Etyolojilere Göre Karaciğer Nakli Yönetimi

Viral Hepatit Dışı Karaciğer Hastalıkları

Metabolik Hastalıklar

(NASH, Wilson Hastalığı, Hemokromatoz)

Prof. Dr. Kadir Demir
İstanbul Tıp Fakültesi,
İç Hastalıkları Anabilim Dalı
Gastroenterohepatoloji Bilim Dalı

Hemokromatoz (Herediter) - Tx

- Pre-Tx
  - Hemokromatozda karaciğer Tx neyi değiştiriyor?
  - Kalp ile birlikte mi yapılmalı?

Wilson Hastalığı - Tx

- Wilson Hstalığında Tx neyi değiştiriyor
- Pre- Tx
  - Akut Karaciğer Yetmezliğinde Tanı
  - Akut Karaciğer Yetmezlikli Wilson hastasında Tx indikasyonu
  - Nöropsikiyatrik Wilson hastasında Tx ???
- PEROPERATİF.....
- Post- Tx
  - Nöropsikiyatrik Wilson hastasında yanıt
  - İmmunsupresifler ile nörolojik sorunlar?

NAFLD - Tx

- ***Pre-Tx***
  - KardiyoVasküler Hastalık (KVH)
  - Obezite
  - Diyabet
- ***Post-Tx***
  - Nüks ("Recurrent")
  - *Yeni ("De novo")*
    - POST-TRANSPLANT METABOLİK

NAFLD / Wilson Hastalığı / Herediter Hemokromatoz

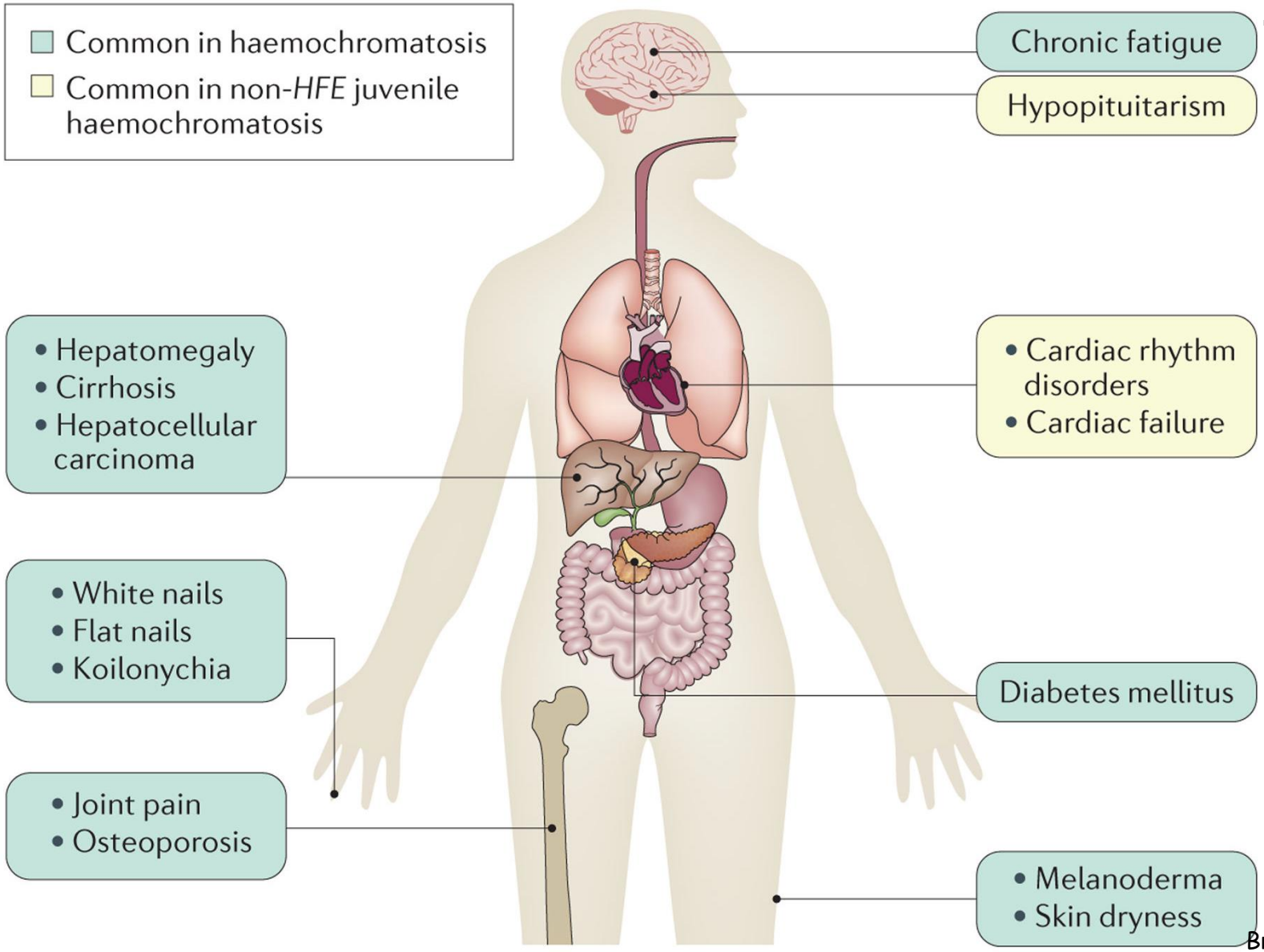
---------- PATOFİZYOLOJİSİ BİLİNMELİ ------

- .....PEROPERATİF.....
  - Hipertansiyon

Hemokromatoz (Herediter) - Tx

- Pre-Tx
  - Hemokromatozdakaraciğer Tx neyi değiştiriyor?
  - Kalp ile birlikte mi yapılmalı?

Herediter Hemokromatoz - Klinik



Ölüm nedenleri:

Kardiyomiyopati

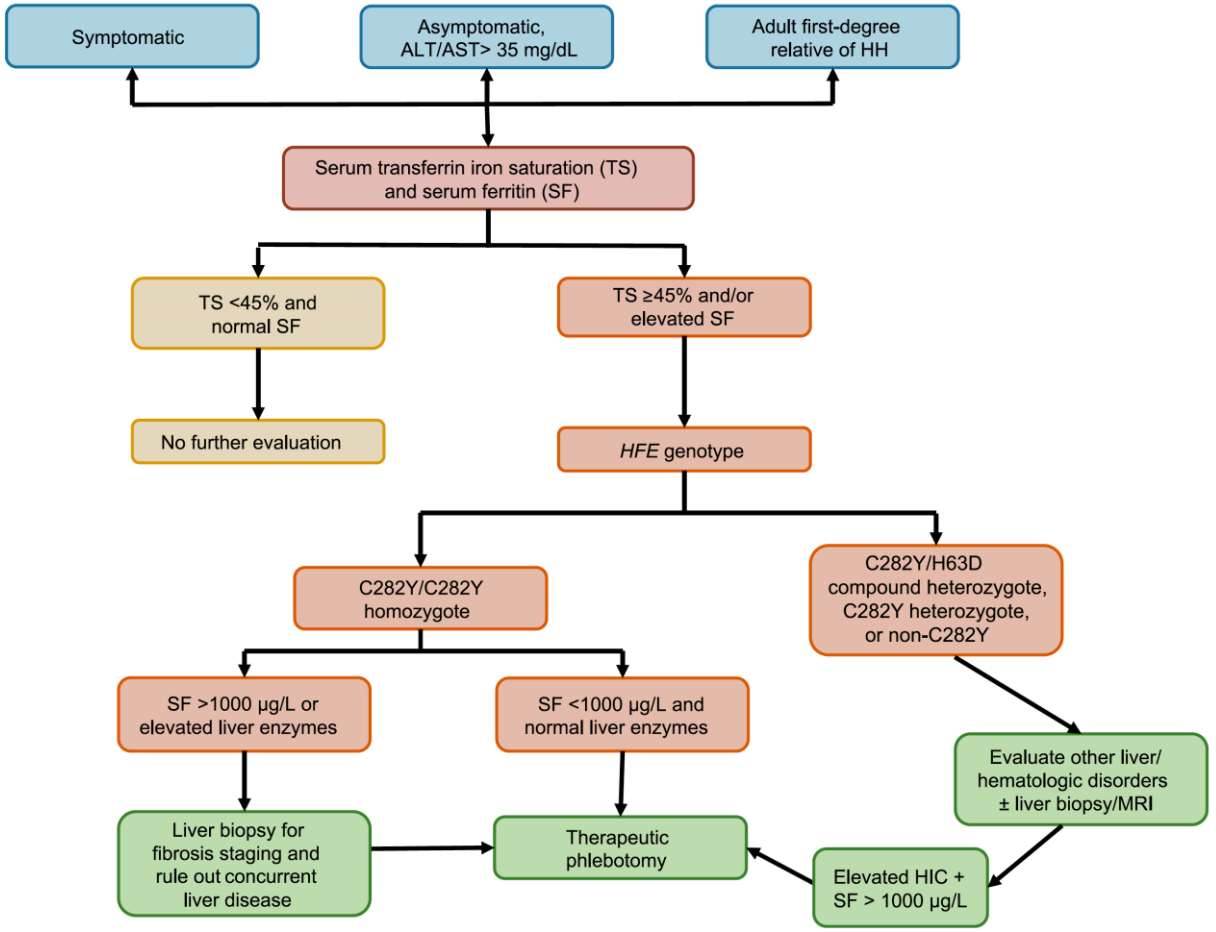
Enfeksiyon (öz. post-Tx)

Malinite (HCC ve ekstrahepatik)

Brissot P et al. , Haemochromatosis Nat Rev Dis Primers 2018 ;4:18016

Hemokromatoz - Tanı

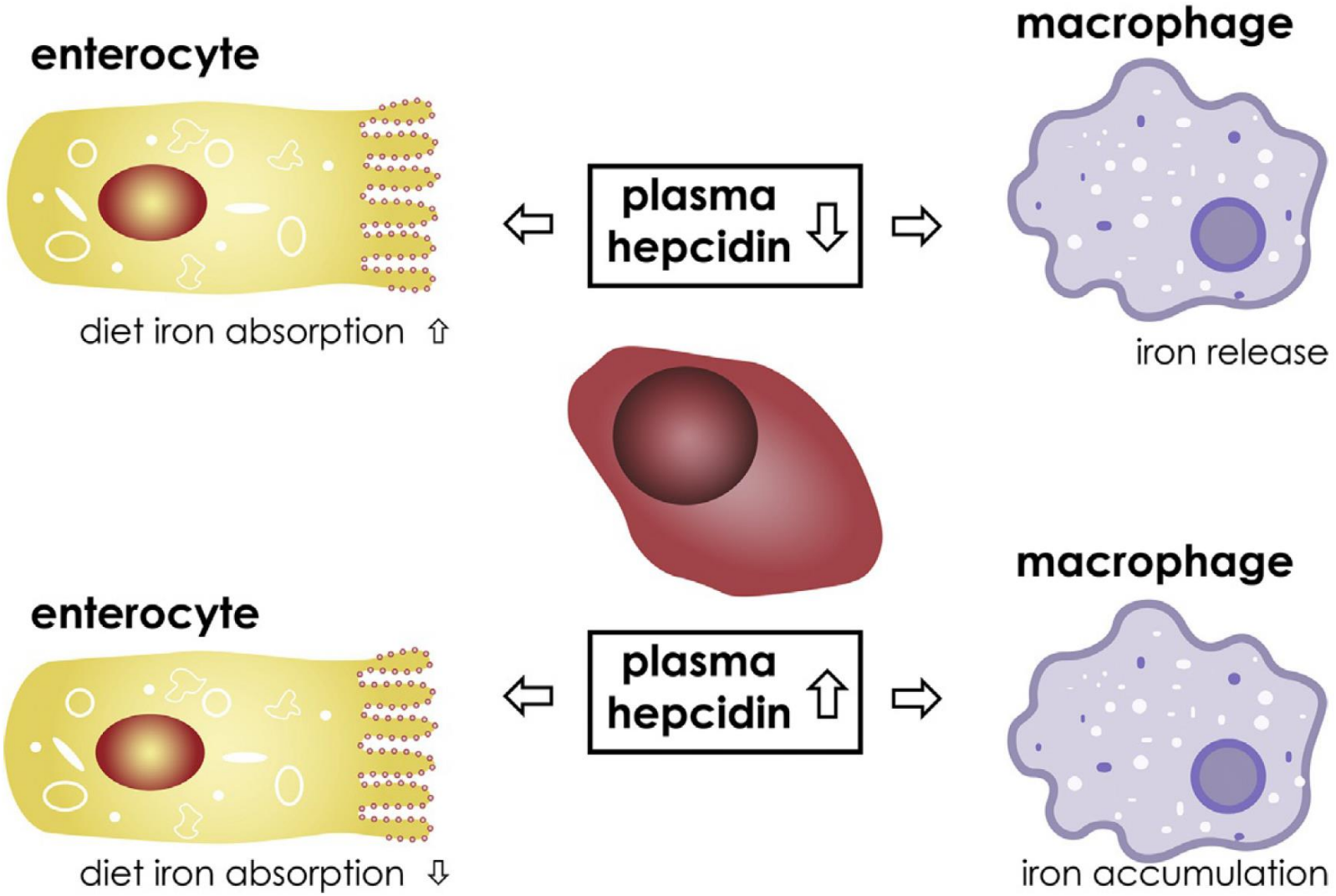
- Transferrin satürasyonu > % 45
- Serum ferritin düzeyi kadında > 200 ng/mL, erkekte >300 ng/mL
- ……

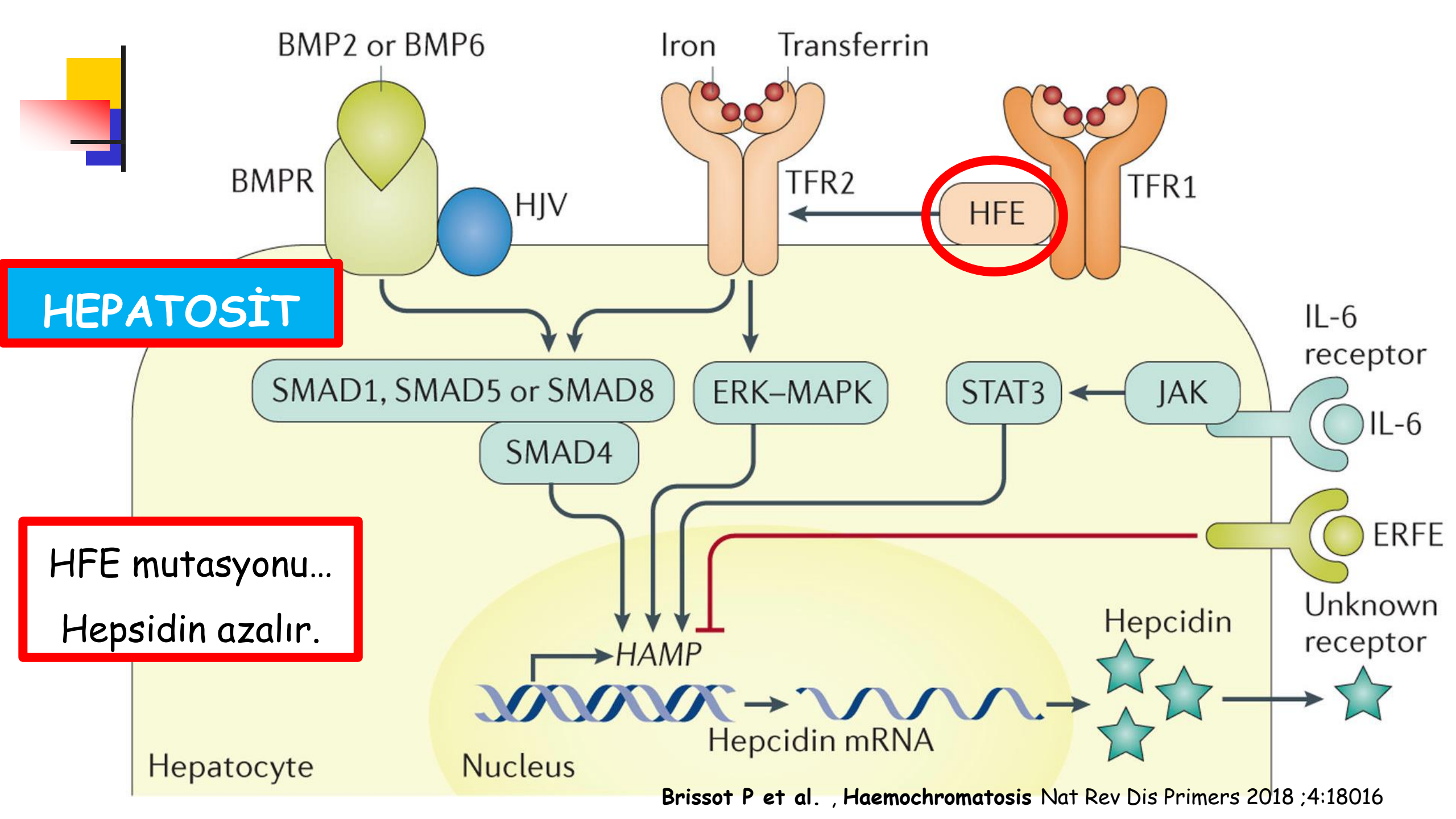


TEDAVİ

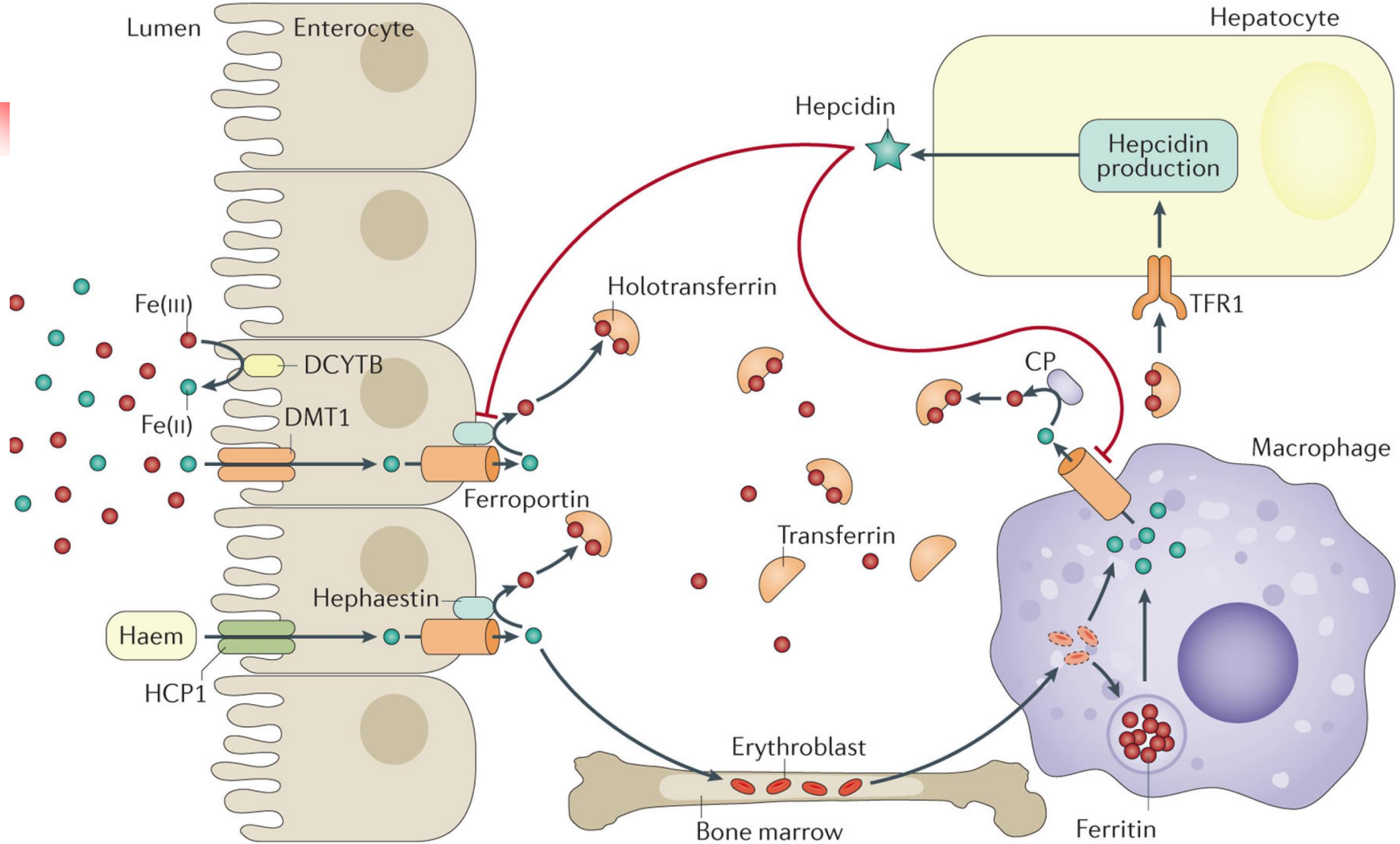
- Flebotomi (Haftalık 400-500 mL, ferritin <50 ng/mL)
- ***Proton pomba inhibitörü***
- …
- **Tx**

Katsarou MS et al. Hemochromatosis: Hereditary hemochromatosis and HFE gene Vitam Horm. 2019;110:201-222.





Brissot P et al. , Haemochromatosis Nat Rev Dis Primers 2018 ;4:18016



Brissot P et al. , Haemochromatosis Nat Rev Dis Primers 2018 ;4:18016

ACG Clinical Guideline: Hereditary Hemochromatosis

Kris V. Kowdley, MD, FACG[1], Kyle E. Brown, MD, MSc[2,3,4], Joseph Ahn, MD, MS, MBA, FACG (GRADE Methodologist)[5] and
Vinay Sundaram, MD, MSc[6]

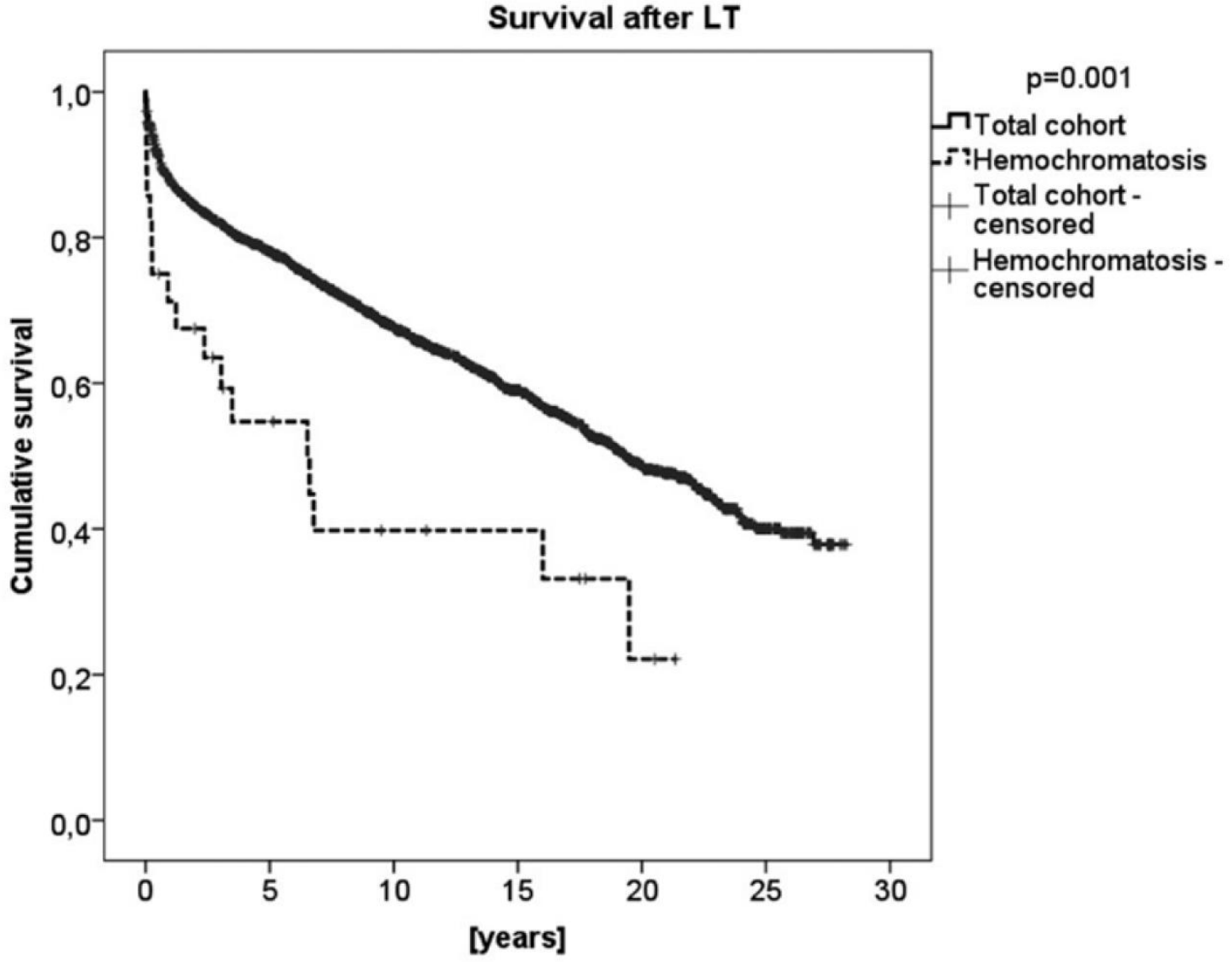
Referral for liver transplantation (LT) should be considered in patients with HH with end-stage liver disease or HCC. LT is curative not only in patients with decompensated cirrhosis and HCC but it also normalizes hepcidin levels and alterations in iron metabolism (167). Although several groups reported inferior out-

EASL clinical practice guidelines for HFE hemochromatosis

European Association for the Study of the Liver*
Journal of Hepatology **2010** vol. 53 | 3–22

Demographic c
age, sex, disea
episodes of rej

Number of patients, r
Median age at LT; (m
Gender, male/female
Median follow-up, y
Indication for LT, n (%
Hereditary HC
Neonatal HC
Hepatocellular carcin
Comorbidities before
Viral hepatitis C
Alcohol abuse
Nonalcoholic steat
Immunosuppression
CNI
CNI + MMF/mTOR
MMF
Rejection, n (%)
Mortality, n (%)
Transplant failure
Thrombosis of hep
Infection
Cardiovascular
HCC recurrence
Other malignancy



	0	5	10	15	20	25	30
Total cohort	2590	1787	1253	781	400	92	0
Hemochromatosis	29	23	18	13	8	3	0

20 (69.0)
2 (6.9)
1 (3.5)
7 (24.1)
4 (13.8)
3 (10.4)
3 (10.4)

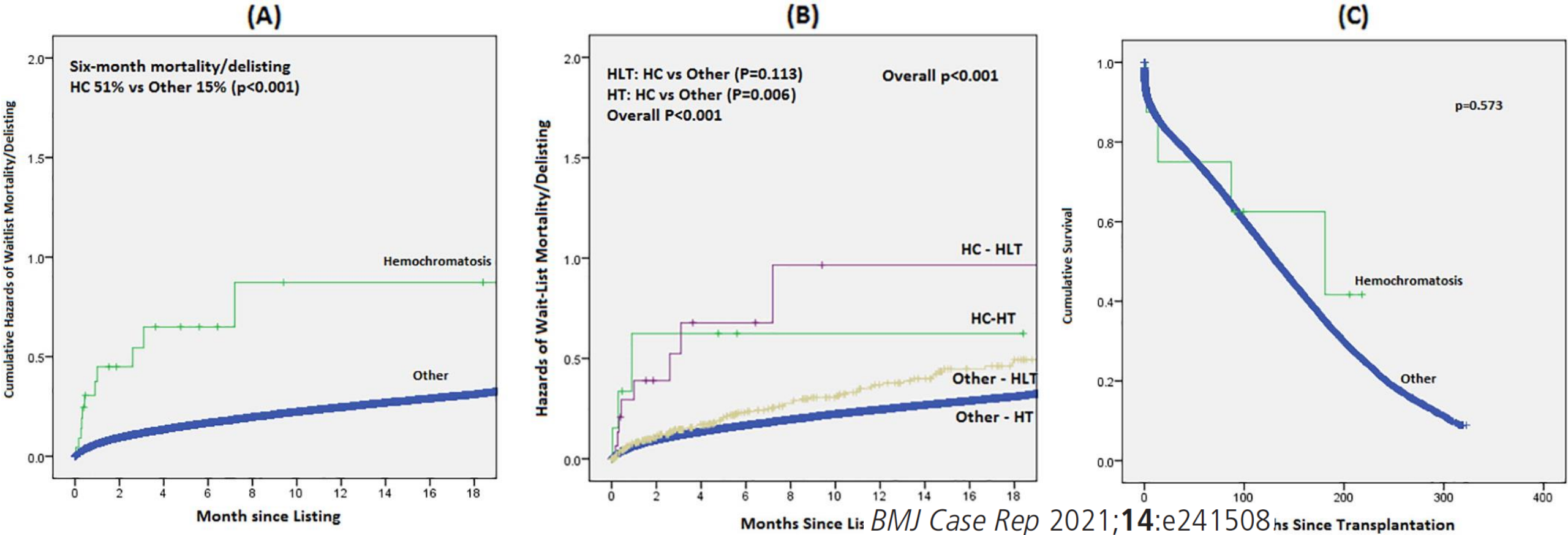
Short communication

Heart and heart-liver transplantation in patients with hemochromatosis

Monique R. Robinson *,[1], Sadeer G. Al-Kindi [1], Guilherme H. Oliveira

Advanced Heart Failure and Transplantation Center, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, United States.

Int J Cardiol. 2017 Oct 1;244:226-228



Combined heart–liver transplantation in a case of haemochromatosis

BMJ Case Rep 2021;**14**:e241508.

Andrew D Shubin, Lucia De Gregorio, Christine Hwang, Malcolm MacConmara

Date	Serum iron (37–145 µg/dL)	TIBC (262–424 µg/dL)	Unsaturated iron binding capacity (112–346 µg/dL)	Ferritin (13–150 ng/mL)
6 August 2016	256	N.C	<30	8978
Transplant				
6 September 2016				
7 September 2016	214	N.C.	<30	3325
21 September 2016	65	200	106	399
11 December 2016	60	254	194	146
13 June 2017				105
24 August 2018				96
23 September 2019				92

Herediter Hemakromatoz

- Flebotomiyi tolere edemeyen, tedavi yetersizliği
- Dekompanse karaciğer sirozu ve HCC lilerde Tx **KÜRATİV**
- Post Tx survi diğer etyolojilerden kötü(?)
- Kardiyomiyopatili hastalarda Kalp-karaciğer dual Tx sürviyi düzeltebilir!!!

Wilson Hastalığı - Tx

- Pre- Tx
  - Akut Karaciğer Yetmezliğinde Tanı
  - Akut Karaciğer Yetmezlikli Wilson hastasında Tx indikasyonu
  - Nöropsikiyatrik Wilson hastasında Tx ???
- PEROPERATİF…….
- Post- Tx
  - Nöropsikiyatrik Wilson hastasında yanıt
  - İmmunsupresifler ile nörolojik sorunlar?

W

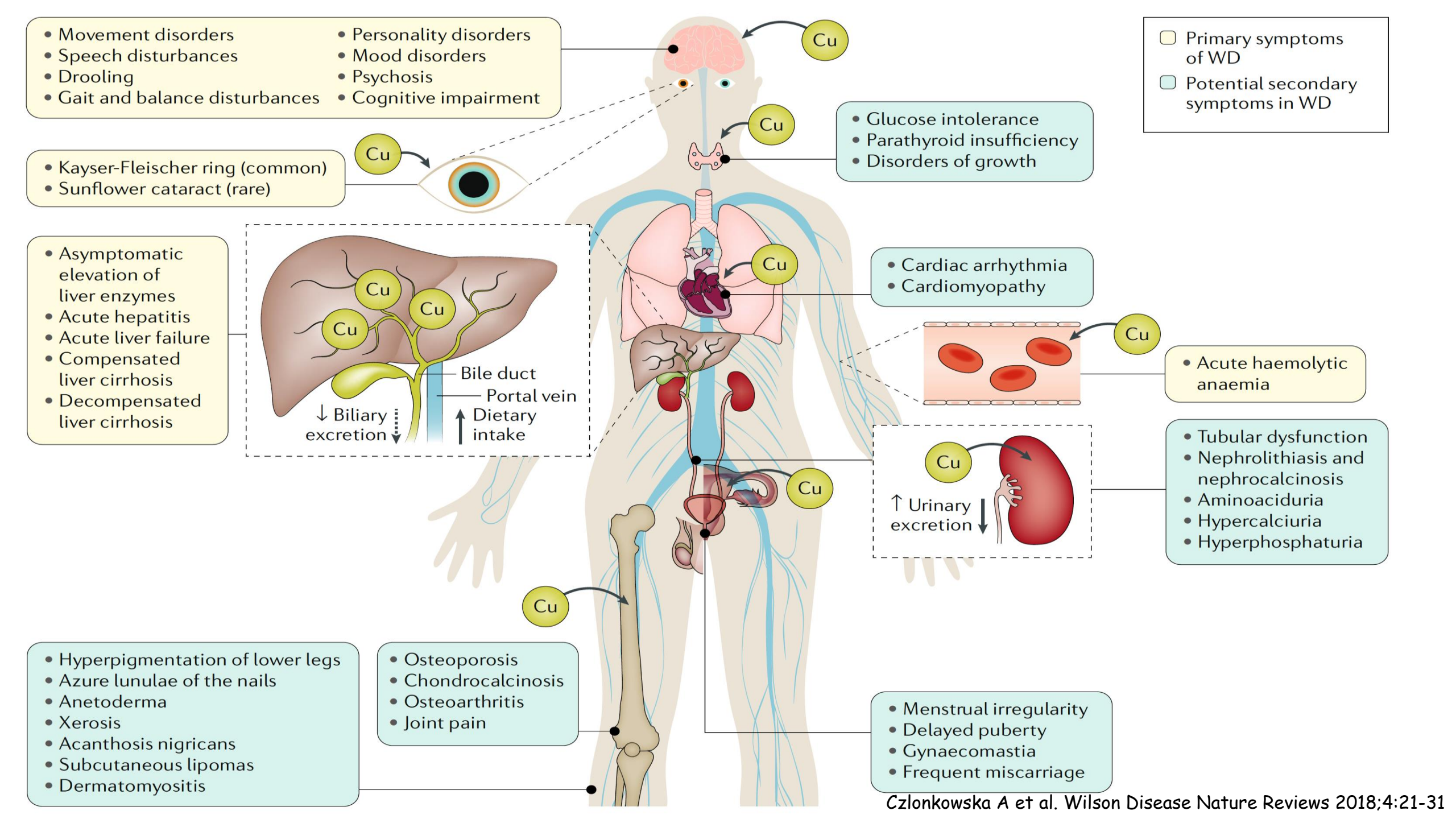
- ***Hepatik form***
  - Asemptomatik hep
  - İzole splenomegali
  - Süreğen aminotran
  - Yağlı karaciğer
  - Akut hepatit
  - Otoimmun hepatit
  - Siroz (kompanse/d
  - Fulminan karaciğer
- ***Psikiyatrik form***
  - Depresyon
  - Nöroz
  - Kişilik bozuklukları
  - Psikoz

Wilson Ha

- ***Hepatik form***
  - ***Asemptomatik hepatomegali***
  - İzole splenomegali
  - Süreğen aminotransferaz yüksekliği
  - Yağlı karaciğer
  - Akut hepatit
  - Otoimmun hepatit benzeri hepatit
  - ***Siroz (kompanse/dekompanse)***
  - ***Fulminan karaciğer yetmezliği***

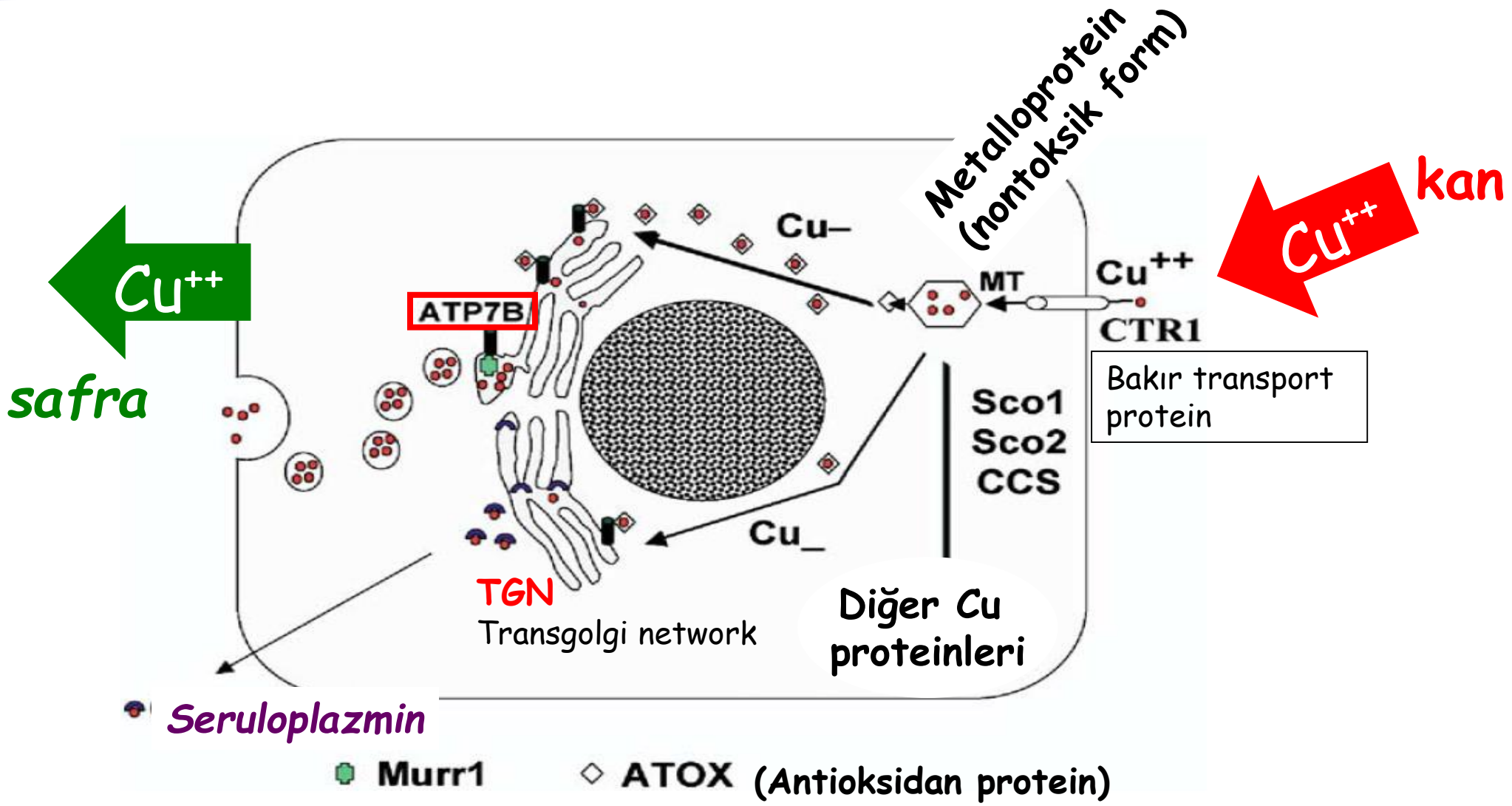
tler)

abortus

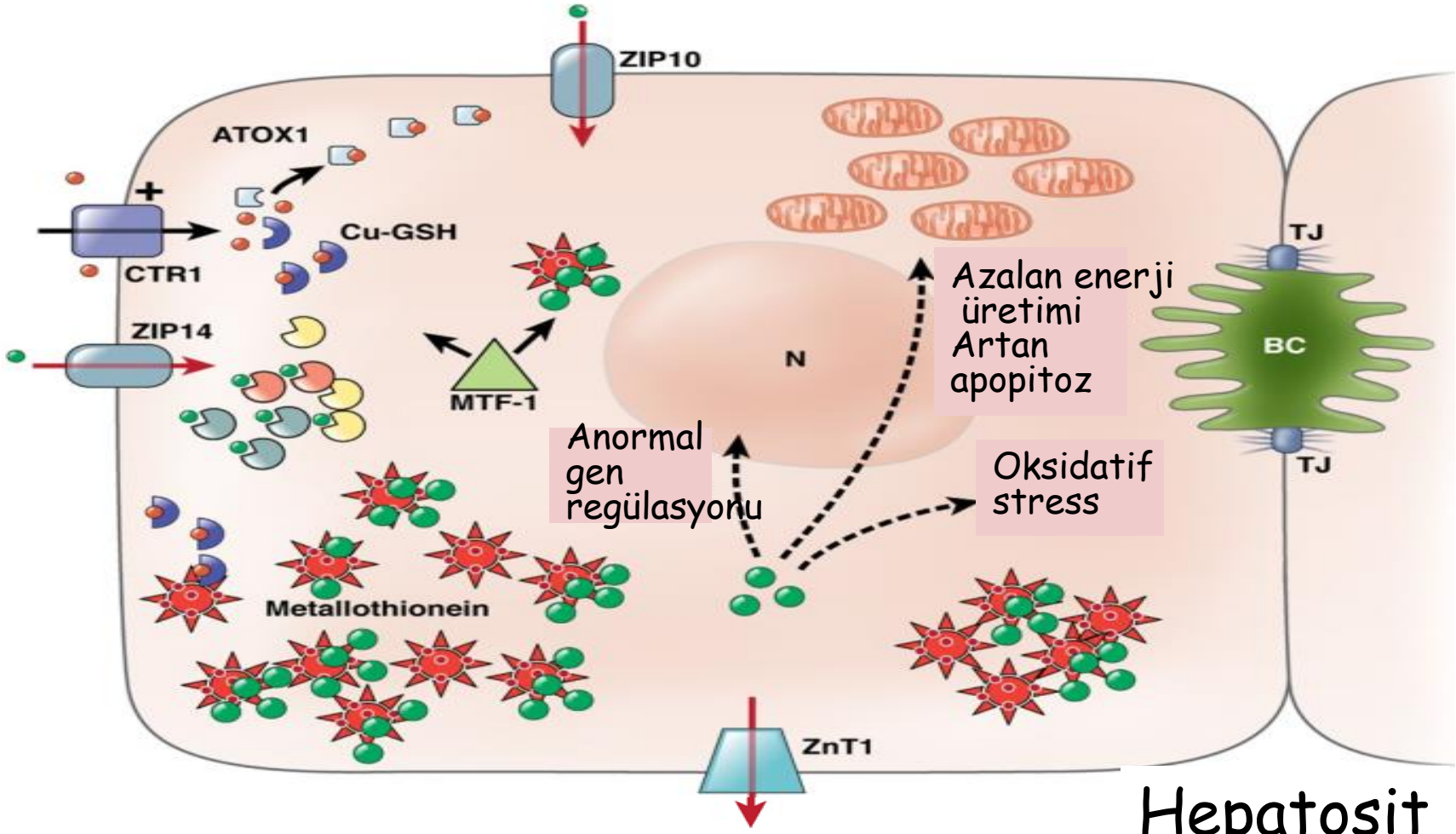


Czlonkowska A et al. Wilson Disease Nature Reviews 2018;4:21-31

Wilson Hastalığı -Patogenez



Wilson Hastalığı -Patogenez



EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Wilson's disease

European Association for the Study of the Liver*

Journal of Hepatology 2012 vol. 56 | 671–685

Typical clinical symptoms and signs	
KF rings	
Present	2
Absent	0
Neurologic symptoms**	
Severe	2
Mild	1
Absent	0
Serum ceruloplasmin	
Normal (>0.2 g/L)	0
0.1-0.2 g/L	1
<0.1 g/L	2
Coombs-negative hemolytic anemia	
Present	1
Absent	0

Other tests	
Liver copper (in the absence of cholestasis)	
>5x ULN (>4 μmol/g)	2
0.8-4 μmol/g	1
Normal (<0.8 μmol/g)	-1
Rhodanine-positive granules*	1
Urinary copper (in the absence of acute hepatitis)	
Normal	0
1-2x ULN	1
>2x ULN	2
Normal, but >5x ULN after D-penicillamine	2
Mutation analysis	
On both chromosomes detected	4
On 1 chromosome detected	1
No mutations detected	0

TOTAL SCORE	Evaluation:
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

Tedavi

- Diyet
- Şelatör Tedavi:
  - British anti-Lewisite (2,3-dimerkaptopropanol)
    - Meso-2,3-Dimerkaptosüksinik asit (DMSA)
    - Sodyum 2,3 Dimerkaptopropan-l-Sülfonate (DMPS)
  - ***D-Penicillamine***
  - ***Trientine***
  - Tetrathiomolybdate
- Çinko
- Methanobactin
- Gen tedavisiAntioksidan tedavi (E vitamini) ?
- Hepatosit transplantasyonu (?) (hayvan çalışmaları)
- KC transplantasyonu

Wilson Disease

Diagnosis, Treatment, and Follow-up

Michael L. Schilsky, MD

Clin Liver Dis 21 (2017) 755–767

score for diagnosing Wilson disease. Medical therapy is effective therapy for most patients; liver transplant can be used to rescue those with acute liver failure or those with liver disease who fail to respond to medical therapy. Treatment monitoring must be done at regular intervals and includes clinical evaluation, liver tests and blood counts, and copper metabolic parameters. Outcomes with medical therapy or transplantation are excellent for most patients with Wilson disease. New advances in treatment may

- Tx sonrası survi diğerlerine benzer

ANCAK

- Nöropsikiyatrik hastalarda ?

Şelatörlerde iyileşme fark ediyor mu?

- Hepatik iyileşme
  - D-peniciilamin ile % 90.7
  - Trientine ile % 92.6
- Nörolojik iyileşme
  - D-penicillamin ile % 67.5
  - Trientine ile % 55
- Nörolojik kötüleşme
  - ***D-penicillamin ile*** ***% 13.8***
  - ***Trientine ile*** ***% 8***

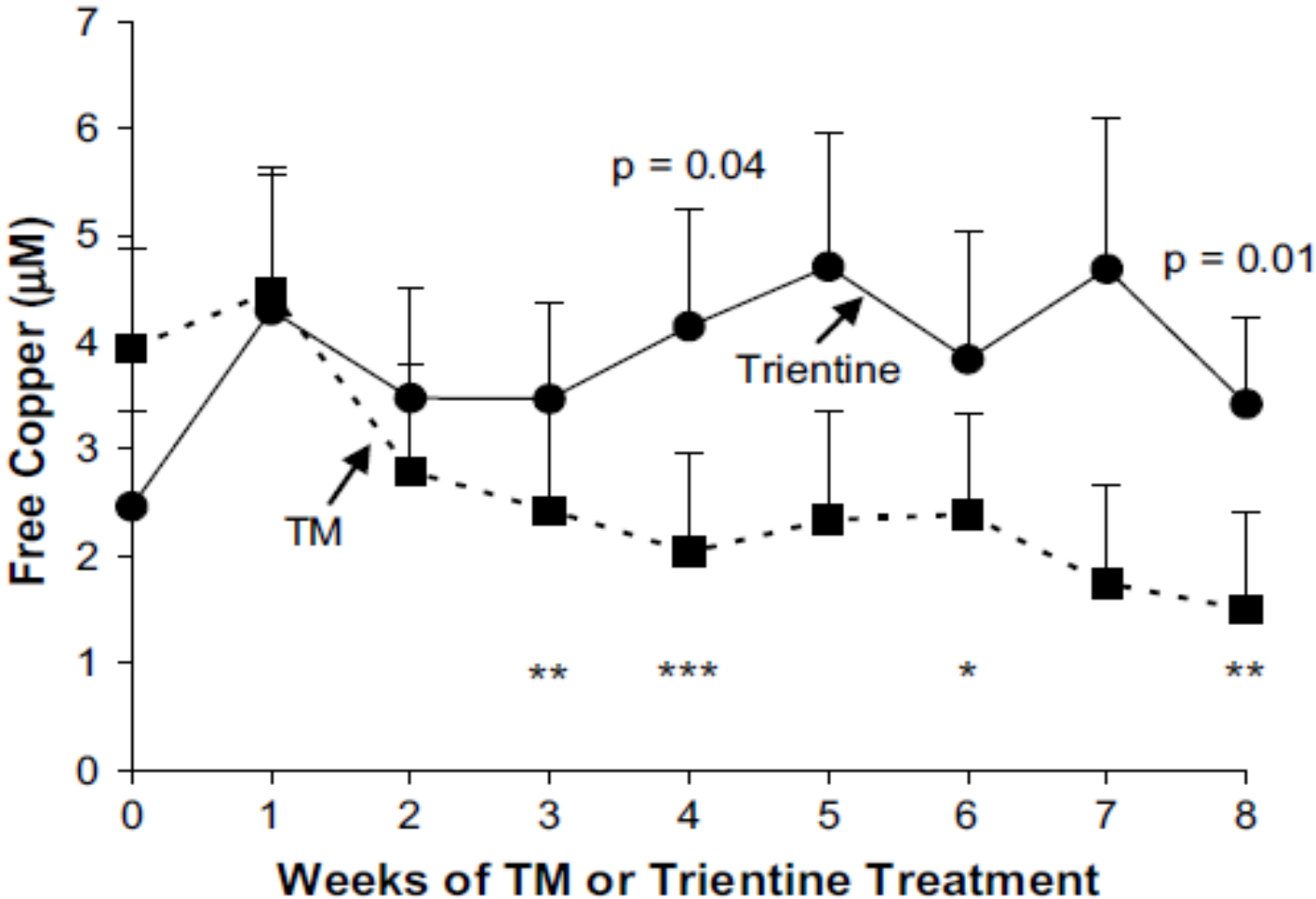
Weiss KH, et al. Efficacy and safety of oral chelators intreatment of patients with Wilson disease. Clin Gastroenterol Hepatol 2013;11(8):1028—35.

Treatment of Wilson's disease with tetrathiomolybdate: V. control of free copper by tetrathiomolybdate and a comparison with trientine

GEORGE J. BREWER, FRED ASKARI, ROBERT B. DICK, JULIA SITTERLY, JOHN K. FINK, MARTHA CARLSON, KAREN J. KLUIN, and MATTHEW T. LORINCZ

ANN ARBOR, MICH

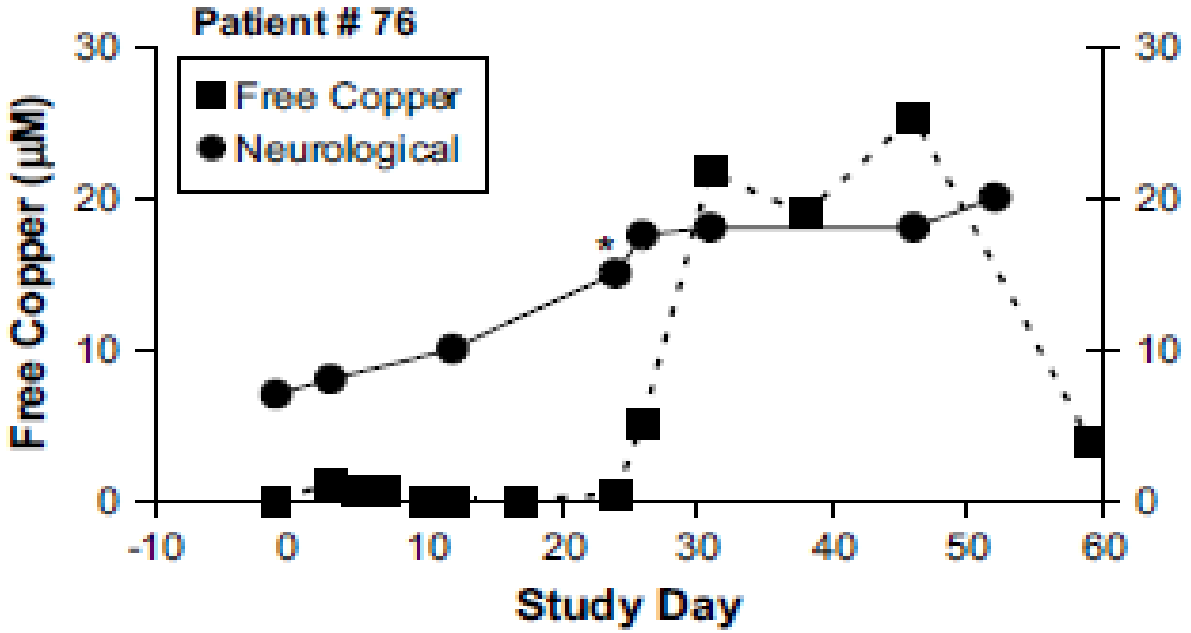
Trans Res, 2009

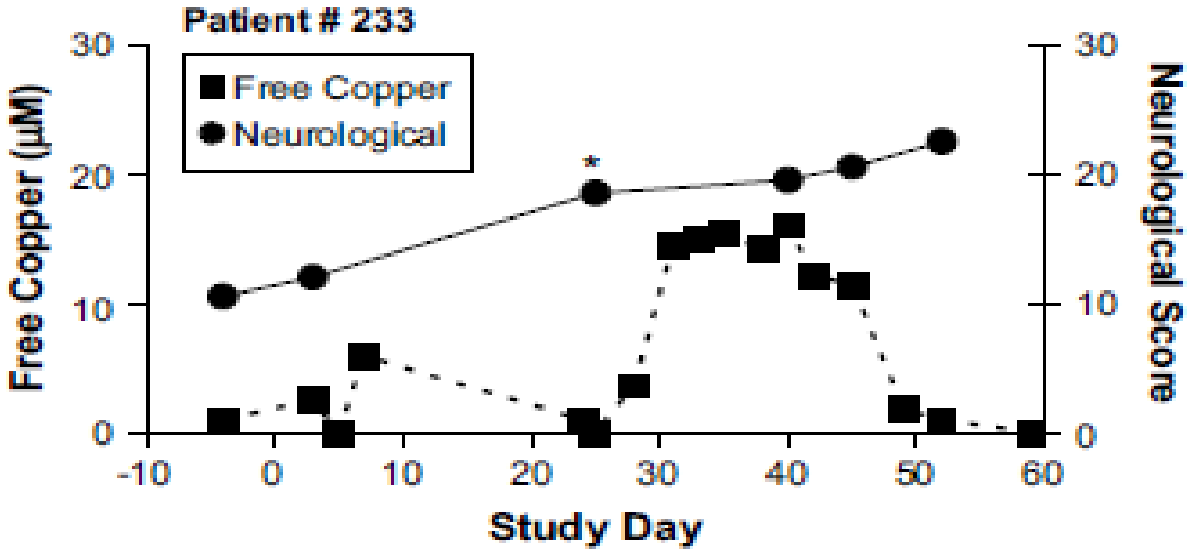


TM: 120 mg /g (3+3 doz)

TR: 500 mg b.i.d (1000mg)

+ Zn^{++} 50 mg b.i.d (her iki kolda da)



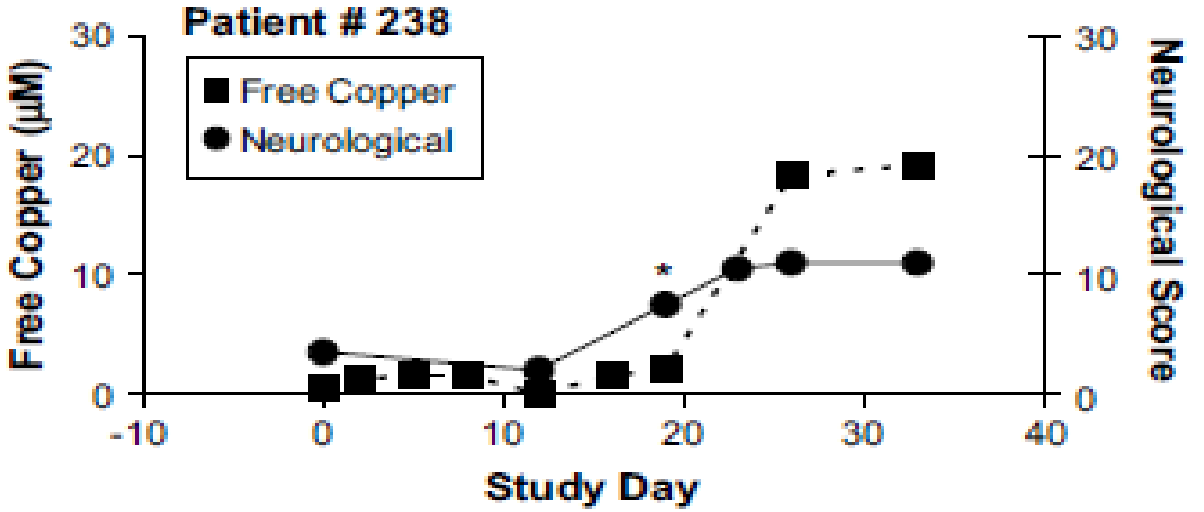


Trientin kullanımı sırasında

ortaya çıkan nörolojik kötüleşme, artmış

serum serbest Cu^{++} pik değerleri ile

paralel…



Şelatör tedavide erken dönemde BOSda bakır artıyor. Nörotoksisite sebebi (?)

Stuerenburg HJ. CSF copper concentrations, blood-brain barrier function, and coeruloplasmin synthesis during the treatment of Wilson's disease. J Neural Transm. 2000;107(3):321-9.

Yr of publication	Period of LT	n	Country	Population	Indication	Follow-up	Patient survival	Graft survival
Schilsky *et al*., 1994	n.a.	55 (62 LT)	USA + Europe	n.a.	CLD 33 ALF 21 Neuro 1	2.5 yr	79% at 1 yr	n.a.
Bellary *et al*., 1995	1981-1991	39 (51 LT)	USA	23 adults 16 children	CLD 17 ALF 22	4.3 yr	79%	74%
Eghstetad *et al*., 1999	1971-1993	45 (56 LT)	USA	26 adults 16 children	CLD 15 ALF 30	5 yr	73% at 5 yr, 69% at 10 yr	58% at 5 yr, 54% at 10 yr
Emre *et al*., 2001	1988-2000	17 (21 LT)	USA	14 adults 3 children	CLD 6 ALF 11	5.3 yr	87.5% at 1 yr	62.5% at 1 yr
Sutcliffe *et al*., 2003	1988-2000	24 (25 LT)	UK	n.a.	n.a.	8 yr	87% at 5 yr	87% at 5 yr
Wang *et al*., 2003	2001-2003	15 (LRLT)	China	n.a.	CLD 14 ALF 1	1.3 yr	93% at 1 yr	80% at 1 yr
Medici *et al*., 2005	1985-2000	37 (41 LT)	Italy	n.a.	CLD 8 ALF 29	n.a.	75% at 5 yr, 60% at 10 yr	70% at 5 yr, 47% at 10 yr
Sevmis *et al*., 2008	2001-2007	24 (24 LT)	Turkey	n.a.	CLD 16 ALF 18	1.8 yr	79% at 5 yr	76% at 5 yr
Cheng *et al*., 2009	2001-2007	36 (LRLT)	China	n.a.	CLD 32 ALF 2 Neuro 2	3.7 yr	75% at 5 yr,	75% at 5 yr
Yoshitoshi *et al*., 2009	1992-2006	32 (32 LRLT)	Japan	8 adults 24 children	CLD 11 ALF 21	6.7 yr	84% at 5 yr, 80% at 10 yr	88% at 5 yr and 83% at 10 yr (ABO compatible), 66.7% at 5 yr and 10 yr (ABO incompatible)
Arnon-(UNOS) *et al*., 2011	1987-2008	570 (n.a.)	USA	400 adults 170 children	n.a.	n.a.	89% (children) and 86% (adults) at 5 yr	n.a.
	2002-2008	170 (n.a.)	USA	119 adults 51 children	CLD 67 ALF 103	n.a.	87.5% and 100% (children) and 89.7% and 90.1 (adults) at 5 yr (respectively for ALF and CLD)	82.5% and 100% (children) and 86% and 85.5 (adults) at 5 yr (respectively for ALF and CLD)
French cohort	1985-2009	121 (140 LT)	France	75 adults 46 children	CLD 55 ALF 36 Neuro 7	6 yr	87% at 5 yr and 10 yr	80% at 5 yr, 79% at 10 yr

The advantage of early liver transplantation for Wilson's disease using living donors

Mehmet Burak Dal, Altan Alim, Koray Acarli

Department of Liver Transplantation, Memorial Sisli Hospital, Istanbul, Turkey

Gastroenterology Rev 2021; 16 (3): 213–218
DOI: https://doi.org/10.5114/pg.2021.108990

Abstract

Aim: The aim of the study was to investigate the surgical timing, results, and advantages of living-donor liver transplantation in patients who underwent liver transplantation due to Wilson's disease.

Material and methods: The study included Wilson's patients who underwent liver transplantation and their live donors. Demographic information, preparations for surgery, liver transplant type, grafts used, results, and complications were examined.

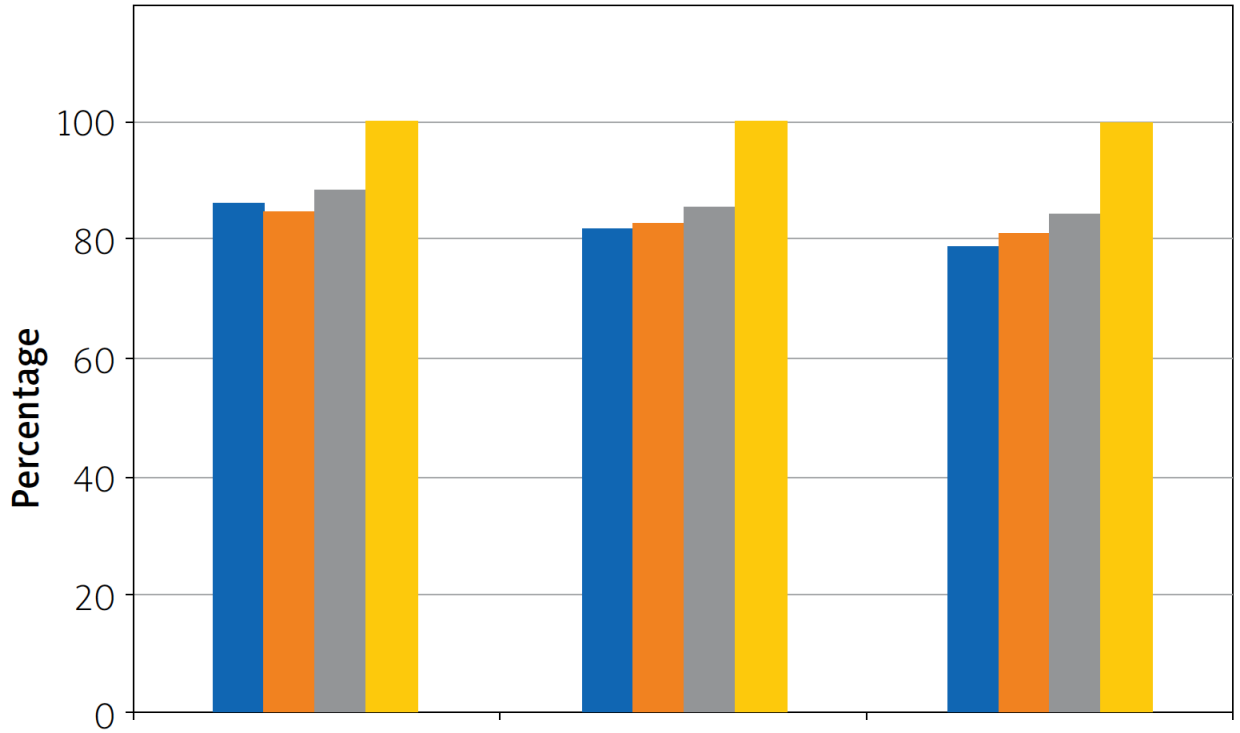
Results: Between 2006 and 2020, 29 liver transplants were performed for 27 Wilson's patients in our clinic. The study included 11 female and 16 male patients, with a mean age of 20.8 ±11.1 years and a mean body mass index of 20.5 ±3.2 kg/m^2. The mean MELD score of the adult patients was 16.5 ±6.3, and the mean PELD score of the paediatric patients was 19.6 ±17.2. Five patients underwent transplantation due to acute liver failure, and 22 patients with low MELD score had liver transplants due to chronic liver disease. Three patients who were referred with acute liver failure died in the perioperative period; no mortality was observed in the 22 elective patients. The overall survival was calculated as 88.8%. The 1-, 3-, and 5-year survival were 100% among elective early transplanted patients.

Conclusions: Liver transplant is the most effective treatment for liver failure caused by Wilson' s disease. When performed promptly, living-donor liver transplantation results in high survival rates in cases of both acute liver failure and chronic liver failure, and it no deterioration of the patient's condition is evident.

The advantage of early liver transplantation for Wilson's disease using living donors

Mehmet Burak Dal, [illegible]

Department of Liver Tra



	1 year	3 years	5 years
LT (1203)	86%	81.6%	78.8%
Pediatric LT (372 cases)	85%	83%	80.9%
Wilson (27 cases)	88.4%	85.7%	84.2%
Elective Wilson (22 cases)	100%	100%	100%

ELSEVIER

Clinical Neurology and Neurosurgery 109 (2007) 71–75

www.elsevier.com/locate/clineuro

Case report

Different neurological outcome of liver transplantation for Wilson's disease in two homozygotic twins

Marco Senzolo [a], Massimiliano Loreno [a], Stefano Fagiuoli [a], Giacomo Zanus [b], Daniele Canova [a], Annalisa Masier [a], Francesco Paolo Russo [a], Giacomo Carlo Sturniolo [a], Patrizia Burra [a,*]

[a] *Gastroenterology, Department of Surgical and Gastroenterological Sciences, University of Padua, Padua, Italy*
[b] *Clinica Chirurgica I, Department of Surgical and Gastroenterological Sciences, University of Padua, Padua, Italy*

Received 21 July 2005; received in revised form 23 January 2006; accepted 25 January 2006

- Şiddetli karaciğer hastalığı bulunmayan şelatör tedavi ile nörolojik bulguları progresyon gösteren 43 WH
- Tx sonrası;
  - Tam düzelme % 30
  - Belirgin düzelme % 48
  - Kötüleşme % 14

ELSEVIER

Clinical Neurology and Neurosurgery 109 (2007) 71–75

www.elsevier.com/locate/clineuro

Case report

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[a] *Gastroenterology, Department of Surgical and Gastroenterological Sciences, University of Padua, Padua, Italy*
[b] *Clinica Chirurgica I, Department of Surgical and Gastroenterological Sciences, University of Padua, Padua, Italy*

Received 21 July 2005; received in revised form 23 January 2006; accepted 25 January 2006

Wilson's disease is a genetic disorder characterized by accumulation of copper in many organs and tissues. Phenotypic manifestations are wide-ranging from neuropsychiatric disorders, to severe liver disease requiring liver transplantation. Clinical presentation is not often related to the genetic defect and siblings may have different type of disease. Liver transplantation is indicated for all patients with Wilson's disease and decompensated liver cirrhosis unresponsive to medical therapy, but its efficacy in resolving the neurological symptoms is still controversial, because as far now, very different outcomes have been reported. We describe here on the exceptional case of two homozygotic twins, both with liver cirrhosis due to Wilson's disease, one of them with severe neuropsychiatric involvement, who both underwent liver transplantation and subsequently had very different outcome despite same genetic background. The presence of neurological clinical manifestations in Wilson's disease should recommend caution indicating liver transplantation, because irreversible brain damage may exist.

- Aynı genetik yapıdaki hastalarda farklı seyir
- İrreversibl nörolojik bulgular mevcut ise TX yapılırken dikkatli olunmalı

Walker G, Hussaini T, Stowe R, et al. Liver transplant can resolve **severe neuropsychiatric** manifestations of Wilson's disease: a case report. Exp Clin Transplant **2018**; 16: 620-4.

Although liver transplant for decompensated cirrhosis secondary to Wilson disease is well accepted, the use of transplant for patients with severe neurologic manifestations of this condition remains controversial, and these can be perceived as a contraindication. Here, we describe a 45-year-old woman who presented with an incidental hepatocellular carcinoma at the time of transplant. The patient had severe neurologic manifestations of Wilson disease pretransplant, including dysarthria, hyperreflexia, asymmetrical ataxia, tremor, bradyphrenia, and shuffling gait. She underwent successful transplant from a hepatic and surgical standpoint, but her postoperative course was marked by protracted mutism, hypophonia, and fluctuating akinesia and immobility that did not respond promptly to withdrawal of calcineurin inhibitors or pramipexole but did respond robustly to amantadine. At 9 months posttransplant, there was marked neurologic improvement, and, at 18 months, she exhibited subtle memory and organizational difficulties but was fully ambulatory and otherwise completely functional. Our experience suggests that even patients with severe neurologic Wilson disease may recover after transplant, albeit slowly, demonstrating the need for a multidisciplinary approach, including pre- and posttransplant neurologic and neuropsychiatric consultations.

- Kalsinörin inhibitörleri kesildi.
- Hareket bozukluğu Pramipexole yanıtsız, Amantadine yanıtlı

- 9. ayda belirgin düzelme
- 18. ayda bellek ve organizasyonel bozukluklar dışında fonksiyonel
- Düzelme yavaş olmakta

Original Paper
Eur Neurol 2017;77:5–15
DOI: 10.1159/000452658

Liver Transplantation in Wilson's Disease with Neurological Impairment: Evaluation in 4 Patients

Chloé Laurencin[a,b] Anne Sophie Brunet[b,c] Jérôme Dumortier[j]
Laurence Lion-Francois[b,e] Stéphane Thobois[a,f,g] Jean Yves Mabrut[i]
Rémi Dubois[d] France Woimant[k] Aurélia Poulois[k] Olivier Guillaud[b,j]

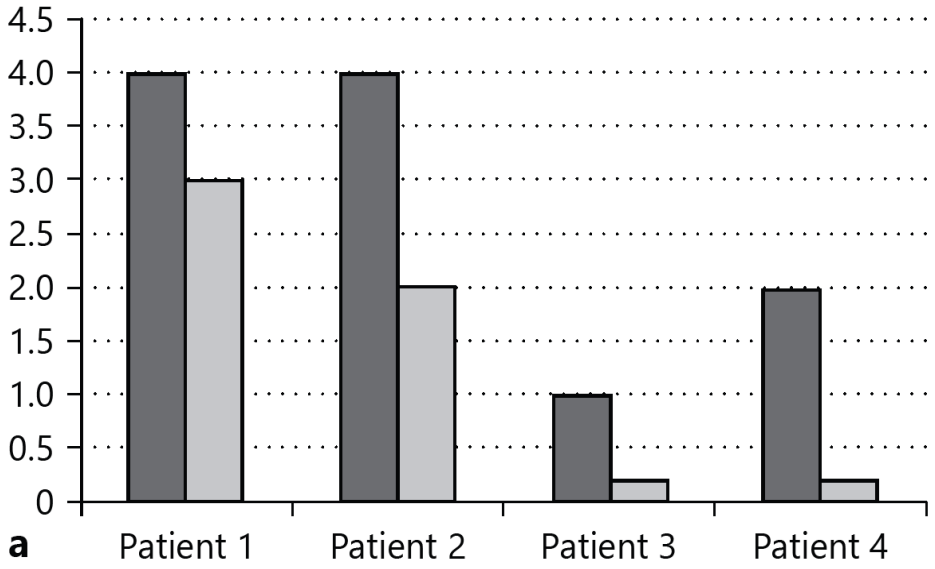
European Neurology

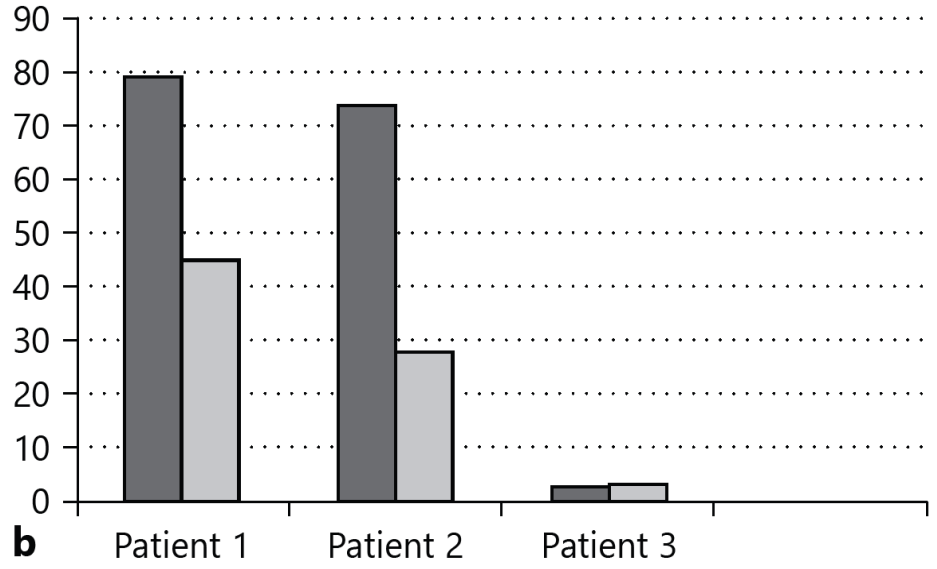
	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Female	Male	Female	Male
Genotype	Homozygous for p. {Lys1020Arg} exon 13	Composite heterozygous p. (Ile1148Thr) exon 16 and p. [Ser1365CysfsX12] exon 20	Composite heterozygous p. {Gln111X} exon 2 and p. {Leu641Ser} exon 6	One mutation: p. {Glu624AsnfsX130} Exon 6
Age at onset, years	15	15	15	17
Age at LT, years	17	19	15	23
Treatement before LT (duration)	Trientine + zinc (5 months) Then: DPA (during 1 year and 6 months, progressive increase 900 mg, then 1,200 mg, then 1,800 mg per day)	Trientine (1 year) Then: DPA + zinc (2 years)	DPA (1 month)	DPA during 3 months Then: trientine (progressive increase: 900 mg during 1 year, then 1,200 mg, then 1,800 mg per day)
Main neurological symptoms before LT	Severe generalized dystonia Severe oromandibular dystonia Severe dysarthria Dysphagia (≥gastrostomy) Unable to walk without help	Generalized dystonia Severe dysarthria Dysphagia (≥Gastrostomy) Walk with help	Micrographia Left hand dystonia	Moderate bradykinesia Moderate rigidity Hypomimia Walk alone but slowly Postural tremor
Complications of LT	None	Transient right brachial plexus deficit Arterial occlusion of the aortohepatic pontus (≥angioplastia) Delayed lymphoma	Moderate and regressive renal failure Marked neurological degradation regressive with DPA	Acute and partialy regressive renal failure
Main neurological symptoms 2–4 years after LT	Moderate generalized dystonia Less pronounced oromandibular dystonia Marked dysarthria Improved dysphagia Walk without help	Partial improvement of dystonia Moderate dysartria No longer dysphagia Walk without help	Discrete dystonia of the left hand	Dystonia of the left arm
MRI abnormal signal intensities before LT	T2 hypersignal of lenticular nuclei, brain stem and pons	T2 hypersignal of caudate nucleus, putamen, brain stem and pons	T2 hypersignal of caudate nucleus and putamen	Discrete T2 hypersignal of the striatum
MRI abnormal signal intensities 2–4 years after LT	T2 hypersignal of the lenticular nuclei	Decrease of the T2 hypersignal in all areas	Decrease of the T2 hypersignal in all areas	No decrease of the T2 hypersignal

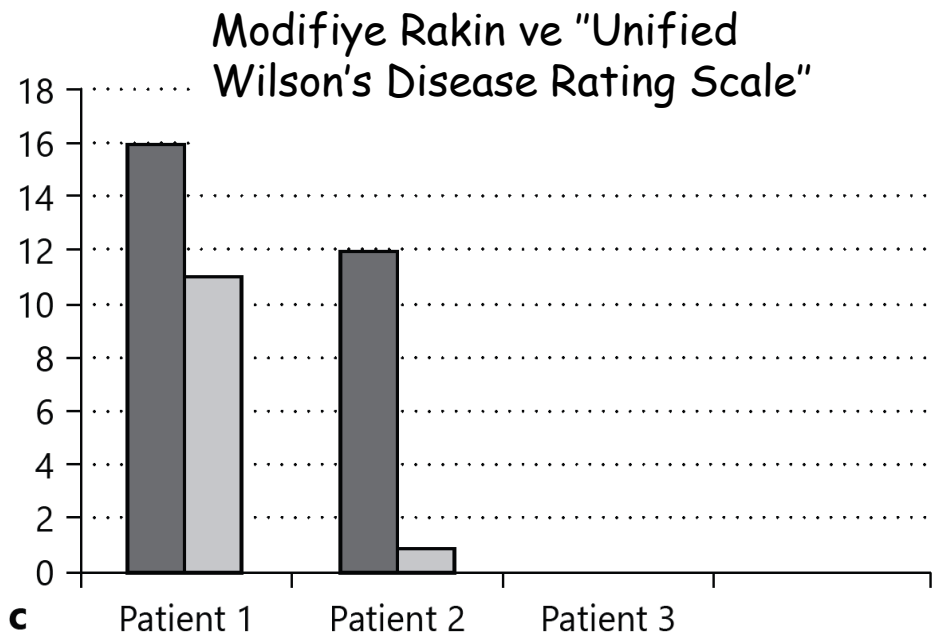
European Neurology
Eur Neurol 2017;77:75–15
DOI: 10.1159/000452658

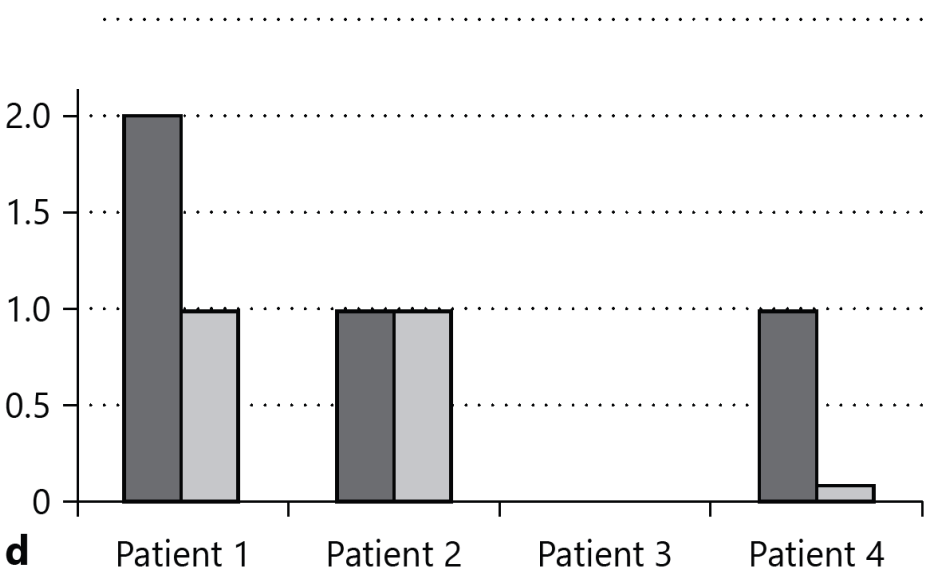
Liver Transplantation in Wilson's Disease with Neurological Impairment: Evaluation in 4 Patients

Chloé Laurencin[a,b] Anne Sophie Brunet[b,c] Jérôme Dumortier[j]
Laurence Lion-Francois[b,e] Stéphane Thobois[a,f,g] Jean Yves Mabrut[j]
Rémi Dubois[d] France Woimant[k] Aurélia Poujois[k] Olivier Guillaud[b,j]
Alain Lachaux[b,c,h] Emmanuel Broussolle[a,b,f,g]







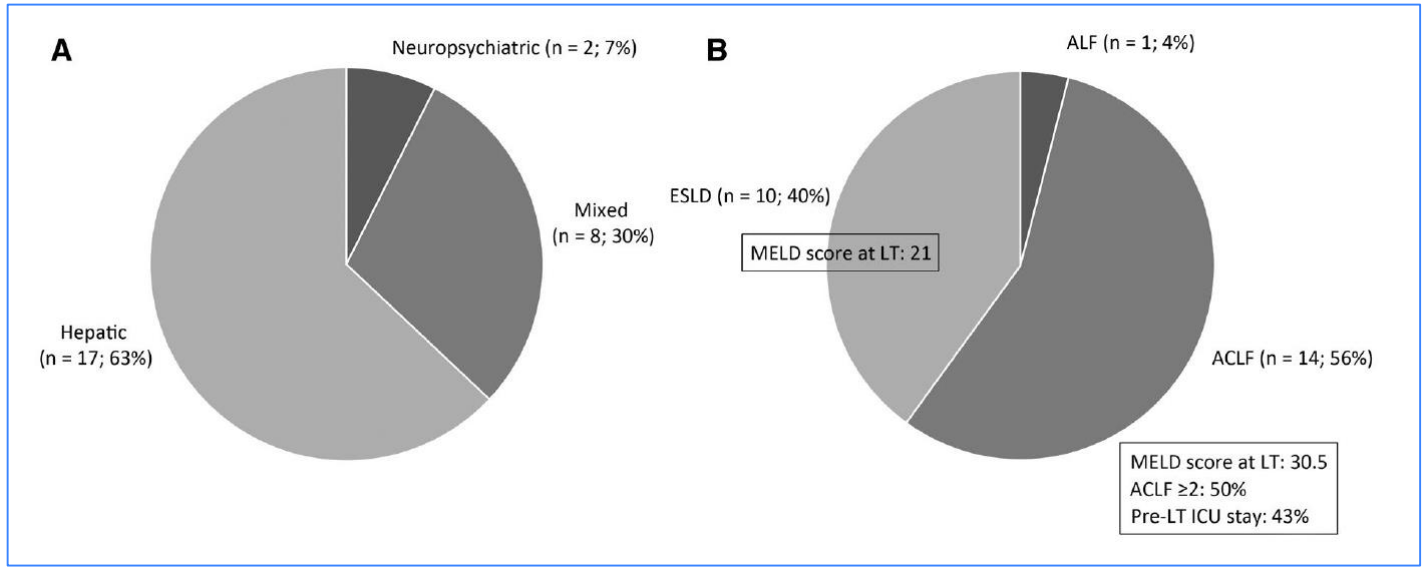


Outcomes of Liver Transplant for Adults With Wilson's Disease

Alberto Ferrarese,[1] Maria Cristina Morelli,[2] Paola Carrai,[3] Martina Milana,[4] Mario Angelico,[4] Giovanni Perricone,[5] Luca Saverio Belli,[5] Giuseppe Marrone,[6] Antonio Grieco,[6] Silvia Martini,[7] Matteo Angelo Manini,[8] Stefano Fagiuoli,[8] Pierluigi Toniutto,[9] Alfonso Galeota Lanza,[10] Sherrie Bhoori,[11] Salvatore Petta,[12] Edoardo G. Giannini,[13] and Patrizia Burra[1]

Liver Transplantation 26 507–516 2020

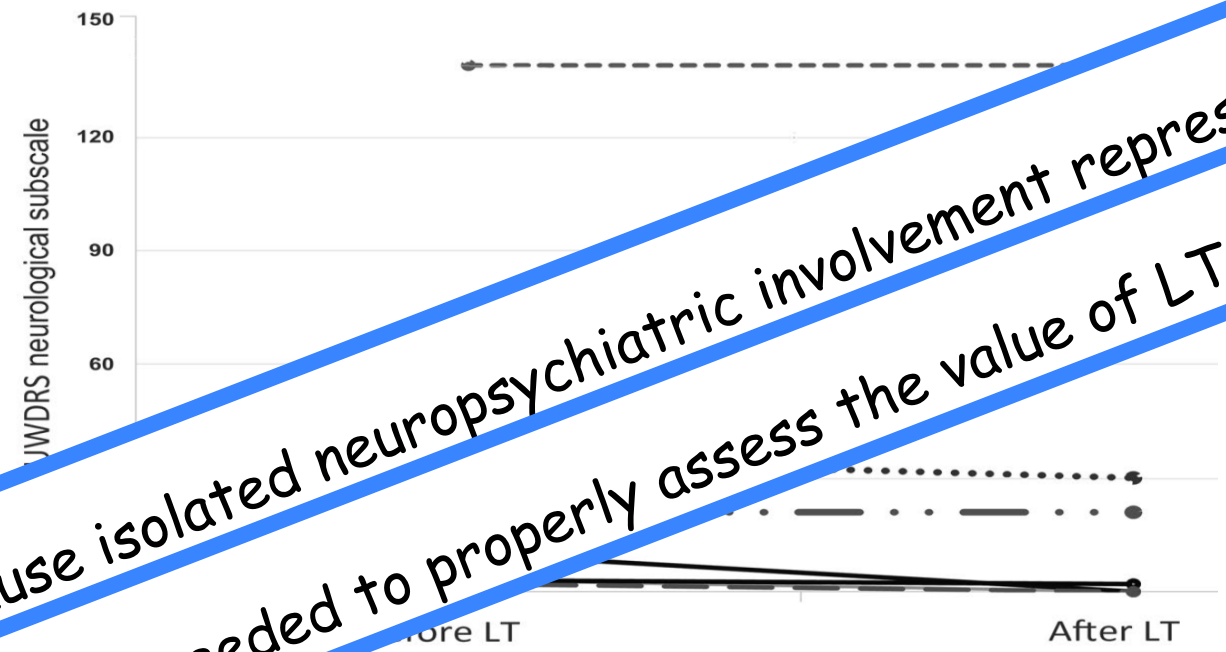
- 2006-2016, 11 İtalyan Tx merkezi,
- 29 erişkin hasta
  - İzole hepatik WH 17,
  - 2 kompanse karaciğer ile nörolojik WH
- 1- ve 5- yıl sürvi, % 88 ve % 83
- Neuropsikiyatrik semptomlar geriledi
- ....



Outcomes of Liver Transplant for Adults With Wilson's Disease

Alberto Ferrarese ,[1] Maria Cristina Morelli ,[2] Paola Carrai ,[3] Martina Milana ,[4] Mario Angelico ,[4] Giovanni Perricone ,[5] Luca Saverio Belli ,[5] Giuseppe Marrone ,[6] Antonio Grieco ,[6] Silvia Martini ,[7] Matteo Angelo Manini ,[8] Stefano Fagiuoli ,[8] Pierluigi Toniutto ,[9] Alfonso Galeota Lanza ,[10] Sherrie Bhoori ,[11] Salvatore Petta ,[12] Edoardo G. Giannini ,[13] and Patrizia Burra [1]

Liver Transplantation 26 507–516 2020



...main before and after LT.

...symptoms of WD after LT, more data are needed to examine the role of LT for WD patients with neuropsychiatric impairment alone.

		atic/ atric = 8)
		26 (21-47)
		3 (37.5)
	8 (0-45)	7 (0-58)
	3 (25.0)*	3 (42.9)†
...ore at LT	12 (7-15)	12 (8-13)
...D score at LT	27 (9-40)	28 (11-49)
Post-LT ICU stay, days	6 (2-22)	7 (3-14)
Post-LT complications		
Overall (at least 1)	10 (58.8)	6 (75.0)
Liver-related complication	7 (41.2)	4 (50.0)
Infections	5 (29.4)	4 (50.0)
Respiratory	4 (23.5)	1 (12.5)
Renal impairment	2 (11.8)	0 (0)
Prolonged nutritional support	2 (11.8)	0 (0)
Post-LT nonadherence	1 (5.9)	3 (37.5)

Because isolated neuropsychiatric involvement represents a rare indication to LT, more data are needed to properly assess the value of LT for WD in this subset of patient

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Journal of Hepatology **2014** vol. 60 | 579–589

Long term results of liver transplantation for Wilson's disease: Experience in France

Olivier Guillaud[1,*], Jérôme Dumortier[1], Rodolphe Sobesky[2,23,24,25], Do
Philippe Wolf[4], Claire Vanlemmens[5], François Durand[6], Yvon
Christophe Duvoux[8], Sébastien Dharancy[9], Nassim Kamar[10], Karir
Pierre Henri Bernard[12], Georges-Philippe Pageaux[13], Ephrem Salamé[14],
Alain Lachaux[16], Dalila Habes[17,25], Sylvie Radenne[18], Jean Hardwigsen[19], C
Jean-Marc Trocello[21], France Woimant[21], Philippe Ichai[2,23,24,25], Sophi
Olivier Soubrane[22], Denis Castaing[2,23,24,25], Emmanuel Jacquemin[17,25], D
Jean-Charles Duclos-Vallée[2,23,24,25]

- Fransa, 1985-2009, retrospektif
- 75 erişkin hasta, 46 çocuk
- % 94 hepatik,
- 7 hasta (% 6) nörolojik WH

7 nörolojik hastanın 6 hasta izlemi:

3 şiddetli Parkinson sendromlu hasta öldü

2. ay pnomöni,

4. ay sellülit,

36. ay bakteriemi)

Diğer 3 hasta:

Distoni ve korealı	79 ay
Ataksi ve frontal sendromlu	47 ay
Distoni ve miyoklonili	18 ay izlemde düzelme

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY
Journal of Hepatology **2014** vol. 60 | 579–589

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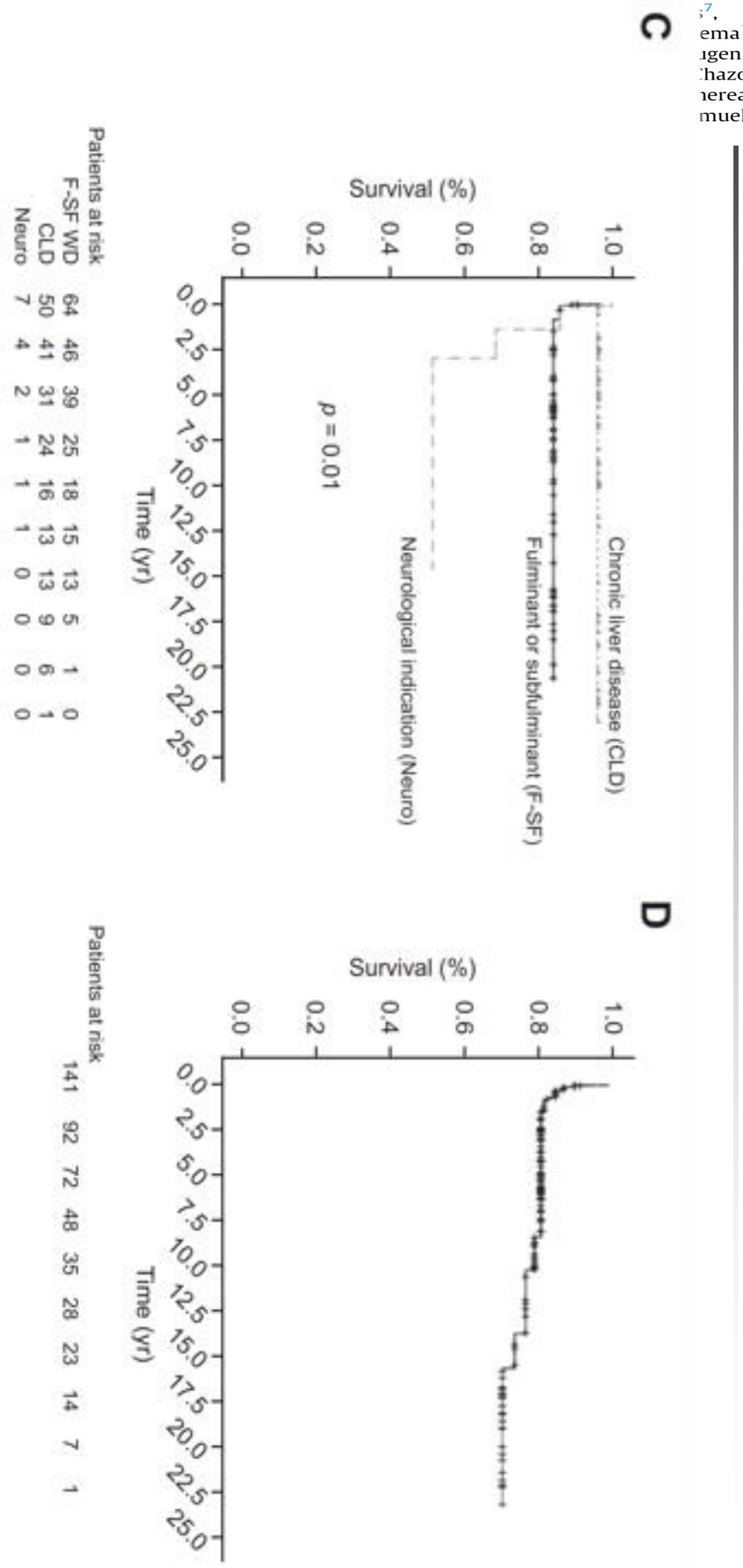
Olivier Guillaud[1,*], Jérôme Dumortier[1], Rodolphe Sobesky[2,23,24,25], Dominique Debray[3], [7], Pierre [11], Alain Lac [15], Jean- [20], Olivier [17,25], [2,23,24,25],



World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v5.i3.127

World J Hepatol 2013 March 27; 5(3): 127-132
ISSN 1948-5182 (online)

BRIEF ARTICLE

Liver transplantation in Wilson's disease: Single center experience from Saudi Arabia

Musthafa Chalikandy Peedikayil, Hamad Ibrahim Al Ashgar, Abdullah Al Mousa, Mohammed Al Sebayel, Khalid Al Kahtani, Faisal Aba Alkhail

- 16 hepatik (4ünde +nörolojik bulgular)
- 15 yıl izlem
- 1. yıllık sürvi % 91, 15 yıllık sürvi % 81

Table 3 Neurological and psychiatric manifestations of Wilson's disease before and after liver transplantation

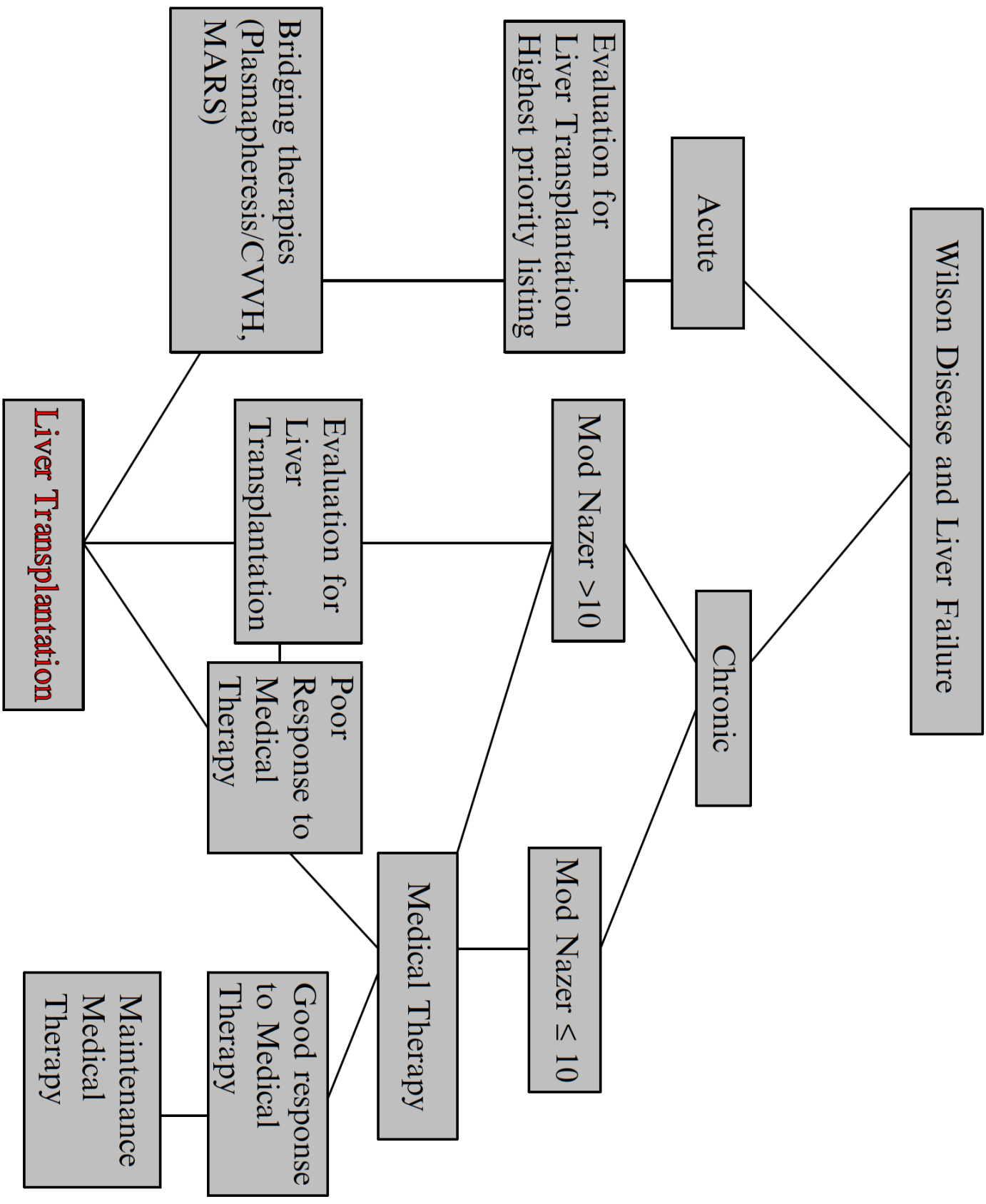
Characteristics	Case 1	Case 11	Case 12	Case 15
Neurological symptoms before transplantation	Akinesia dysarthria abnormal movement	Tremor dysarthria abnormal movement	Tremor nystagmus	Abnormal movement
Psychiatric abnormalities before transplantation	Negative	Negative	Depression restlessness	Delusion of persecution depression restlessness hallucination
MRI brain before transplantation	No available data	High signal intensities involving the thalami, mid brain, and pons	Bilateral and symmetrical abnormal hyper-intensity at level of basal ganglia	High signal intensity in the basal ganglia and substantia nigra with mild cerebral atrophy
KF ring before transplantation	Positive	Positive	Positive	Positive
Neurological symptoms after transplantation	Negative	Negative	Negative	Negative
Psychiatric abnormalities after transplantation	Negative	Negative	Negative	Negative
MRI brain after transplantation	No available data	Normal MRI of the brain	No available data	No available data
KF ring after transplantation	Negative	Negative	Negative	Negative

Handbook of Clinical Neurology, Vol. 142 (3rd series)
Wilson Disease
A. Członkowska and M.L. Schilsky, Editors
http://dx.doi.org/10.1016/B978-0-444-63625-6.00016-1

Chapter 16

Liver transplantation for Wilson disease

AHSAN AHMAD[1], EURIKO TORRAZZA-PEREZ[2], AND MICHAEL L. SCHILSKY[3]*
[1]*Section of Transplantation and Immunology, Department of Surgery, Yale University School of Medicine, New Haven, CT, USA*
[2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of New Mexico, Albuquerque, USA*
[3]*Section of Digestive Diseases and Transplantation and Immunology, Department of Medicine and Surgery, Yale University School of Medicine, New Haven, CT, USA*



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Chapter 16

Liver transplantation for Wilson disease

AHSAN AHMAD[1], EURIKO TORRAZZA-PEREZ[2], AND MICHAEL L. SCHILSKY[3]*

[1]*Section of Transplantation and Immunology, Department of Surgery, Yale University School of Medicine, New Haven, CT, USA*

[2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of New Mexico, Albuquerque, USA*

[3]*Section of Digestive Diseases and Transplantation and Immunology, Department of Medicine and Surgery, Yale University School of Medicine, New Haven, CT, USA*

Abstract

Liver transplantation (LT) is a life-saving and curative treatment for Wilson disease (WD), providing restoration of function of the liver and mitigation of portal hypertension. Indications for LT in patients with WD include acute liver failure or end-stage liver disease not treatable by medical therapy. LT is also used to treat hepatocellular carcinoma when it develops in patients with WD when tumor resection is not feasible. LT solely for neurologic or psychiatric WD remains controversial. Living liver donation as well as cadaveric orthotopic and auxiliary LT are options for transplantation for WD. Outcomes for LT for WD are excellent, and supportive measures while awaiting transplantation help bridge the patient to a more successful outcome. Future hepatocyte or stem cell transplantation may augment or supplant current LT for WD.

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Chapter 16

Liver transplantation for Wilson disease

AHSAN AHMAD[1], EURIKO TORRAZZA-PEREZ[2], AND MICHAEL L. SCHILSKY[3]*
[1]*Section of Transplantation and Immunology, Department of Surgery, Yale University School of Medicine, New Haven, CT, USA*
[2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of New Mexico, Albuquerque, USA*
[3]*Section of Digestive Diseases and Transplantation and Immunology, Department of Medicine and Surgery, Yale University School of Medicine, New Haven, CT, USA*

Post Tx 6. ayda bakır metabolik parametreler

- normale döner.

Seruloplazmin, serum bakır düzeyi ve idrar bakırı

with time with a functioning graft. Psychiatric symptoms did not appear to undergo significant changes before, during, or after LT; however, the use of steroids and post-LT delirium due to stays in intensive care may affect any transplanted patient.

- Tacrolimus konvulziyon eşiğini düşürür. Siklosporin / mTOR inh. tercih edilmeli
- Kalsinörin inh dozu minimalize edilmeli
- Serum Mg^{++} düzeyi izlenmeli ve replase edilmeli

Clinical Issue

PROGRESS in TRANSPLANTATION

The Need for Consensus About Liver Transplantation For Patients With Neuropsychiatric Wilson's Disease

Progress in Transplantation
2021, Vol. 31(2) 168-170

DOI: 10.1177/15269248211002806
journals.sagepub.com/home/pit
SAGE

Alberto Ferrarese, MD[1] and Patrizia Burra, MD, PhD[1]

Liver transplantation is considered an effective therapeutic option for Wilson's disease (WD) patients with hepatic phenotype, since it removes the inherited defects of copper metabolism, and is associated with excellent graft and patient outcomes. The role of liver transplantation in WD patients with mixed hepatic and neuropsychiatric phenotype has remained controversial over time, mainly because of high post-operative complications, reduced survival and a variable, unpredictable rate of neurological improvement. This article critically discusses the recently published data in this field, focussing in more detail on isolated neuropsychiatric phenotype as a potential indication for liver transplantation in WD patients.

PROGRESS in TRANSPLANTATION

Progress in Transplantation
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SAGE

The Need for Consensus About Liver Transplantation For Patients With Neuropsychiatric Wilson's Disease

Alberto Ferrarese, MD[1] and Patrizia Burra, MD, PhD[1]

Table 1. Pros and Cons of Liver Transplantation for Patients with Wilson's Disease and Isolated Neuropsychiatric Phenotype.

Pros	Co
Prevention of further neuropsychiatric d due to co the	clusion etrospective europsychiatric provement currently unknown. High rate of post-operative complications.

İzole nöropsikiyatrik WH da Tx standart yaklaşım olarak düşünülmemeli

Summary

Liver tr wed as a standard procedure to VD patients with isolated neuropsychia pe, since more data are needed to properly ass e real role of transplant in this disease (Table 1). Nevertheless, it is worth mentioning that strong efforts for a better knowledge of this condition have recently been made, for this indication to be less neglected than in the past. In our

Liver Transplantation for Wilson's Disease in Non-adult Patients: A Systematic Review

Z. Garoufalia[a,*], A. Prodromidou[a], N. Machairas[a,b], I.D. Kostakis[a], P. Stamopoulos[a], N. Zavras[b], I. Fouzas[c], and G.C. Sotiropoulos[a]

Transplantation Proceedings, 51, 443–445 (2019)

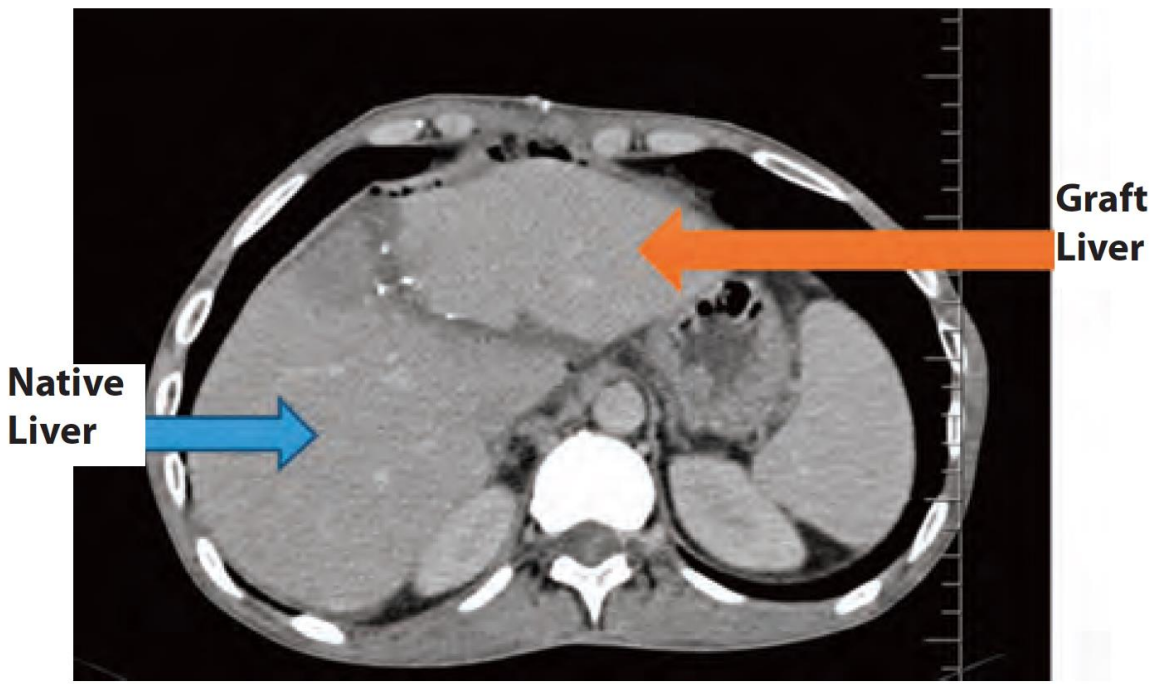
Results. Six studies were included in the present review, which involved 290 children. The main indications for LT included chronic liver failure and fulminant liver failure. The average 1-year survival rate was 91.9%, while the average 5-year survival rate was 88.2%. Retransplantation was performed in 16 patients due to transplant rejection. In general, patients transplanted for WD displayed an excellent quality of life after LT.

Conclusion. LT is a safe and efficient procedure in selected pediatric patients with WD, demonstrating excellent long-term outcomes and quality of life.

Auxiliary Partial Orthotopic Living Liver Transplant for Wilson Disease

Mehmet Haberal,[1] Aydincan Akdur,[1] Gokhan Moray,[1] Sedat Boyacioglu,[2] Adnan Torgay,[3] Gulnaz Arslan,[3] Binnaz Handan Ozdemir[4]

[1]Experimental and Clinical Transplantation (2017) Suppl 1: 182-184



Here, we report a successful auxiliary partial orthotopic liver transplant in a patient without cirrhosis and with neurologic disorder due to WD. Our patient was followed for 7 months. Normal ceruloplasmin level (20 mg/dL), normal liver function tests, and normal neurologic symptoms were observed. To our knowledge, we are the first to report on the efficacy of auxiliary partial orthotopic liver transplant in WD. This case showed that progressive neurologic deterioration with no hepatic insufficiency is considered a suitable indication for auxiliary partial orthotopic liver transplant. Therefore, we suggest that this procedure may also be considered for WD patients with combined hepatic and neurologic involvement. However, orthotopic liver transplant for patients with severe neurologic impairment is still open to debate.

Effect of Liver Transplant on Neurologic Manifestations and Brain Magnetic Resonance Imaging Findings in Wilson Disease

Ruhsen Öcal,[1] Ebru H. Ayvazoğlu Soy,[2] Sibel Benli,[1] Fuldem Dönmez,[3] Muhteşem Ağıldere,[3] Serkan Öcal,[4] Mehmet Haberal[2]

[1]Experimental and Clinical Transplantation (2020) Suppl 1: 84-87

Table 1. Frequency of Wilson Disease Symptoms and Magnetic Resonanc Imaging Findings Before and After Liver Transplant

	Before LT	After LT	Symptom Regression	New-Onset Symptom	Normal MRI	Abnormal MRI
Dystonia + tremor	1	1	1			
Tremor	3	4	3	1	1	3
Asymptomatic	11	10			9	1
Total	15		4	1	10	5

Neurologic recovery and radiologic regression can be achieved by LT; as such, this treatment is effective in improving the quality of life of patients with WD. In our study, neurologic recovery was also seen in patients after LT. Regression in cranial MRI was seen in 1 patient; however, we have no data about duration of regression of cranial MRI findings. One patient in our study had new-onset tremor after LT; however, the patient's MRI had no changes, and this situation was correlated with immunosuppressive therapy. There have been case reports on neurologic and radiologic changes in patients with WD after LT.[12-15] However, prospective trials should be designed on this issue.

Original Article

Journal of Child Neurology
Volume 23 Number 3
March 2008 293-300

10.1177/0883073807309233
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

Neurologic Complications of Liver Transplantation in Pediatric Patients With the Hepatic Form of Wilson's Disease

Ilknur Erol, MD, Füsun Alehan, MD, Figen Ozcay, MD, Oguz Canan, MD, and Mehmet Haberal, MD

J Child Neurol. 2008;23:293-300.

- Tacrolimus 10, siklosporin 2 toplam 16 atak.
- Ataklar serum düzeyleri ile ilişkili
- 4 atak diğer nedenlere bağlı
- Hipomagnezemi ve hipokolesterolemi nörotoksisiteyi arttırıyor

Kronik Wilson hastasında Tx

- Elektiv yapılan hepatik olgularda survi diğer etyolojiler gibi (mükemmel)
- Nöropskiyatrik veya izole nöropsikiyatriklerde sürvi ? (çelişkili sonuçlar)

AMA

- Post Tx nörolojik komplikasyonlara dikkat
  - Tacrolimustan kaçınmalı
  - Serum Mg^{++} düzeyini izlemeli
  - Kolesterol düzeyini izlemeli
- Parkinson bulguları barizlerde Enfeksiyona dikkat!!!

Wilson Hastalığı
Akut karaciğer yetmezliği - TANI

- Başlangıçta aminotransferazlarda ılımlı artış (< 2000 U/L)
- Normal veya belirgin azalmış ALP (< 40 IU/L)
- Belirgin yüksek serum bilirubin düzeyi (> 20 mg/dL)
- Düşük serum ürik asid düzeyi
- **Artan AST/ALT oranı** (>4*, **>2.2****)
- **Düşük ALP artışı/ total bilirubin artışı** (<2*, **<4****)
- Hızlı gelişen renal yetmezlik (tubuler hasar)
- Coombs negatif hemolitik anemi (kadın > erkek)

*Berman DH et al. Clinical differantion of fulminant wilsonian hepatitis from other causes of hepatic failure. Gastroenterology **1991**;1000:1129-1134
Korman JD et al. Screening for Wilson disease in acute liver failure: A comparison of currently available diagnostic tests. Hepatology **2008;48:1167-1174.
Roberts EA, Schilsky MI. Hepatology, 2003

Wilson hastalığı prognostik indeksi (WHPİ, Nazer skoru)

- King's College Hospital and School of Medicine and Dentistry,
- Retrospektif: 27 indeks (6-33 yaş), 7 asemptomatik (6 ay-21 yaş)
- 13 indeks olgu eks (1-53 gün, 5'i ilk 5 günde)
- Değerlendirme: prospektif 11 indeks

Nazer H et al. Gut 1986;27:1377-1381

	0	1	2	3	4
Serum bilirubin (μmol/L)	<100	100-150	151-200	201-300	>300
(mg/dL)	< 5.85	5.85-8.77	8.78-11.7	11.71-17.54	>17.54
Serum aspartat transferaz (IU/L)	<100	100-150	151-200	201-300	>300
PTde uzama (sn)	<4	4-8	9-12	13-20	>20
INR	<1.3	1.3-1.6	1.7-1.9	2-2.4	>2.5

Revize edilmiş King's College skoru (revizyonlu WH prognostik indeksi, RWHPİ)

- King's College Hospital and School of Medicine and Dentistry
- Retrospektif: 74 çocuk (5.9-17.9 yaş)
- Değerlendirme: prospektif 14 indeks

Dhawan A et al. Liver Transplantation 2005;11:441-448

	0	1	2	3	4
Serum bilirubin (μmol/L)	<100	100-150	151-200	201-300	>300
(mg/dL)	< 5.85	5.85-8.77	8.78-11.7	11.71-17.54	>17.54
INR	<1.3	1.3-1.6	1.7-1.9	2-2.4	>2.5
Serum aspartat transferaz (IU/L)	0-100	101-150	151-300	301-400	>401
Lökosit (10^9/L)	0-6.7	6.8-8.3	8.4-10.3	10.4-15.3	>15.4
Albumin (g/L)	>45	34-44	25-33	21-34	<20

Erişkin Wilson hastalarında, transplantasyonu ön görmede prognostik skorlar

	Duyarlılık (%)	Özgüllü	(%)	NPD (%)
WHPI (>7)		.0	92.8	90.4
RWHPI (>1		**95.2**	**92.8**	**90.4**
MEL	63.6	100	100	61.9

Kronik dekompanse hastalık
MELD< 30, WDPI≤7, RWDPI ≤11 ise TX gerekmez

rasek J et al. Revised King's college score for liver transplantation in adult patients with Wilson's disease. Liver Transplantation 2007;13:55-61.

HİÇBİR BAKIR METABOLİZMA PARAMETRESİ TEK BAŞINA TANI İÇİN YETERLİ DEĞİL

(İNDEKS OLGUDA MUTASYON – AİLE TARAMASI DIŞINDA)

ŞÜPHELENDİĞİNDE ARANMALI

AKUT HEPATİTLERDE SERUM VE İDRARTÜM BAKIR PARAMETRELERİ BOZULUR

Serum seruloplazmin düzeyi
Günlük idrar bakırı
Kayser Fleischer halkası
Karaciğer enzimleri

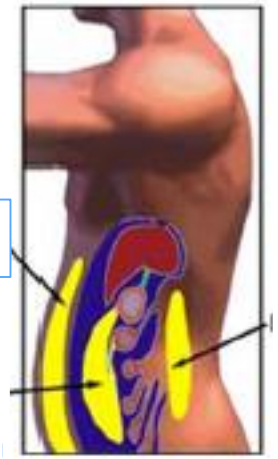
NAFLD - Tx

- ***Pre-Tx***
  - Kardiya Vasküler Hastalık (KVH)
  - Obezite
  - Diyabet
  - ……
    - Kronik Böbrek Yetersizliği (KBY)
- ……PEROPERATİF…….
- ***Post-Tx***
  - Nüks ("Recurrent")
  - *Yeni ("De novo")*
    - POST-TRANSPLANT METABOLİK SENDROM
    - Obezite
    - Yeni Başlayan Diyabet
    - Dislipidemi
    - Hipertansiyon

Aşırı Kalori

(Alım Fazlalığı veya Az Harcama)

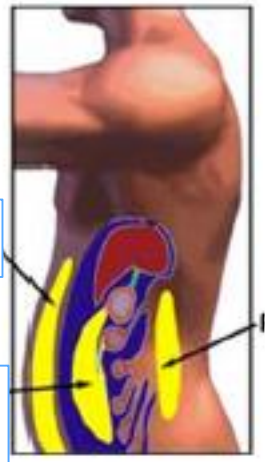
Subkutan



Aşırı Kalori

(Alım Fazlalığı veya Az Harcama)

Subkutan



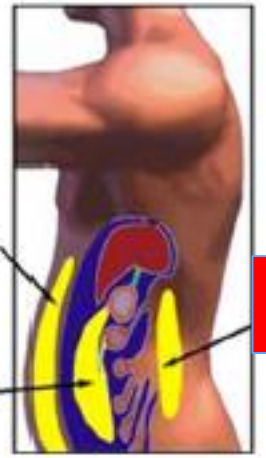
Subkutan Birikim Kapasitesi Aşılırsa

(Genler, etnisite, yaşlanma…)

Aşırı Kalori

(Alım Fazlalığı veya Az Harcama)

Subkutan



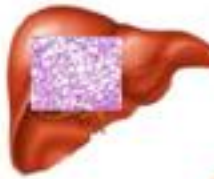
Retroperitoneal

Visseral

Subkutan Birikim Kapasitesi Aşılırsa

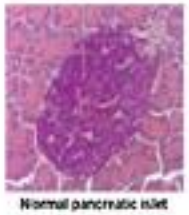
YAĞ

"Taşma"



Hepatik
Lipid Birikimi

Kas
Lipid Birikimi



Beta Hücre Lipid Birikimi

Perivasküler Yağ
Endotelyal Disfonksiyon (Değişen Kan Akımı)

İnsulin Direnci

Beta Hücre Disfonksiyonu

Hiperglisemi

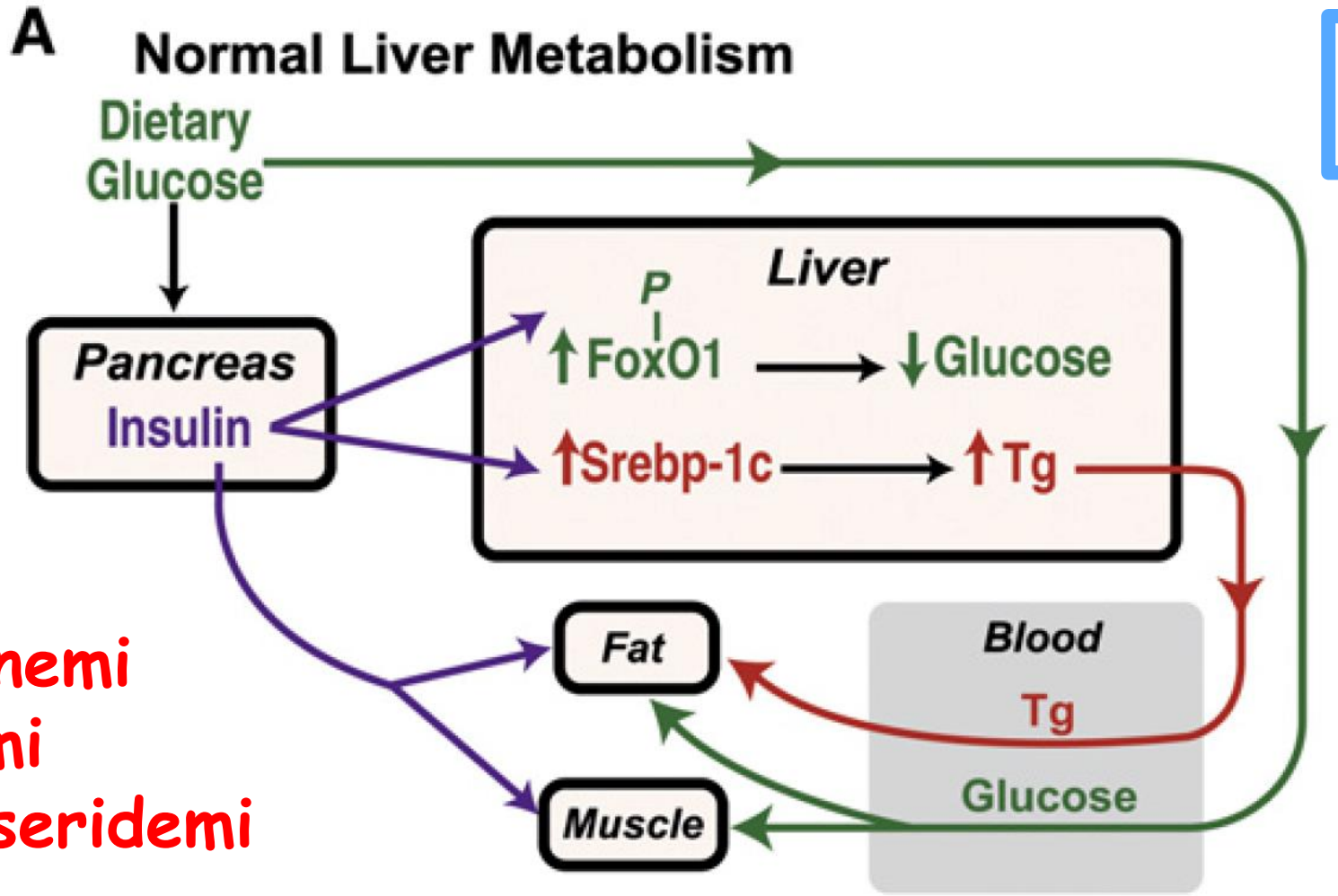
HİPERTRİGLİSERİDEMİ

Cell Metabolism
Previews

Cell Metabolism 7, February 2008 ©

Selective versus Total Insulin Resistance: A Pathogenic Paradox

Michael S. Brown[1,*] and Joseph L. Goldstein[1,*]
[1]Departr



Glukoneogenez ↓
Glukojenoliz ↓

Normoinsülinemi
Normoglisemi
Normotrigliseridemi

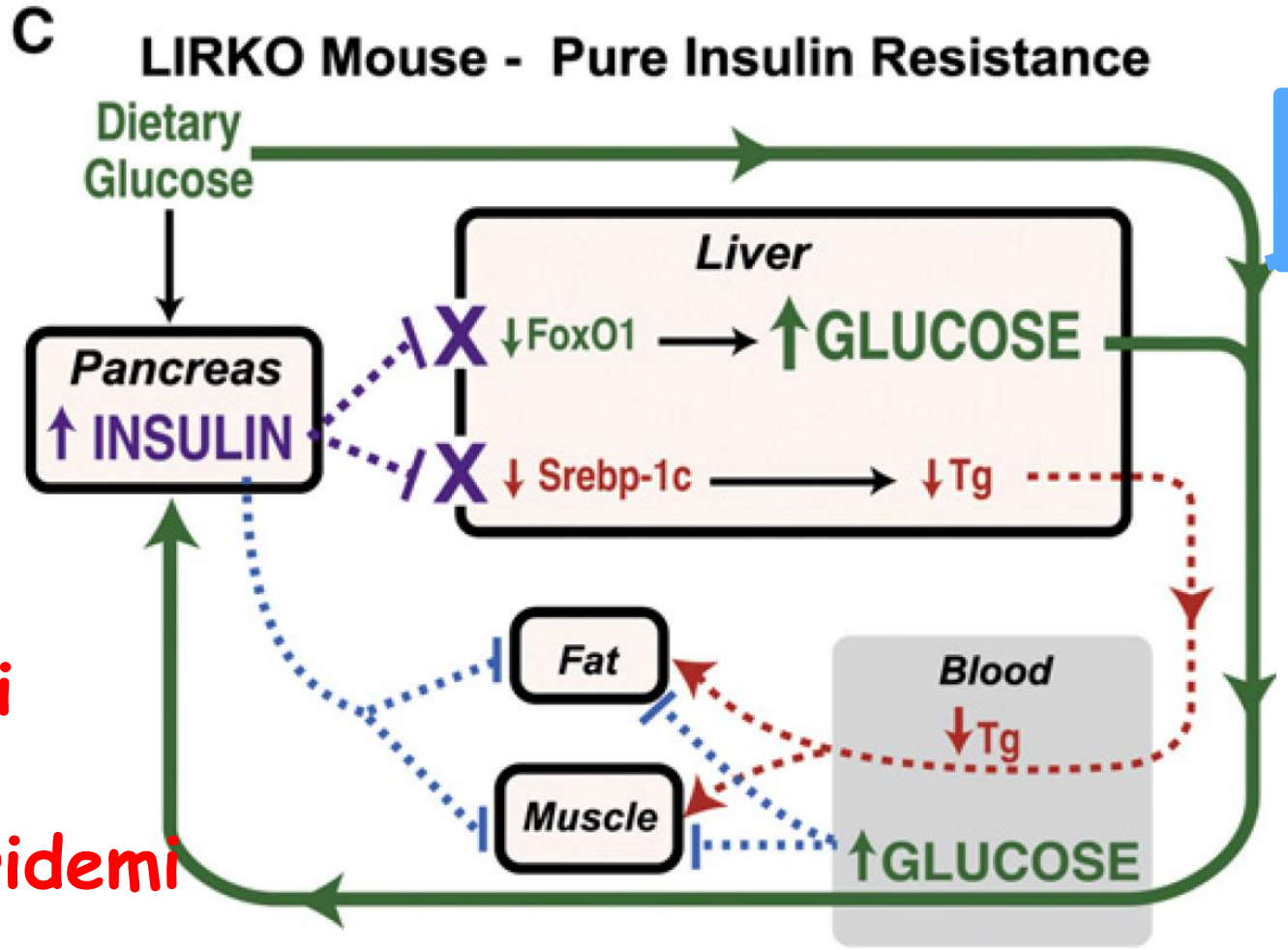
Lipogenez ↑
Glukojen sentezi ↑

Cell Metabolism
Previews

Cell Metabolism 7, February 2008

Selective versus Total Insulin Resistance: A Pathogenic Paradox

Michael S. Brown[1,*] and Joseph L. Goldstein[1,*]
[1]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA



Hiperinsülinemi
Hiperglisemi
Normotrigliseridemi

~~Glukoneogenez ↓~~
~~Glukojenoliz ↓~~

~~Lipogenez ↑~~
~~Glukojen sentezi ↑~~

Hepatic Insulin Resistance Is Sufficient to Produce Dyslipidemia and Susceptibility to Atherosclerosis

Sudha B. Biddinger,[1,5] Antonio Hernandez-Ono,[2,5] Christian Rask-Madsen,[1] Joel T. Haas,[1] José O. Alemán,[3] Ryo Suzuki,[1] Erez F. Scapa,[4] Chhavi Agarwal,[2] Martin C. Carey,[4] Gregory Stephanopoulos,[3] David E. Cohen,[4] George L. King,[1] Henry N. Ginsberg,[2] and C. Ronald Kahn[1,*]

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[2]Department of Medicine, Columbia University, New York, NY 10032, USA
[3]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[4]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[5]These authors contributed equally to this work.
*Correspondence: crkahn@joslin.harvard.edu
DOI 10.1016/j.cmet.2007.11.013

Cell Metabolism 7, 125–134, February 2008

LIRKO faresi

Liver-spesific insülin reseptör knockout

Hepatositte İNSÜLİN RESEPTÖRLERİ YOK

Sadece hepatik İNSÜLİN DİRENCİ VAR

HEM DE TOTAL HEPATİK İNSÜLİN DİRENCİ

Hepatik İnsülin Direnci

- TOTAL - LIRKO fareleri
- SELEKTİV - Tip 2 Diyabet

Cell Metabolism
Previews

Cell Metabolism 7, February 2008

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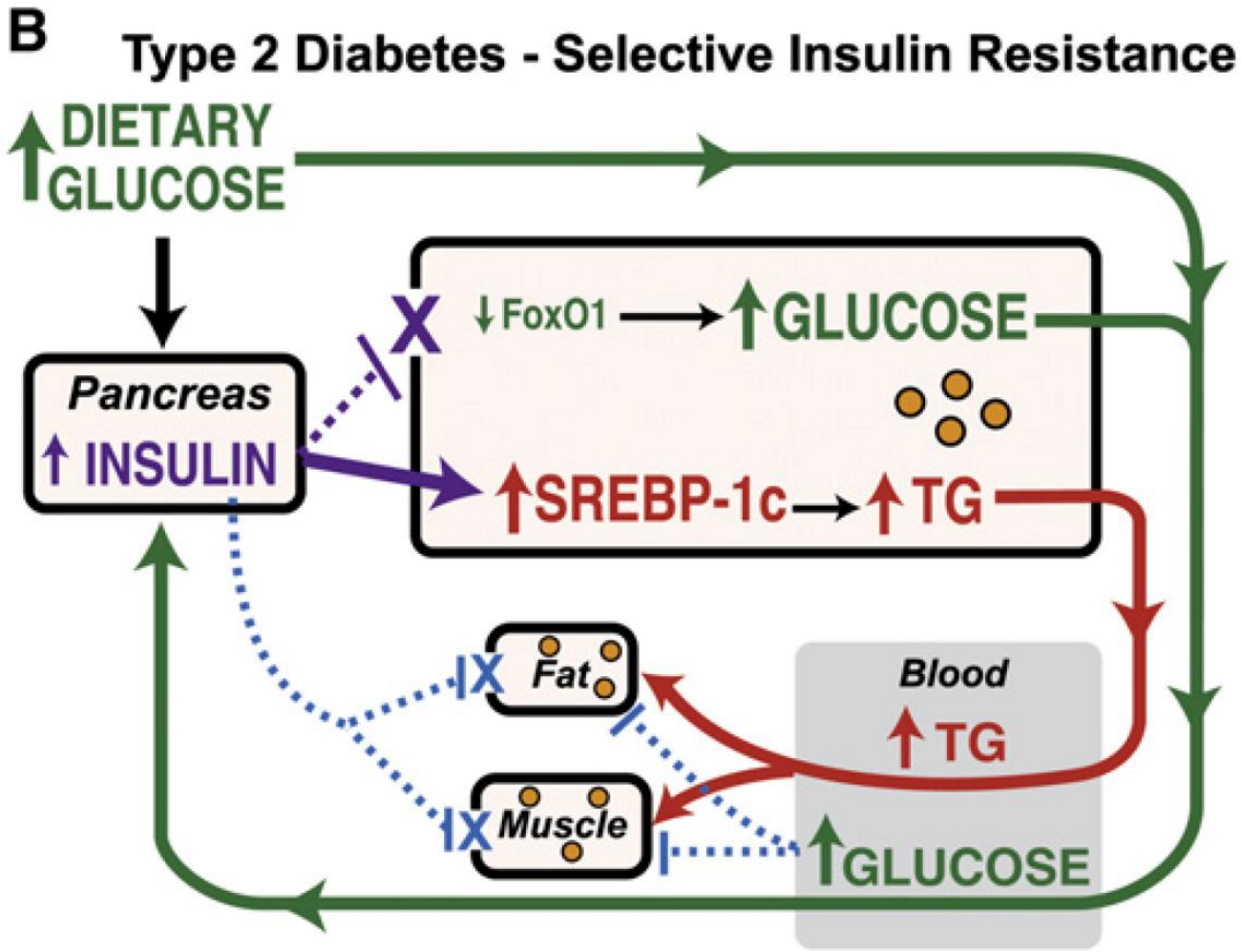
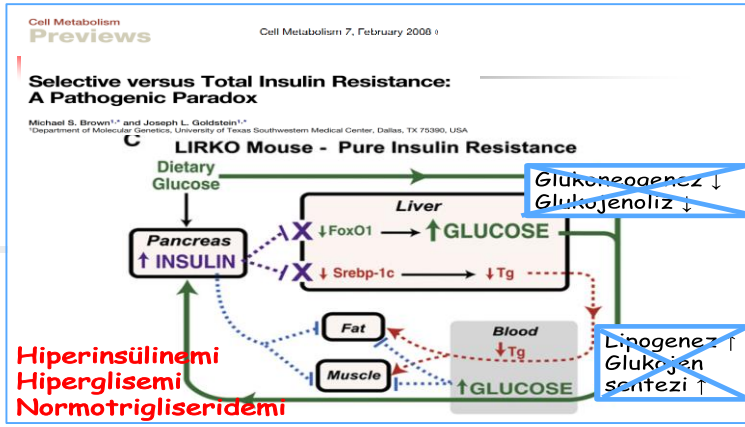
Michael S. Brown[1,*] and Joseph L. Goldstein[1,*]
[1]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA





Glukoneogenez ↓
Glukojenoliz ↓

Glukojen sentezi ↑

Cell Metabolism
Previews

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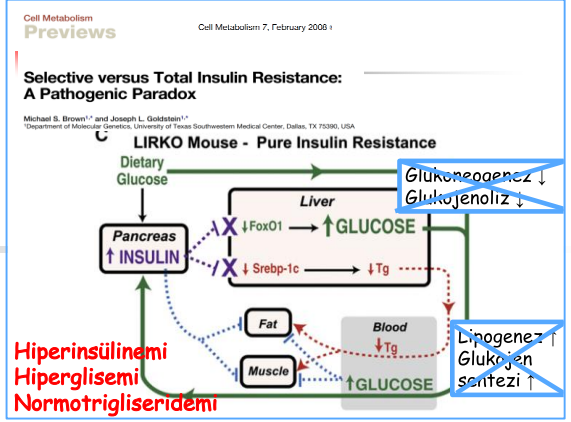
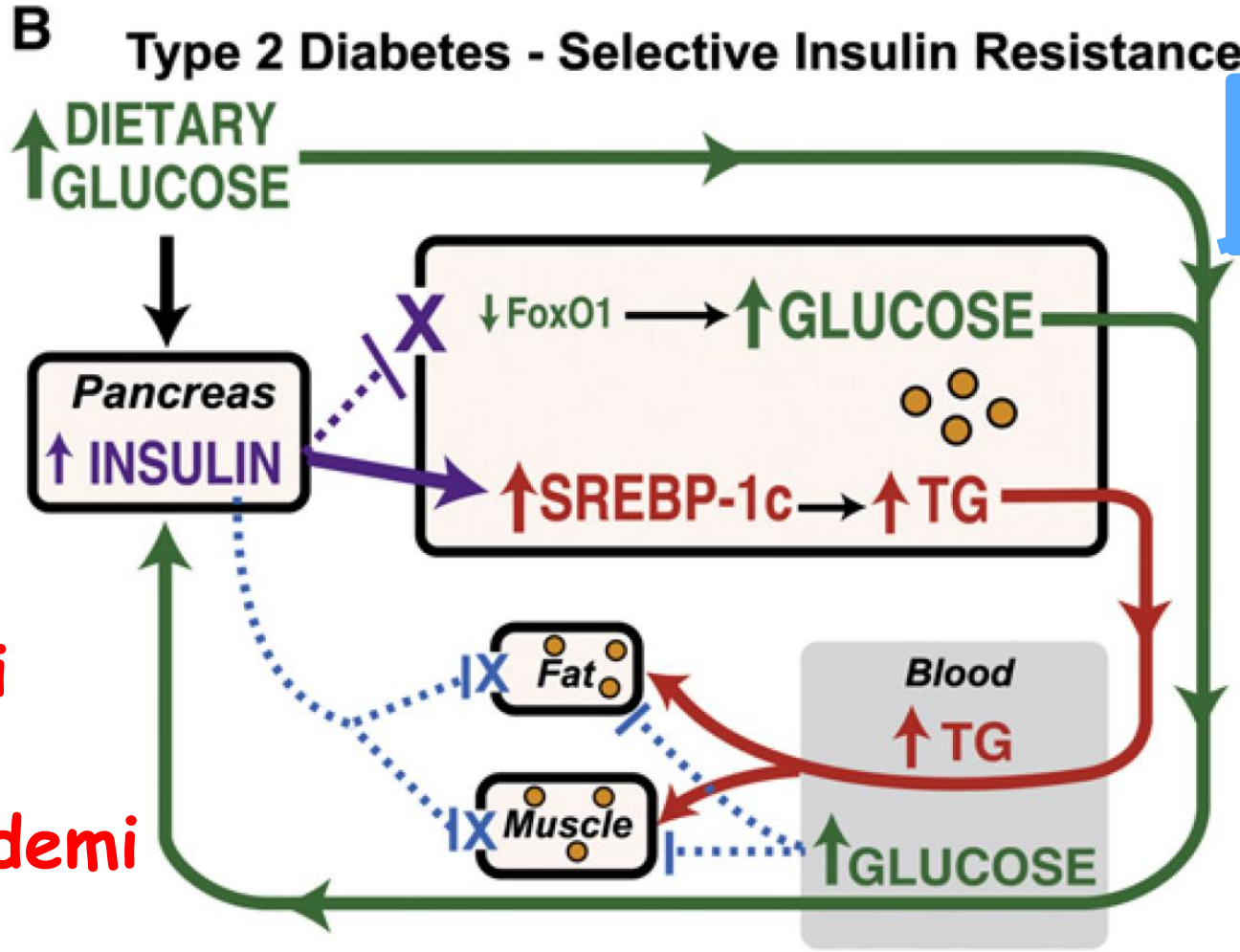




Glukoneogenez ↓
Glukojenoliz ↓

Hiperinsülinemi
Hiperglisemi
Hipertrigliseridemi

Lipogenez
↑
Glukojen sentezi ↑

Lipidomik analizler
NAFLD'da saptanan hepatosit yağları

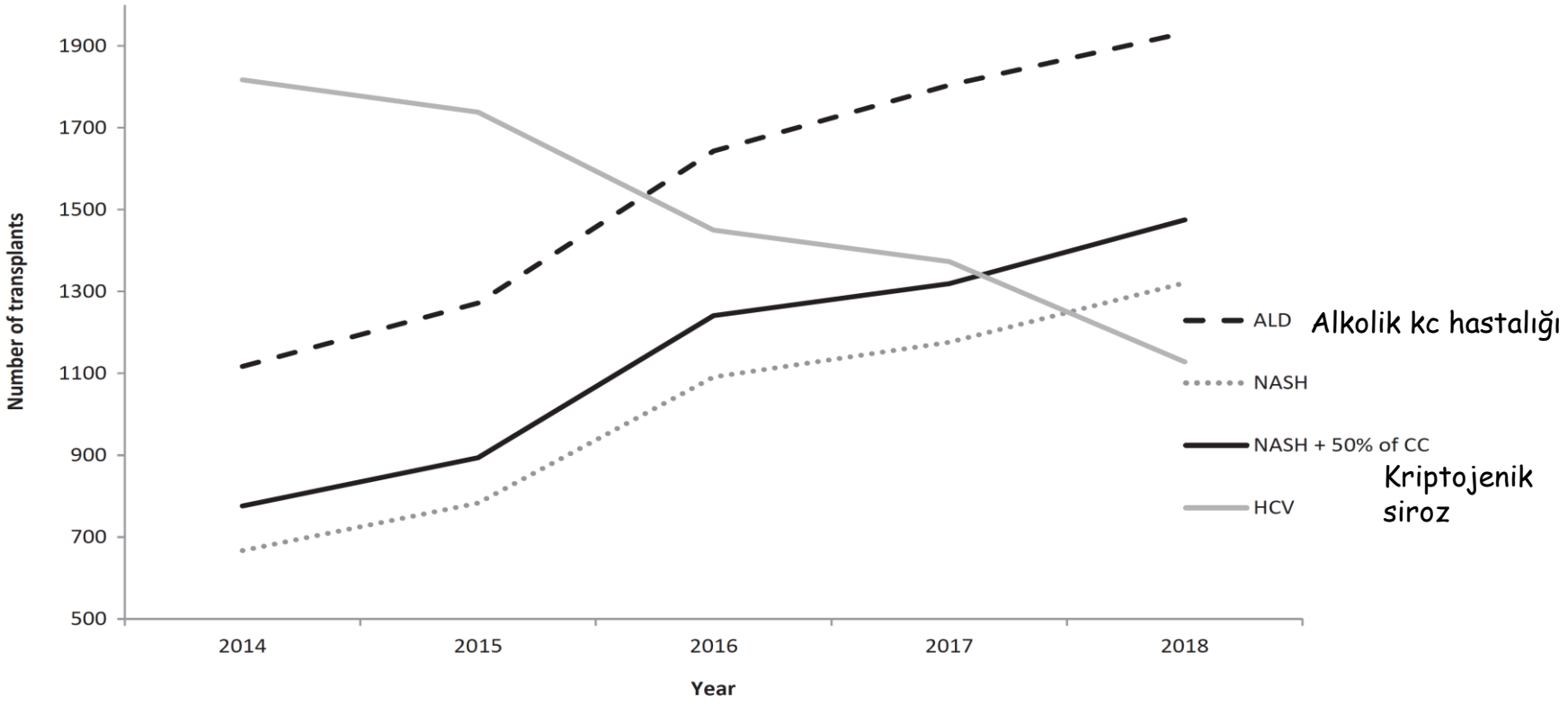
- Trigliserid (triaçil gliserol) **GÖRÜNEN YAĞ**
- **Diaçil gliserol (DAG)**
- **Serbest yağ asitleri** (kısa, orta, **uzun zincirli**)

  (**doymuş**, doymamış)
- Kolesterol
  - **Serbest kolesterol**
  - Kolesterol esterleri
- Fosfolipidler
  - Seramid
  - Sfingomiyelin
  - Fosfoditilkolin
  - ……

GÖRÜNMEYEN YAĞLAR

ABD de 2 . Neden NASH

ABD transplantasyon verileri



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DOI: 10.3748/wjg.v24.i14.1491
World J Gastroenterol 2018 April 14; 24(14): 1491-1506
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
REVIEW

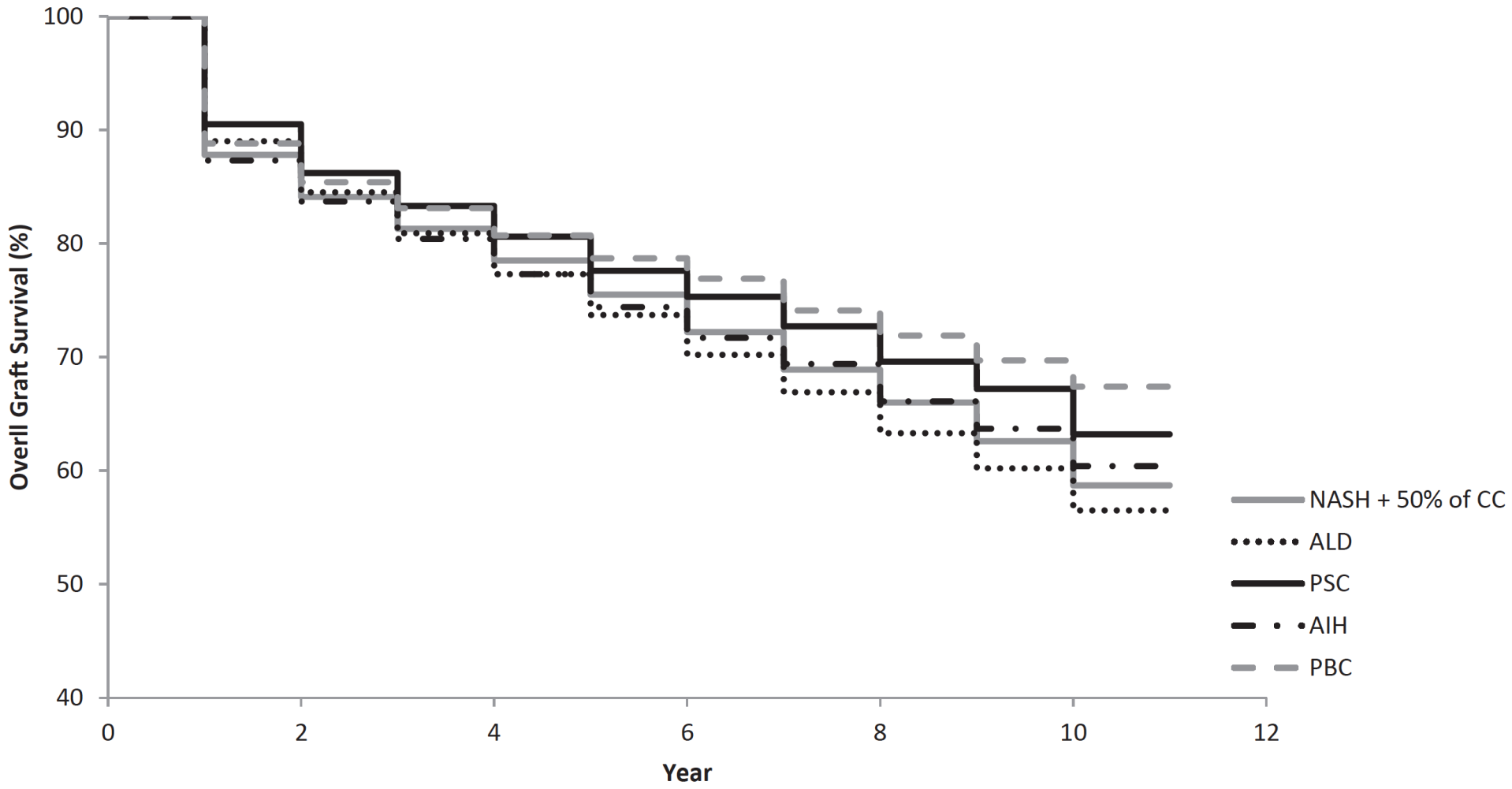
Nonalcoholic fatty liver disease and liver transplantation - Where do we stand?

Ivana Mikolasevic, Tajana Filipec-Kanizaj, Maja Mijic, Ivan Jakopcic, Sandra Milic, Irena Hrstic, Nikola Sobocan, Davor Stimac, Patrizia Burra

Ref.	Study size	NASH group survival (%)	Non-NASH group survival (%)	Study period
Malik *et al*[62]	98 NASH	30-d - 93.9	30-d - 94.4-98.0	1997-2008
	686 Non-NASH group (PBC/PSC, ALD, HCV, CC)	1-yr - 79.6	1-yr - 81.6-87.2	
		5-yr - 72.4	5-yr - 65.3-80.6	
Bhagat *et al*[63]	71 NASH	1-yr - 82	1-yr - 92	1997-2007
	83 ALD	5-yr - 75	5-yr - 86	
		9-yr - 62	9-yr - 76	
Barritt *et al*[64]	21 NAFLD	30-d - 80.9	30-d - 97	2004-2007
	83 Non-NAFLD (ALD, HCV, HBV, PBC/PSC, AIH)	1-yr - 76.2	1-yr - 89.5	
		3-yr - 76.2	3-yr - 83.5	
Agopian *et al*[65]	144 NASH	90-d - 90	90-d - 90-96	1993-2011
	1150 Non-NASH (HBV, HCV, ALD, CC, PBC/PSC)	1-yr - 84	1-yr - 79-87	
		5-yr - 75	5-yr - 54-70	
Kennedy *et al*[66]	129 NASH	1-yr - 90	1-yr - 92	1999-2009
	775 Non-NASH - etiologies not defined	3-yr - 88	3-yr - 86	
		5-yr - 85	5-yr - 80	
Park *et al*[67]	71 NASH	1-yr - 78	1-yr - 87	1998-2008
	472 Non-NASH	2-yr - 78	2-yrs - 85	
Vanwagner *et al*[44]	115 NASH	1-yr - 81.3	1-yr - 88.1	1993-2010
	127 ALD	3-yr - 73.3	3-yr - 85.3	
		5-yr - 60.3	5-yr - 68.8	
Afazali *et al*[68]	1810 NASH	1-yr - 87.6	Variable	1997-2010
	3843 CC	3-yr - 82.2		
	48.085 Non-NASH	5-yr - 76.7		
Charlton *et al*[14]	1959 NASH	1-yr - 84	1-yr - 87	2001-2009
	33822 Non-NASH	3-yr - 78	3-yr - 78	

Cotter TG, Charlton M. Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transplantation 2020;26:141–159

- Diğer etyolojilere benzer greft sürvi



EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
2019, VOL. 13, NO. 2, 173–178
https://doi.org/10.1080/17474124.2019.1551132

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REVIEW

Nonalcoholic steatohepatitis before and after liver transplant: keeping up with the times

Stefano Gitto[a], Fabio Marra[a], Nicola De Maria[b], Florian Bihl[c], Erica Villa[b], Pietro Andreone[d] and Patrizia Burra[e]

- Post Transplant Metabolik Sendrom (PTMS)
- Post Tx NAFLD / NASH
  - Nüks
  - De novo

Kriptojenik Sirozlar Nasıl Değerlendirilmeli???

Lipidomik analizler
NAFLD'da saptanan hepatosit yağları

- Trigliserid (triaçil gliserol)
- **Diaçil gliserol (DAG)**
- **Serbest yağ asitleri** (kısa, orta, **uzun zincirli**)
  (**doymuş**, doymamış)
- Kolesterol
  - **Serbest kolesterol**
  - Kolesterol esterleri
- Fosfolipidler
  - Seramid
  - Sfingomiyelin
  - Fosfoditilkolin
  - .....

Gitto S et al. Nonalcoholic steatohepatitis before and after liver transplant: keeping up with the times Expert Review Of Gastroenterology & Hepatology 2019;13(2):173-178

First author, year	Kind of liver disease	Design	Patients (*n*)	Follow-up (months)	Main conclusion
Malik, 2009	Recurrent	Retrospective	98	36	Features of metabolic syndrome were associated with NASH recurrence; at 18 months, 18% of recipients showed severe NASH
Yalamanchili, 2010	Recurrent	Retrospective	257	120	Advanced fibrosis due to NASH recidivism was uncommon; NASH recurrence did not impair survival
Dureja, 2011	Recurrent	Retrospective	88	60	Features of metabolic syndrome were associated with NASH recurrence; 8.8% of recipients showed severe NASH
Sourianarayanane, 2017	Recurrent	Retrospective	185	60	Patients with NASH recurrence showed a slower fibrosis growth than patients with alcohol-related liver disease
Bhagat, 2009	Recurrent	Retrospective	154	6	One-third of recipients showed NASH recurrence; none developed a severe fibrosis
Bhati, 2017	Recurrent	Retrospective	103	180	Recurrent NASH occurred in nearly 88% of transplanted patients; a quarter of recipients developed advanced fibrosis
Contos, 2001	Recurrent	Retrospective	30	60	All patients developed allograft steatosis at 5 years; 3.3% developed severe fibrosis
Dumortier, 2010	*De novo*	Retrospective	599	120	Thirty-one percent of patients developed allograft steatosis; *de novo* NASH was present in 3.8% of cases
Kim, 2014	*De novo*	Retrospective	156	35	NAFLD was present in 27.1% of cases; pre-LT alcoholic cirrhosis, obesity, and preexisting donor graft steatosis were main risk factors
Gitto, 2018	*De novo*	Retrospective	194	120	Posttransplant NAFLD represented a strong cardiovascular risk factor; *de novo* NASH was an independent predictor of long-term mortality

Recurrent, de novo NAFLD and advanced fibrosis after LT.

Study	Population, N	Time after LT	NAFLD**,#	NASH#	Fibrosis#	Comments
Contos 2001 *	NASH and CC N = 27	1 year	52%	11%	≥F3: 4%	Time-dependent risk of allograft steatosis: at 5 years 100% of assessable patients developed fatty liver. Recurrent NASH developed later than fatty liver alone. Cumulative dose of steroids correlated with time to NAFLD development.
Charlton 2001 *	NASH N = 15	1 year	60%	33%	≥F2: 33%	Cirrhosis developed in 12.5% of patients. 1 patient required re-transplantation for graft failure after 27 months.
Ong 2001 *	CC N = 51	2 years	25.4%	16%	≥F3:4%	Bridging fibrosis occurred in patients with post LT NASH.
Seo 2007§	Non-NAFLD CLD N = 68	2 years	18%	9%	-	Increase of BMI of >10% was associated with post LT NAFLD
Bhagat 2009 *	NASH N = 64	>6 months	-	33%	-	No cirrhosis or re-transplantation because of recurrent disease. 24% of patients developed graft failure over follow-up.
Malik 2009 *	NASH N = 98	5 years	-	25%	-	Recurrent NASH did not adversely affect survival. 6 patients in NASH group were re-transplanted within 60 days after LT.
Yalamanchili 2010 *	NASH and C N = 257					Advanced fibrosis was more frequent amount those with post LT NASH (31%) than simple steatosis (6%)
Dumortier 2010§	Non-NAFLD CLD N = 421	>6 months	31%	5.3%	≥F3: 2.25%	Most of the patients (52%) had grade 1 steatosis. The evolution of NAFLD during follow-up was: regression (48%), stability (22%), progression (30%). PTMS and liver graft steatosis were independent predictors of *de novo* NAFLD.
Dureja 2011 *	NASH or CC N = 88	1 year	39%	28%	≥F2: 9%	Only 9% of recurrent NAFLD had NAS ≥5. NAFLD recurrence was associated with increased risk for CV disease and correlated with post-transplant BMI, post LT TG levels and corticosteroids dose at 6 month.
El Attrache 2012 *	NASH and CC N = 83	1.5 years	-	24%	≥F3: 3.6%	The recurrence rate was significantly higher amoung patients with PTMS (34% *vs.* 13% in patients without MS). 3 patients were re-transplanted secondary to graft failure from NASH recurrence.
Kim 2014§	Non-NAFLD CLD N = 156	>1 year	27.1%	6.7%	F2: 4.4%	Obesity and donor graft steatosis were independent predictors for post LT NAFLD.

Kısmen çelişkili sonuçlar!!!

Cotter TG, Charlton M. Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transplantation 2020;26:141–159

- Post Tx 5. yılda;
  - Nüks NAFLD % 39-40 , de novo NAFLD % 10-20
  - Nüks NASH % 7-30, de novo NASH % 5-9
- Nüks daha erken ve daha agresiv (farklı antiteler mi?
- Histolojik olarak nüks / de novo/ preTx NASHten histolojik farklılık yok

Seo S, et al. De novo nonalcoholic fatty liver disease after liver transplantation. Liver Transpl 2007;13:844-847., Vallin M, et al. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. Liver Transpl 2014;20:1064 1071., Yalamanchili K, et al. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. LiverTranspl 2010;16:431-439. Contos MJ, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis Liver Transpl 2001;7:363-373. , Dureja P, et al. NAFLD recurrence in liver transplant recipients. Transplantation 2011;91:684-689.

- 17 çalışma metanaliz, 2378 post Tx hasta
- 5. yılda
  - nüks NAFLD % 82, de novo NAFLD % 78
  - nüks NASH % 38, de novo NASH % 17

Saeed N, et al. Incidence and risks for non alcoholic fatty liver disease and steatohepatitis post liver transplant: systematic review and metaanalysis. Transplantation 2019;103:e345-e354.

Nüks / De novo NAFLD farklı antite mi?

- *De novo* ve nüks NAFLD
  - Histolojik özellikleri ile ayırt edilemez
  - Doğal seyri FARKLI
- Nüks NAFLD daha şiddetli, erken başlar
- 5. yılda köprüleşen fibroz
  - Nüks NAFLD da % 71
  - *de novo* NAFLD da % 12.5

Vallin M et al. Recurrent or de novo nonalcoholic fatty liver disease after liver transplantation: natural history based on liver biopsy analysis. Liver Transpl. 2014; 20:1064–1071.

- De novo NAFLD artan kardiyavasküler hastalık ve nonhepatik kanserler ile sürviyi azaltır.

Gitto S et al. De-novo nonalcoholic steatohepatitis is associated with long-term increased mortality in liver transplant recipientsEur J Gastroenterol Hepatol 2018;30(7):766-773.

Management of Recurrent and De Novo NAFLD/NASH After Liver Transplantation

Giacomo Germani, MD, PhD,[1] Marie Laryea, MD,[2] Laura Rubbia-Brandt, MD,[3] Hiroto Egawa, MD,[4] Patrizia Burra, MD,[1] John O'Grady, MD,[5] and Kymberly D. Watt, MD[6]

Transplantation 2019;103: 57–67

- Histolojik özellikler farklı değil
- Nüks NAFLD daha fazla ve agresiv

Risk factors for NAFLD/NASH post-LT

Known [14,18-22]	Possible
• Diabetes	• Tacrolimus-based immunosuppresion [5]
• Hypertension	• Female sex
• Hyperlipidemia	
• Renal dysfunction	
• Obesity/weight gain	
• Genetic polymorphism PNPLA3 [33, 34]	
• PFIC-1 as indication for liver transplantation [36]	

Cotter TG, Charlton M. Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transplantation 2020;26:141–159

- Post Transplant Metabolik Sendrom (PTMS): obezite, diyabet, hipertansiyon, dislipidemi
- NASH / Kriptojenik sirozlularda % 90
- Bağımsız risk faktörleri:
  - İleri yaş (OR, 1.04),
  - Yüksek VKİ (OR, 4.68),
  - Hipertrigliseridemi (OR, 1.01),
  - Düşük HDL kolesterol (0.96),
  - Diyabetin varlığı (OR, 5.95),
  - Kriptojenik siroz (OR, 3.42)

Outcome	CS	TAC	Cyclosporine	mTORi
Obesity	++	+	+	–
Yeni başlayan DM	+++	+	+	<–>
Dyslipidemia	+	+	++	+++
Hypertension	+	++	++	<–>

NOTE: +: relative effect in promoting facet of metabolic syndrome (+<++<+++); –: decreased frequency of facet of metabolic syndrome; <–>: no change.

Laish I, et al. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver Transpl 2011;17:15-22.

- Ölüm nedenleri:
  - Malinite %33
  - Kardiyovasküler olay % 24
  - Serebrovasküler olay % 7

Adam R, et al.; for European Liver Transplant Association. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl 2003;9:1231-1243.

Post Transplant Metabolik Sendrom

- PTMSlilerin
  - Nüks NAFLD % 34 ü
  - *De novo* NAFLD prevalansı ???

Metabolik risk faktörleri; Obezite, Hipertansiyon, Hipertrigliseridemi, Düşük HDL kolesterol, İR, Diyabet …)

1 faktör + ise	% 12
2 faktör	% 22
3 faktör	%29
4 faktör	% 65
5 faktör	% 81
6 faktör	% 100

El Atrache MM, et al. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. Clin Transplant. 2012; 26:E505-E512.

Effects of immunosuppressive regimens on PTMS components.

PTMS features	Corticosteroids	Calcineurin inhibitors		mTOR inhibitors (sirolimus, everolimus)
		Tacrolimus	Cyclosporine	
Abdominal obesity	+	–	–	–
New-onset diabetes	+++	++	+	–
Dyslipidemia	+	+	+	+++
Hypertension	+	++	++	+

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REVIEW

Nonalcoholic steatohepatitis before and after liver transplant: keeping up with the times

Stefano Gitto[a], Fabio Marra[a], Nicola De Maria[b], Florian Bihl[c], Erica Villa[b], Pietro Andreone[d] and Patrizia Burra[e]

- Bekleme listesinde de mortalite morbitide yüksek (Diyabeti hiperlipidemi, obezite..)
- Kardiyovasküler hastalıklar, neoplastik hastalıklar,..
- Post Tx nutrisyonel durum düzelir ve kalori alımı artar, etyolojiden bağımsız,

Merli M, et al. Improvement of nutritional status in malnourished cirrhotic patients one year after liver transplantation. e-SPEN. 2011;6:e142–e147.

- Öz. İlk 6 ayda belirgin, 1. yılda 5.1 kg, 3. yılda 9.5 kg kilo aslır

Richards J,et al. Weight gain and obesity after liver transplantation. Transpl Int. 2005;18:461–466.

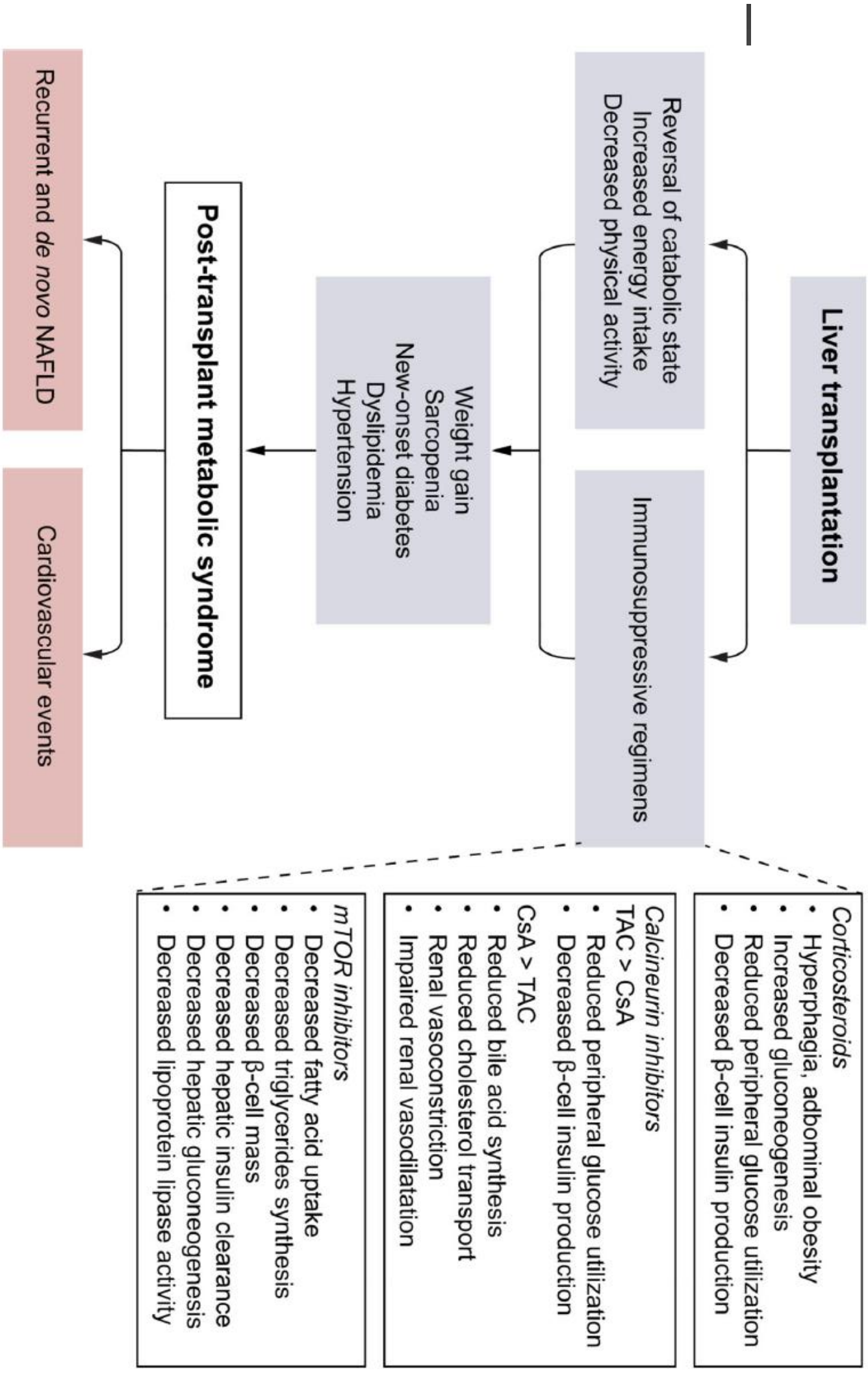
- 4 yılda % 58 fazla kilolu, % 21 obez

Anastàcio LR, et al. Body compositionand overweight of liver transplant recipients. Transplantation. 2011;92:947–951.

J Hepatol. 2016 December ; 65(6): 1245–1257. doi:10.1016/j.jhep.2016.07.033.

NAFLD and liver transplantation: Current burden and expected challenges

Raluca Pais[1,2,*], **A. Sidney Barritt 4th**[3], **Yvon Calmus**[1,2], **Olivier Scatton**[4], **Thomas Runge**[3], **Pascal Lebray**[1], **Thierry Poynard**[1,2], **Vlad Ratziu**[1,2,†], and **Filomena Conti**[1,2,†]



NAFLD and liver transplantation: Disease burden, current management and future challenges

Patrizia Burra,[1,*] Chiara Becchetti,[1,2] Giacomo Germani[1]

JHEP Reports **2020** vol. 2 | 100192

Condition	Recommendations
Diabetes mellitus	• OGTT is the gold standard for diagnosis of diabetes mellitus. • HbA1c if used should be associated to continuous blood glucose monitoring. • Adequate glycaemic control should be achieved. • Careful assessment of severity of liver disease is mandatory to identify the best therapeutic approach.
Nutritional status	• Assessment of nutritional status is mandatory before LT. • For obese patients, lifestyle modification represents the first-line intervention. • Healthy diet should be promoted according to indication shown in Figure 2. • Physical exercise should focus on preservation of residual motility. Caution should be taken in malnourished and sarcopenic patients to avoid increase of catabolism and muscle loss. • In obese patients not responding to diet and physical exercise pharmacological therapy or bariatric surgery can be carefully considered.
Cardiovascular disease	• Pre-LT cardiovascular risk stratification is mandatory. • Specific algorithm of cardiac work-up should be followed as shown in Fig. 1.
Kidney dysfunction	• Kidney function should be adequately monitored before LT. • Combined liver-kidney transplantation should be reserved for patients according to internationally recognised indications.
Malignancies	• Screening for pre-LT malignancies should follow the same protocols applied to patients with no-NAFLD related cirrhosis. • Particular attention should be paid to the gastrointestinal tract and genital system.

HbA1c, glycated haemoglobin; LT, liver transplant; NAFLD, non-alcoholic fatty liver disease; OGTT, oral glucose tolerance test.

Condition	Recommendations
Diabetes mellitus	• Immunosuppressive drug modulation is recommended including early tapering of steroids, and minimisation of CNIs by adding anti-metabolites or mTORi. • The use of oral anti-diabetic drugs such as metformin, rosiglitazone, pioglitazone and sulfonylureas can be considered alone or in association with insulin to minimise its use. • GLP-1 RAs and DPP-4 inhibitors are now routinely used in solid organ transplanted patients; however, attention must be paid to their interactions with immunosuppressive therapy. • In patients not achieving therapeutic goals, insulin remains the therapy of choice.
Obesity	• Lifestyle modification should include healthy diet and regular mild to moderate physical activity. • No data are available on pharmacological treatments in the post-LT setting. • When lifestyle modifications are not effective bariatric surgery can be considered, with sleeve gastrectomy preferred to Roux-en-Y gastric bypass. • Endoscopic bariatric therapy is a potential new approach for obese patients after LT.
Dyslipidaemia	• Lifestyle modification is the first-line treatment, although this condition is usually refractory to dietary interventions. • In patients not responding to lifestyle modifications, statins represent the first-line option. • Attention should be paid to interactions between statins and immunosuppressive drugs. • Fibrates can be considered when statins are not tolerated. • Attention should be paid to the development of myopathy. • Omega-3 fish oil can be beneficial for isolated post-LT hypertriglyceridaemia.
Arterial hypertension	• Lifestyle modification, such as low-sodium diet and cessation of smoking, is the first-line treatment. • Modulation of immunosuppressive therapy is necessary with minimisation of CNIs by adding anti-metabolites or mTORi. • In patients without proteinuria, dihydropyridine calcium channel blockers represent the first choice. • Otherwise ACE inhibitors or angiotensin II receptor blockers can be considered. • Beta-blockers find their primary indication when heart decompensation or arrhythmia are present.
Cardiovascular disease	• Patients with specific risk factors, such as age >55 years old, male sex, diabetes mellitus and kidney failure, should be adequately monitored in the post-LT period. • In patients presenting specific risk factors, a cardiovascular follow-up with echocardiography at 6, 12, and 24 months after LT can be suggested.
Kidney dysfunction	• In patients presenting with CKD at LT, immunosuppressive minimisation strategies should be used, alongside interventions to prevent/treat metabolic complications, such as diabetes and hypertension.

ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CNI, calcineurin inhibitors; DPP-4, dipeptidyl peptidase-4; GLP1 RAs, glucagon-like peptide-1 receptor agonists; LT, liver transplant; mTORi, mammalian target of rapamycin inhibitors.

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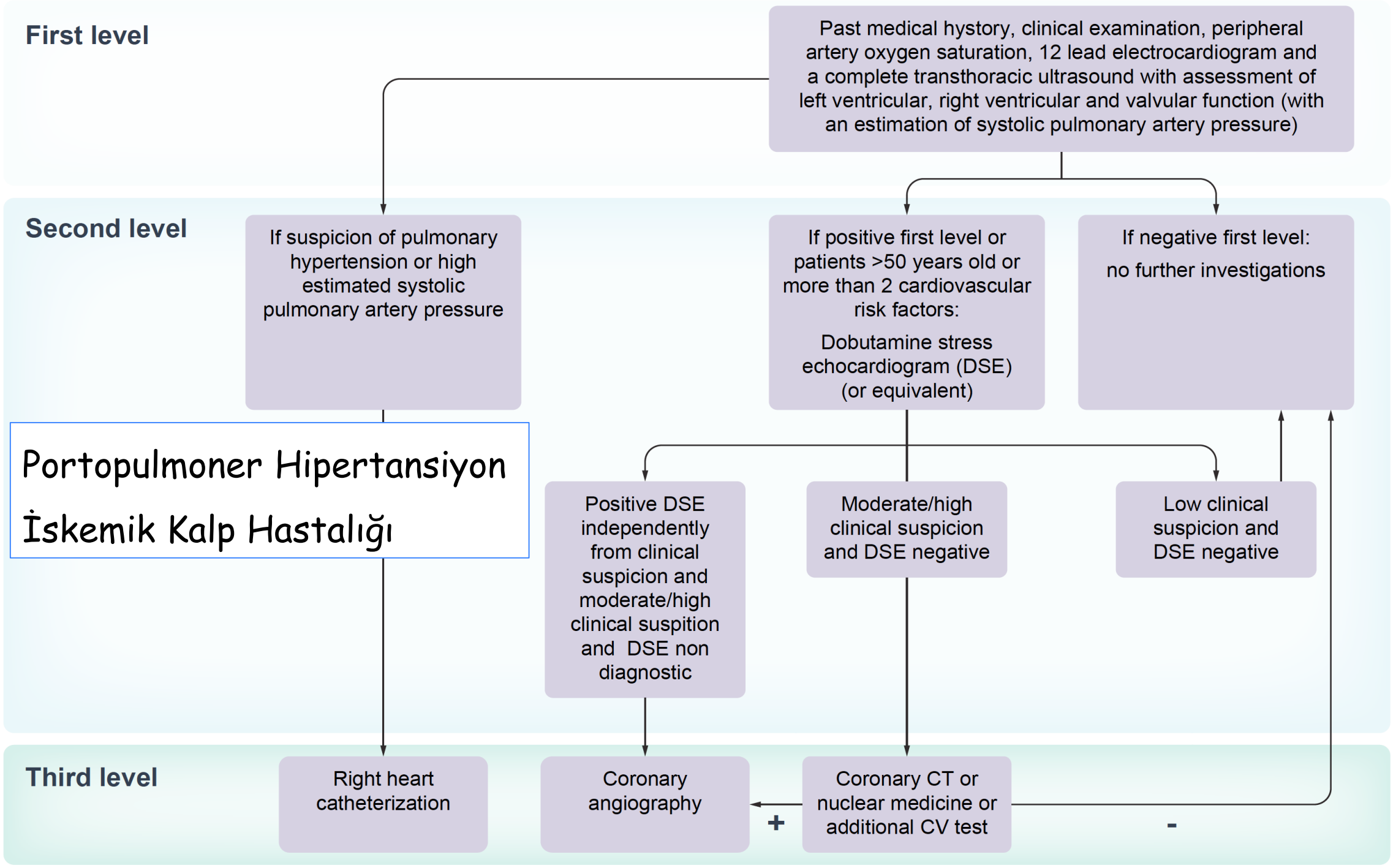

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
2019, VOL. 13, NO. 2, 173–178
https://doi.org/10.1080/17474124.2019.1551132

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REVIEW

Nonalcoholic steatohepatitis before and after liver transplant: keeping up with the times

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- **Pre /post Tx sadece karaciğer değil KardiyoVasküler (KVS) risk göz önünde tutulmalı (MELD?, MELD-Na?)**

- Presirotik dönemde HCC gelişimi beklemede handikap
- Post Tx : KVS fazla, sepsis fazla (obezite, diyabet), kronik böbrek yetersizliği fazla

Pre Tx obezlerde

- Portal hipertansiyon ve hepatik disfonksiyondan bağımsız dekompansasyon fazla (% 15 vs % 43 (p = 0.011)

Berzigotti A, et al.; for Portal Hypertension Collaborative Group. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011;54:555-561.

- Sarkopeni daha fazla

Hong HC, et al. Relationship between sarcopenia and nonalcoholic fatty liver disease: the Korean Sarcopenic Obesity Study. Hepatology 2014;59:1772-1778.
Issa Det al. Presence of sarcopenia (muscle wasting) in patients with nonalcoholic steatohepatitis. Hepatology 2014;60:428-429
.

- Ameliyat süresini uzun, YBÜ kalışı, enfeksiyöz ve biliyer komplikasyonlar fazla

LaMattina JC, et al. Complications associated with liver transplantation in the obese recipient. Clin Transplant 2012;26:910-918.

- Obezite ve diyabet nedeniyle post Tx infeksiyöz risk daha fazla

Wang X, et al. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:394-402
.

- Pre- ve post Tx kardiyovasküler sorunlar ve post Tx renal yetersizlik fazla

VanWagner LB, et al. Impact of renal impairment on cardiovascular disease mortality after liver transplantation for nonalcoholic steatohepatitis cirrhosis. Liver Int. 2015;35:2575-2583.
Fussner LA, et al. The impact of gender and NASH on chronic kidney disease before and after liver transplantation. Liver Int. 2014;34:1259-1266.

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Every meal

- Use healthy oils, like olive oil, for cooking or on salad. Limit butter and avoid trans-fats.
- Drink preferentially water according to clinical indication, when fluid restriction is prescribed. Avoid all kind of sugary beverages and alcohol.
- Limit the use of salt on food. Eventually use onions, garlic or spices to flavour the food.
- When other comorbidities may be present (*i.e.* diabetes or overweight/obesity), specific dietary adjustments can be required.
- Specific counseling can be required to address barriers towards a healthy diet.

Vegetables

- More than 2 vegetables.
- Variety of coulor and seasonality preferred.

Fruits

- 1-2 fruits
- Diabetic patients should preferred less naturally sugary fruits.

Whole grain

- 1-2 portions of whole grains (like pasta, bread, brown rice and other cereals)
- Diabetic patients should limit at 1 per/day.
- Limit the use of refined grains.

Daily

- Drink coffee with moderation (2 cups per day)
- Split food intake into 3 main meals (breakfast, lunch and dinner) and 3 snacks (mid-morning, mid-afternoon, late evening). The late-evening snack is the most important and adding an amount of protein is advisible

Dairy products

- 1-2 portions per/day (like yoghurt, milk, cheese)
- Low-fat products preferred.

Healthy proteins

- 1 portion per/day varying between fish, poultry or white meat, beans, eggs and nuts.

Weekly

- Stay active. Regular physical activity according to clinical condition, either aerobic or not, at least two times per week.

Red meat

- Less than 2 portions per week
- Avoid bacon, cold cuts, sausages and processed meat

Cake and pastries

- Less than 1 portion per week
- Should be avoided by obese patients

Cotter TG, Charlton M. Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transplantation 2020;26:141–159

- Düşük kalorili Akdeniz diyeti, 60 mL zeytinyağı ve yer fıstığı yemek, et ve hayvansal yağlardan uzak durmak önerilir.
- 2 kupa filtre kahve fibrozu azaltır, >4 kupa mortaliteyi % 12 azaltır.
- Espresso ve çay etkisi (?)

Anty R, et al. Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery. J Hepatol 2012;57:1090-1096.

- Kolesterol hepatositi
  - TNF alfa ve Fas ligandına hassas kılar

Mar. M, et al. Mitochondrial free cholesterol loading sensitizes to TNFand Fas-mediated steatohepatitis. Cell Metab 2006;4:185-198

.

  - Mitokondrial glutatyonu azaltır, membran integrasyonu bozulur, fonksiyon ve sayı azalır. Glutatyon replasmanı NASH histolojik bulguları ve mit fonksiyonları düzeltebilir

Caballero F, et al. Specific contribution of methionine and choline in nutritional nonalcoholic steatohepatitis: impact on mitochondrial S-adenosyl-l-methionine and glutathione. J Biol Chem 2010;285:18528-18536., Mar. M, et al. Mitochondrial glutathione, a key survival antioxidant. Antioxid Redox Signal 2009;11:2685-2700., Leiter LA, et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebocontrolled study with a 28-week extension. J Am Geriatr Soc 2014;62:1252-1262.

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- Verici karaciğerinde > % 30 makroveziküler yağlanma istenmez
- Preservativ hasarı artar. Vasküler ve biliyer komplikasyonlar, erken allogreft disfonksiyonu, primer gerft yetmezliği

Potansiyel obez vericiye uygulanacak protokol

- 2-8 hafta protein zengin hipokalorik diyet (1000 kcal/gün)
- Egzersiz programı (600 kcal /gün yakacak)
- Bezofibrat 400 mg ile hasar minimalize edilebilir.

Pre Tx Bariyatrik cerrahi

- Ppre Tx Bariyatrik cerrahide mortalite:
  - Kompanse sirozda % 0.9,
  - Dekompanse sirozda % 16

Mosko JD, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. Clin Gastroenterol Hepatol. 2011; 9:897–901. [PubMed: 21782772]

- Tx + sleeeve gastrektomi kombinasyonu
  - VKİ ort. 48 kg/m2 den 29 kg/m2 azalır
  - post Tx diyabet ve steatoz azalır

Heimbach JK, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. Am J Transplant. 2013; 13:363–368.

- 22 hastalık seri komplikasyon % 32, mortalite % 13.6

Lazzati A, et al. Bariatric surgery and liver transplantation: a systematic review a new frontier for bariatric surgery. Obes Surg. 2015; 25:134–142.

Management of Recurrent and De Novo NAFLD/NASH After Liver Transplantation

Giacomo Germani, MD, PhD,[1] Marie Laryea, MD,[2] Laura Rubbia-Brandt, MD,[3] Hiroto Egawa, MD,[4] Patrizia Burra, MD,[1] John O'Grady, MD,[5] and Kymberly D. Watt, MD[6]

Transplantation 2019;103: 57–67

- Histolojik özellikler farklı değil
- Nüks NAFLD daha fazla ve agresiv

Potential impact on NASH of medications currently used in the management of MS (based on data from nontransplant patients)

Improve steatosis	• ACE inhibitors [6] • Fish oil/Omega 3 [29, 30] • Pioglitazone [31] • Vitamin E [46] • GLIP-1 agonist [100]
Improve necroinflammatoryinfiltrate/ steatohepatitis	• Ace inhibitors [6] • Fish oil/Omega 3 [30] • Pioglitazone [31], Vitamin E [46] • GLIP-1 agonist [100]
Improve fibrosis	• Ace inhibitors [27] • Fish oil/Omega 3 [27]

Yeni Başlayan Diyabet

- 1/3 ünde gelişir.
- % 80 ilk ayda
- Metilprednisolon bolusları, obezite, HCV enfeksiyonu
- Erken dönemde insülin ve diyabet diyeti
- Metformin (yan etkileri !), sülfanilüre ve tioglitazonlara tercih (kilo alımı)

Post Tx Hipertansiyon

- Steroidler, mineralokortikoid etki, kardiyak kontraktiliteyi artırır, vasküler direnci arttırır
- Kalsinörin inh renovasküler ve sistemik vazokonstriksiyon (mTORinh lerinden daha fazla HT)
- Kalsiyum kanal blokerleri Amlodipin ilk seçenek (Nifedipin p450 inh dikkat)
- Loop diüretikler ve betablokerler ikincil seçenek
- ARB ve ACE inh CNIlerin renal toksistesini azaltabilir AMA hiperkalemiye dikkat
- Nonloop diüretiklere dikkat (metabolik etkiler)

Post Tx Dislipidemi

- CNİ dislipidemik ajanlar (Cyclo>> TAC)
- mTOR potent dislipidemi
- Sirolimus insülin sinyalizasyonunu da bozar, CNİ kombinasyonu DİKKAT
- Pravastatin 20 mg/dL güvenli (p450 ilgisiz) Atorvastatin ve rozuvastatin de iyi
- Statinler TAC ve Cyclo seviyesini azaltabilir
- Ezetimid (hepatotoksik) post Tx güvenli AMA etkisiz

TG > 200 mg/dL tedavi düşün

- Fish oil 2X1000 mg hipertrigliseridemide ilk seçenek
- Gemfibrozil, fibratlarda iyi (lipofilik CNİleri etkilemez yada az etkiler)

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Drug	Mechanism of Action	Dosing	Efficacy*	Disadvantages
Orlistat	Pancreatic and gastric lipase inhibitor	Capsule: 120 mg 3 times daily†	8% weight loss from baseline	30% with gastrointestinal intolerance
Lorcaserin	5-HT2C receptor agonist	Tablet: 10 mg bid Discontinue at 12 weeks if 5% weight loss from baseline not achieved	5.8 kg of weight loss	Adverse effects include headaches and nausea
Pheniramine/ Topiramate	Norepinephrine-releasing agent/GABA receptor modulation agent	Capsule: 3.75/23 mg, >1 tablet daily increasing to a maximum of 4 tablets daily Discontinue or escalate after 12 weeks if 3% weight loss from baseline not achieved	8-10 kg of weight loss	Use with caution in cardiac disease
Naltrexone/ Bupropion	Opioid antagonist/ dopamine and norepinephrine reuptake inhibitor	Tablet: 8/90 mg, >1 tablet once daily increasing to a maximum of 2 tablets bid Discontinue at 12 weeks if 5% weight loss from baseline not achieved	5%-6.1% weight loss from baseline	Black box warning for increased risk of suicidal ideation (bupropion)
Liraglutide	GLP-1 agonist	SubQ injection: 6 mg/mL: 0.6 mg once daily gradually increasing to 3 mg once daily Discontinue at 16 weeks if 4% weight loss from baseline not achieved	4-6 kg of weight loss	High cost Injection required Nausea (up to 40%)

*In addition to behavioral therapy and exercise.
†Prescription dose.

- SGLT2 inhibitörleri, **Bariyatrik cerrahi**

Post Tx Obezite – Bariyatrik Cerrahi

- Farmakoterapi uygun değil (İlaç etkileşimleri ve yetersizlik)
- Bariyatrik cerrahi, ilk 9 ay öz. ilk 3 ayda % 10 mortalite
- Sleeve gastrektomi 1 yılda > % 50 den fazla aşırı kilolardan kurtulma % 80.

Lazzati A, et al. Bariatric surgery and liver transplantation: a systematic review a new frontier for bariatric surgery. Obes Surg 2015;25:134-142.

- İmmunsupresifler ve Bariyatrik cerrahi
  - MMF mideden emilir
  - TAC, mTOR inh. duodenumdan emilir
  - Siklosporin safra tuzlarına bağlı emilimi mevcut
  - TAC ve mTOR inhi. metabolizması sitokrom p450 ile ilişkili
  - RYGB da TAC, MMF, mTORi için % 40-50 azalır.
  - Sleeve gastrektomide MMF % 40 azalır

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Sonuç olarak

- NASH / Kriptojenik siroza bağlı dekompanse karaciğer sirozu / HCC ve bunlara bağlı TX ler artıyor
- PreTx metabolik değerleri düzeltmek, post Tx metabolik sorunları azaltır
- PreTx Kardiyovasküler hastalık, böbrek yetmezliği, nonhepatik (öz. Kolon Ca) maliniteler araştırılmalı
- PostTx Metabolik sendrom unutulmamalı, önlemler alınmalı
- Post Tx kulllanılan immunsupresiv ajanın seçimi önemli (Hiperglisemi/dislipidemi)
- Sarkopenik obezlerin sıklığının fazla olduğu unutulmamalı
- Metabolik sendrom bileşenleri preTx ve post Tx tedavi edilmeli