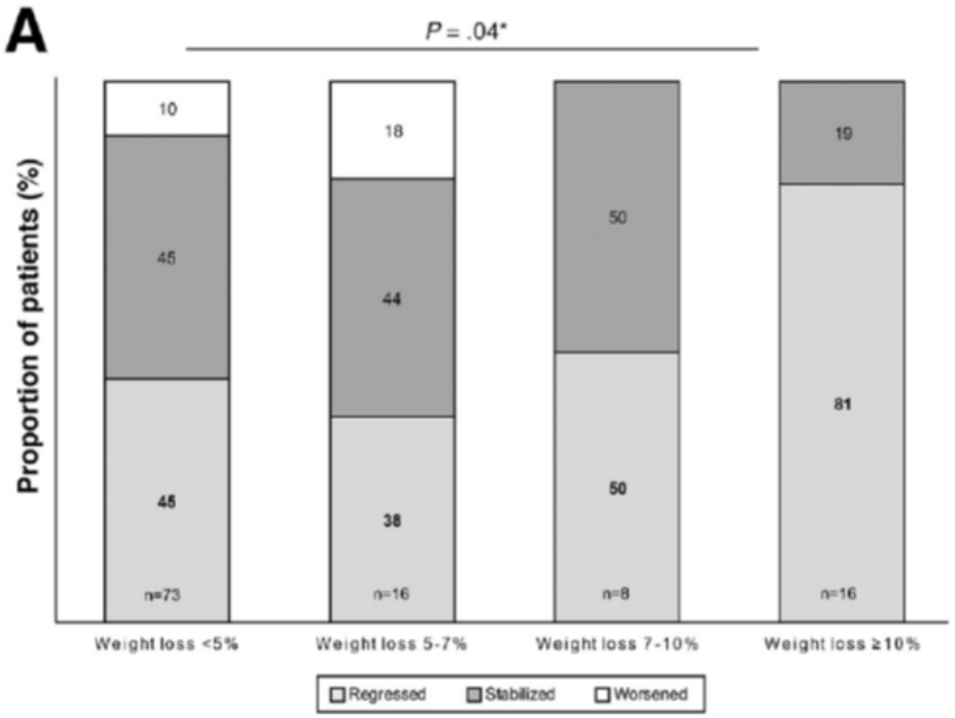
Maksasteatoosi ravi

- Hetkel tõestatud medikamentoosset ravi ei ole

- Oluline: metaboolse sündroomi/kardiovaskulaarsete haiguste optimaalne ravi
  - Nii statiine kui ka metformiini võib patsientidele määrata (düslipideemia/diabeedi ravi eesmärgil)!!
  - Ravi statiiniga katkestada 10 x transaminaaside tõusu puhul või püsiva 5 x transaminaaside tõusu puhul
  - Metformin: kliiniliselt relevantne maksakahjustus: < 10 juhtumit maailmas kirjeldatud. Võimalik positiivne mõju maksasteatoosile.

Maksasteatoosi ravi: elustiili muutus

- Kaalu langetamine vähendab maksasteatoosi!!
  - 337 patsienti steatohepatiidiga
  - 52 nädalat interventsioon: dieet pluss aeroobne trenn 200 min/nädalas
  - Maksabiopsia enne ja pärast interventsiooni
  - Kriitiline piir: vähemalt 7% kaalulangust
  - Vähemalt 5% kaalulangust saavutasid ainult 30% patsientidest



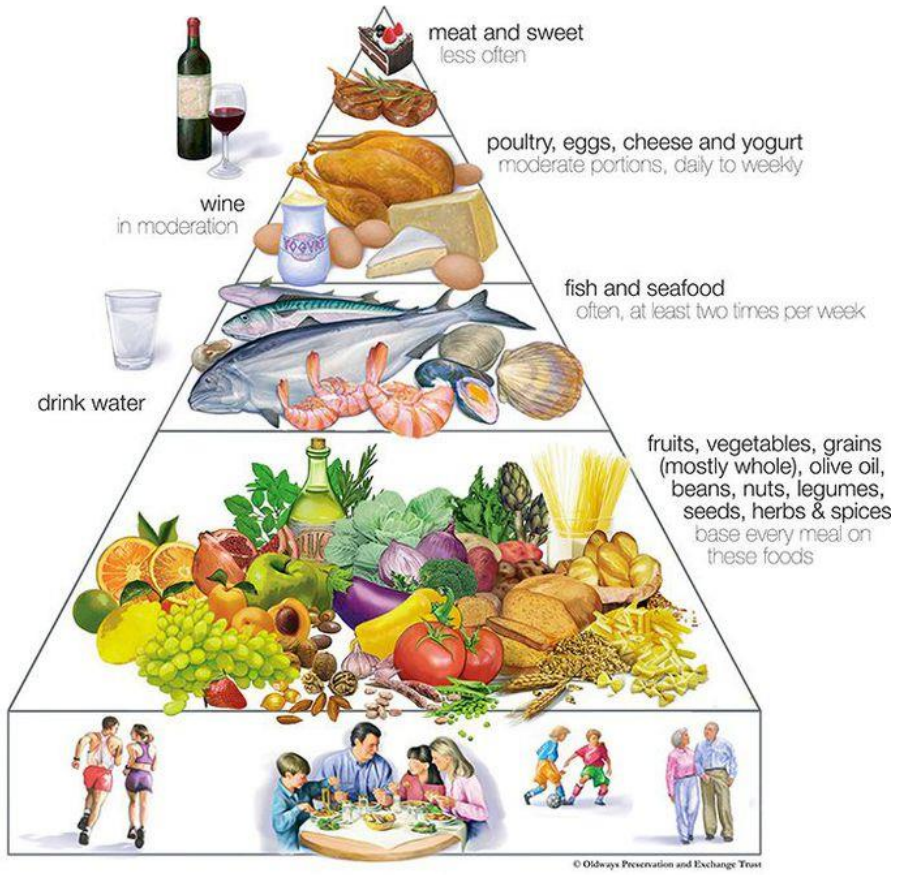
Vilar-Gomez E et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015 Aug;149(2)

Maksasteatoosi ravi: elustiili muutus

- Kaalu langetamine 7 - 10% kehakaalust 6-12 kuu jooksul

- Dieet:
  - Vähendada kaloraazi 500 – 1000kcl võrra päevas
  - Vahemere dieet (palju köögivilju, kiudaineid, kala (omega-3)
  - Fruktoosi mitte tarvitada!
  - Alkoholi tarvitamist piirata
  - Juua kohvi (2-3 tassi päevas)

- Liikuda
  - aeroobne trenn 150 - 200 min nädalas



Maksasteatoosi ravi: bariaatriline kirurgia

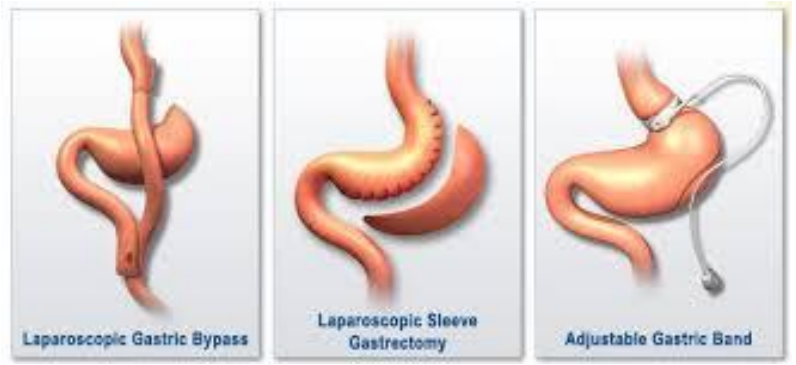
- Maksasteatoos/steatohepatiit **ei ole** bariaatrilise kirurgia näidustus, aga:
- Erinevad uuringud näitavad maksasteatoosi olulist positiivset dünaamikat pärast bariaatrilist lõikust
- Metaanalüüs:
  - Steatoosi paranemine: 88% patsientidest
  - NASHi paranemine: 59% patsientidest
  - Fibroosi paranemine: 30% patsientidest

Eesti Haigekassa võtab inimeselt ravi eest tasumise kohustuse üle juhul kui on täidetud sellised tingimused:

Eesti Haigekassa kindlustatu, kehamassiindeks (BMI) *>40 kg/m2* või kehamassiindeks (BMI) *>35 kg/m2* koos olulise ülekaaluga seotud haigusega, mis eeldatavasti leevendub operatsiooni järgselt, näiteks:

- II tüüpi diabeet
- Hüpertoonia
- Obstruktiivne uneapnoe
- Degeneratiivne liigeshaigus
- Metaboolne häire (hüperlipideemia jt.)

Nende tingimuste puudumisel tuleb ravi eest tasuda inimesel endal.



Fakhry et al. Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis. Surg Obes Relat Dis. 2019 Mar;15(3):502-511

Class	Drug	Latest phase of development in NAFLD	Pre-clinical data	Clinical data
Incretin based therapy	Liraglutide (GLP-1 analogue)	Proof of concept phase IIb trial completed (approved for use in type 2 diabetes)	Improved steatosis, ALT, and insulin sensitivity; hypertension and cardiac hypertrophy also reduced [27]	Histology: NASH resolution[a] [28,32] Nonhistological: weight loss, improved diabetic control
	Exenatide (Synthetic exendin-4)	Proof of concept p… completed in patie… and diabetes (app… type 2 diabetes)		
	Sitagliptin (DDP-4 inhibitor)	Phase IIa trial in NA… Approved for use … diabetes		
SGLT-2 inhibitor	Canagliflozin Ipragliflozin Luseogliflozin	Ipragliflozin: Roden… completed. Luseogliflozin: Ro… completed (all app… type 2 diabetes)		
PPAR agonists	Pioglitazone (PPARγ agonist)	Phase IIb trial comp… Approved for use … diabetes		
	Elafibranor (Dual PPARα/δ agonist)	Phase IIb trial in NA… Global phase III tr…		
	Saroglitazar (Dual PPARα/γ agonist)	Phase IIa trial in NA… diabetes complete… Approved for trea… dyslipidaemia in d…		
	MSDC -0602 (PPARγ sparing TZD)	Phase IIb		
FXR-bile acid axis	Obeticholic acid (Synthetic bile acid)	Phase IIb trial in NA… in US, Global phas… recruiting Approved for use … US		
	GS-9674 (Selective Farnesoid X receptor agonist)	Phase IIa recruiting		
	INT-767 (Dual FXR/ TGFR agonist)	Phase I trial anticipated	Improved histological NASH in mice[125]	–
	Volixibat ASBT inhibitor	Phase IIa trial in NASH recruiting	Improved glycaemic control in rats[78]; improved glucose tolerance, reduced hepatic triglyceride and total cholesterol concentrations, and improved NAFLD activity scores in mice[84]	–
	Sevelamer (Bile acid sequestrant)	Animal studies only	Reduced steatosis and lobular inflammation in mice [79]	–

Class	Drug	Latest phase of development in NAFLD	Pre-clinical data	Clinical data
Hormone signalling	BMS-986036 (Fibroblast growth factor 21 analogue)	Phase IIa trial evaluating effect on hepatic fat content measured by MRS in NASH registered but not yet recruiting	Improved insulin sensitivity, reduced hepatic fat content, and de novo lipogenesis in rats[91]	–
	NGM-282	Phase IIa trial in NASH recruiting	Reduction of hepatic fat, ALT, and …d NAS scores[93]	–
			…de novo …sis[104,105]	Nonhistological: reduction in liver fat content by MRS at higher dose[106]
			… fatty acid oxidation, …lipogenesis and hepatic …ent, and improved insulin …ty in rats[107]	Nonhistological: reduced de novo lipogenesis in obese adults[108]
			…hepatic steatosis as well …ed plasma FFA and …ides[110]	Reductions in LDL cholesterol of up to 30%, and trend to reduce triglycerides[109]
			…steatohepatitis [126] and …27	Histology: reduced steatosis and improved NAS scores[c] Nonhistological: reduced ALT [59,75]
				Results of proof of concept phase IIb trial not published Nonhistological: reduced AST, ALT and CK-18 fragment levels (children)[128]
			… NAS score and …01	Nonhistological: reduced ALT and markers of apoptosis[102]
			…hepatic fibrosis, …, and insulin resistance …a	Histology: improved fibrosis demonstrated in phase IIb trial using selonsertib in combination with simtuzumab (with no additional benefit of simtuzumab)[99]
				Histology: Did not meet primary endpoint of 2 point reduction in NAS, but reduced fibrosis (secondary endpoint)[96]
			…ta: reduced …atory cell recruitment …osis (mice)[100]	–
			… ALT and glucose …e[111]	–
Anti-fibrotic	Simtuzumab (LOXL2 antibody)	Phase IIb trial terminated	Reduced collagen cross linking in fibrosis models only[129]	Results of phase IIb trial in NASH and fibrosis not published Histology: no benefit from the addition of simtuzimab to selomsertib in phase IIb combination trial[99]
	GR-MD-02 (Galectin inhibitor)	Phase IIa trial completed, further proof of concept phase IIb in NASH related cirrhosis and portal hypertension ongoing	Reduced hyaluronic acid in mice[116]	Results of phase IIa trial not published

Väga erinevad toimemehanismid:

- Glükoosimetabolism: inkretiinanaaloga, SGLT-2 inhibitorid, PPAR agonistid
- Sapphappe retseptor agonistid
- Apoptoosi inhibiitorid
- Põletikuvastased ravimid
- Fibroosi vastased ravimid

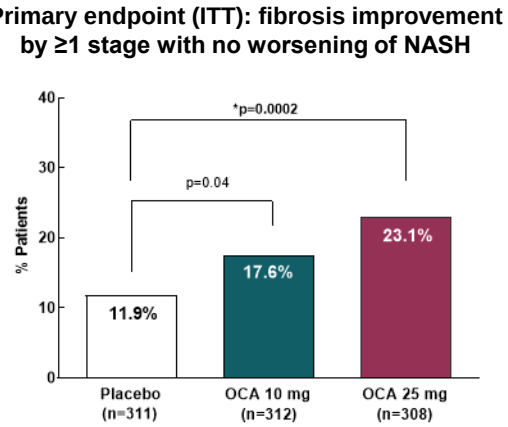
Ilmselt ei piisa ühest ravimist – vajalikud on kombineeritud toimemehhanismid

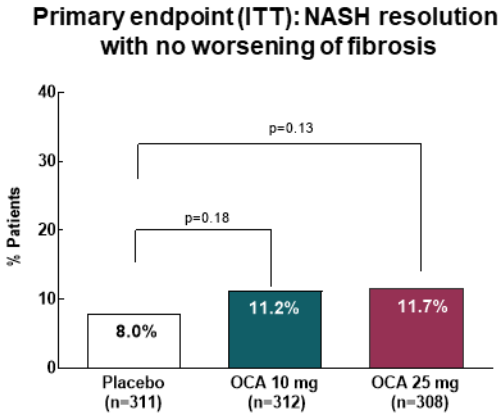
Ida-Tallinna-Keskhaigla:
Alates veebruarist 2020: 2. faasi kliiniline uuring
Aastaks 2020/2021 plaanis 3. faasi kliiniline uuring

Townsend SA: Aliment Pharmacol Ther. 2017;46:494 – 507.

Maksasteatoos – ravi: Obetihoolhape

- FXR retseptori agonist (sapphappe retseptor)
- Aktiveerimine parandab glükoosi metabolismi; lisaks põletikuvastane ja fibroosivastane toime
- Euroopa maksanädal 2019: 3. faasi uuring tulemused („REGENERATE“): 1,5 aasta etapp analüüs
- Kõrvaltoimed: LDL tõus, sügelus





- 2. näidustus: primaarne biliaarne kolangiit (Ocaliva®)
  - 1kuu ravi Saksamaal: 3079€
  - Odavam palgata füsioterapeute ja toitumisnõustajaid?!

Kokkuvõte

- Hetkel on hepatoloogia gastroenteroloogia kõige kiiremini arenev eriala
- C- viirus hepatiit: probleem ei ole enam raviefektiivsuses, vaid patsientide identifitseerimises ja ravi kättesaadavuses. Riskirühmad: määrata Anti-HCV IgG
- Maksasteatoos/steatohepatiit:
  - Sage, põhiprobleem kardiovaskulaarne haigestumus ja suremus
  - Steatohepatiit: võib areneda tsirroosiks; kõrgem maksavähirisk
  - Medikamentoosne ravi tuleb, hetkel: elustiili muutus, optimaalne metaboolse sündroomi ja kardiovasulaarsete haiguste ravi
  - Jälgimine:
    - Maksasteatoos: perearst (gastroenteroloog iga 3-5 aasta tagant)
    - Steatohepatiit (NASH): gastroenteroloog iga 6 – 12 kuu tagant