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An update on Wilson disease

David Cassiman

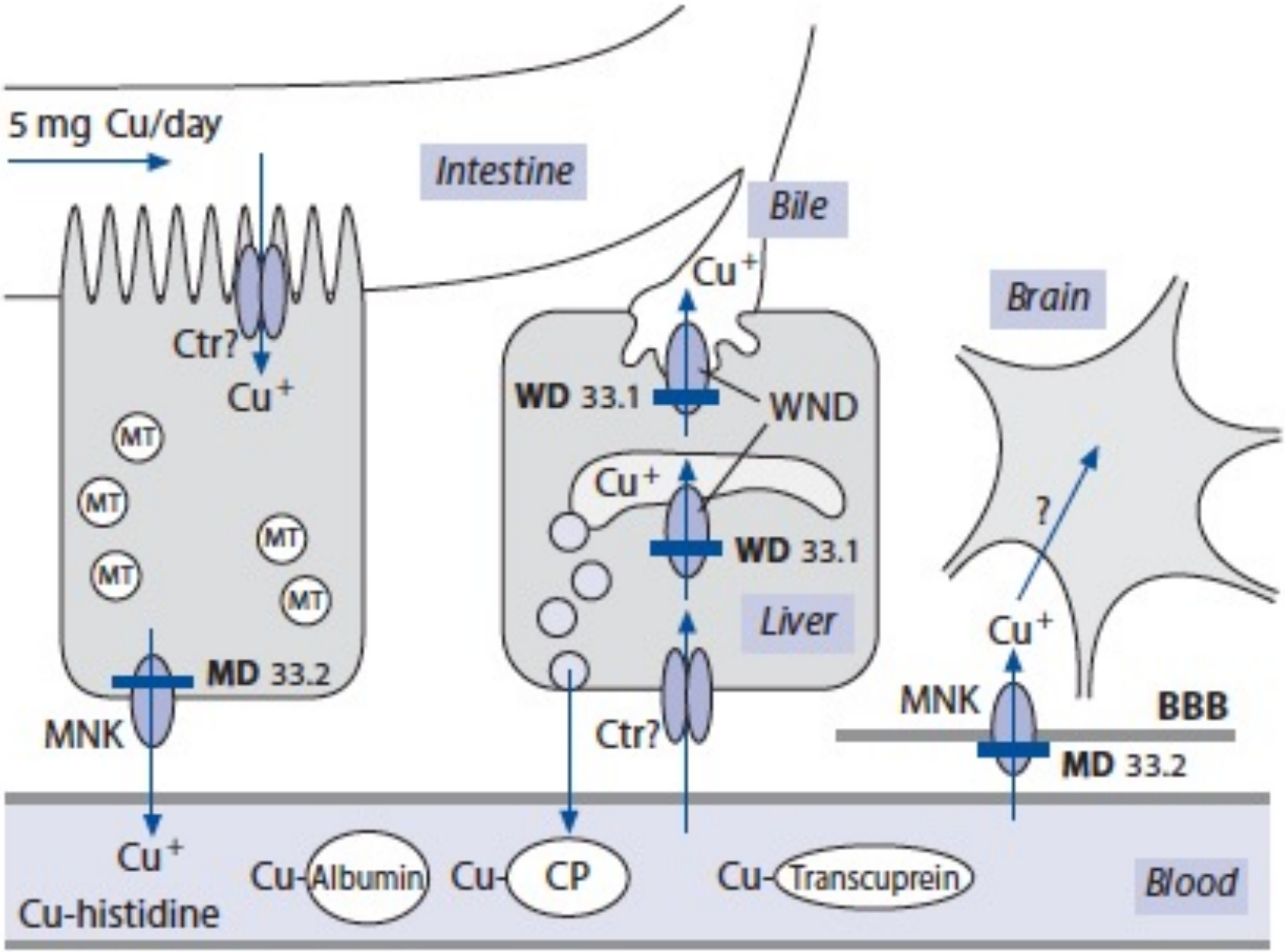
Hepatology and Metabolic Center

UZ Leuven

Wilson disease

= Autosomal-recessive intracellular copper accumulation in liver, brain, bone, kidney, cornea, placenta

- Incidence: 1/30.000 to 1/100.000
- ATP7b gene, a copper-transporting ATPase
- > 250 mutations known (in 5-10% no mutations found)
- Most often compound heterozygosity


5 mg Cu/day
Intestine
Bile
Brain
Ctr?
Cu+
MT
MT
MT
MT
MT
MD 33.2
MNK
Cu+
Cu-histidine
Cu-Albumin
Cu-CP
Cu-Transcuprein
Blood
Cu+
WD 33.1
WND
Cu+
WD 33.1
Liver
Ctr?
?
Cu+
MNK
BBB
MD 33.2

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When to think of Wilson?

- All chronic liver disease patients negative for HBV, HCV, alcohol, HH, auto-immune hepatitis
- Especially when Parkinson-like movement disorder (tremor, dysarthria, dysphagia, incoordination, dystonia)
- Or with psychiatric complaints: depression, personality change, dementia
- Acute liver failure, especially when associated with Coombs-negative hemolysis

  (Alk Phos low compared to bilirubin // AST:ALT > 2.2)
- Coombs-negative hemolysis
- Kidney: tubulopathy (glucosuria, amino-aciduria, phosphaturia)

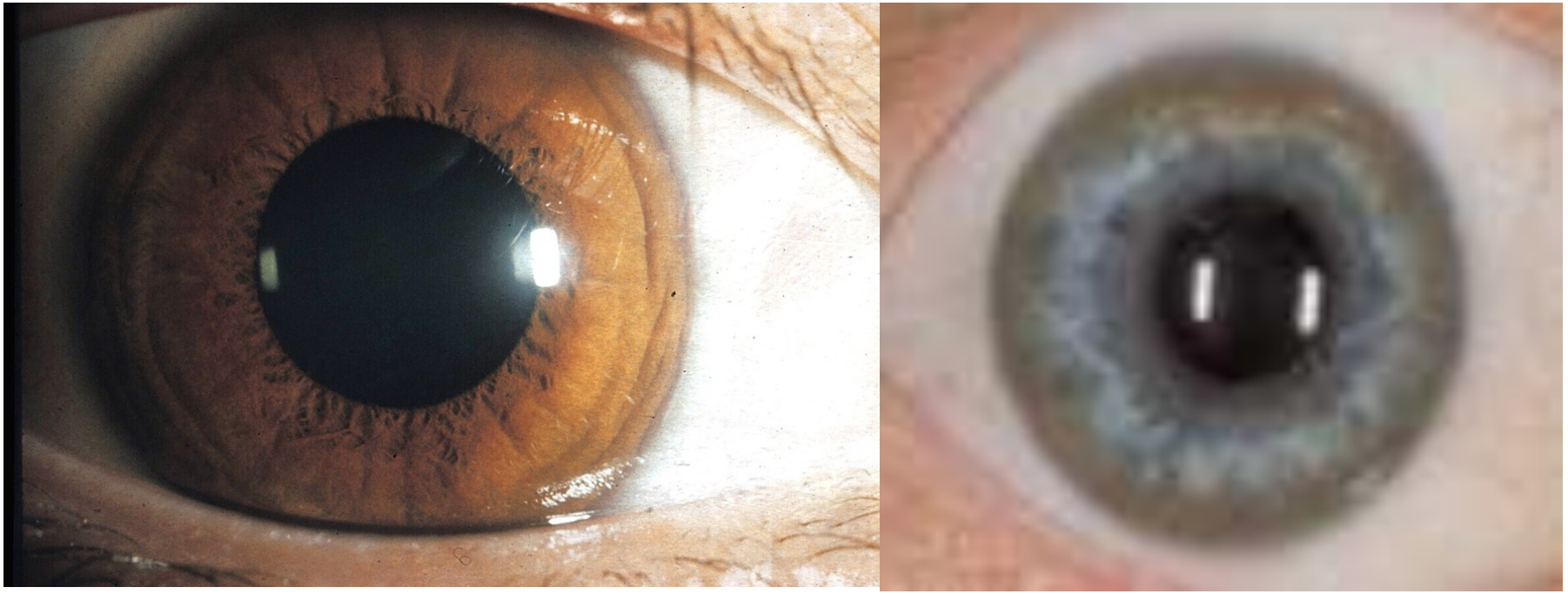
How to diagnose Wilson?

- Decreased ceruloplasmin and/or copper in blood
- Increased urinary copper (D-penicillamine challenge = kids)
- Kayser-Fleischer ring
- Increased liver copper (>250 mg/g)

Cave: hepatitis, ALF, cholestasis → FALSE negative/positive

- ATP7b genetics: 2 mutations (Sheffield)

Kayser-Fleischer ring



Treatment

Chelation: 1. Penicillamine
2. Trientine (not reimbursed)
3. TMB (not registered)

Cu uptake inhibition: Zinc

ALF ➔ liver transplantation

No trials to prove superiority or inferiority

Wilson's disease: long-term follow-up of a cohort of 24 patients treated with D-penicillamine

Klaartje F. Lowette[a], Koen Desmet[d], Peter Witters[b], Wim Laleman[c], Chris Verslype[c], Frederik Nevens[c], Johan Fevery[c] and David M. Cassiman[c]

Background and study aims Detailed data on long-term effectiveness of various drug therapies in Wilson's disease (WD) are lacking. Therefore, we retrospectively reviewed our patient cohort treated with D-penicillamine.

Patients and methods This study reports on the clinical presentation, the diagnostic evaluation, and the disease course in 24 WD patients treated long-term (15 ± 12 years, between 1969 and 2009) with D-penicillamine.

Results The overall survival in our cohort was 91.6%. Twenty-two of 24 patients had liver disease at presentation, 17 of 24 patients (71%) had cirrhosis, 11 of whom had complications of cirrhosis. Six of 11 of these patients showed hepatological improvement (five of six) or stabilization (one of six), three of 11 were transplanted, one of 11 died, one of 11 discontinued follow-up. In the six of 17 cirrhotic patients without complications, improvement (four of six) or stabilization (two of six) occurred. Of all other patients (seven of 24), five of seven showed improvement (three of five) or stabilization (two of five), hepatological deterioration occurred only in one patient due to poor therapy compliance and one of seven discontinued follow-up. Neuropsychiatric symptoms were present in 13 of 24 at presentation and resolved in one of 13, decreased in seven of 13, stabilized in four of 13 and worsened in one of 13 patients (due to poor compliance). In general, we observed a favorable hepatological and neurological evolution with D-penicillamine.

Conclusion Despite the presence of liver disease or neuropsychiatric symptoms at baseline in all but one of the patients, we report beneficial results on liver and neurological disease after very long-term treatment with D-penicillamine, thereby adding to its reputation as 'first-line' therapy in WD. *Eur J Gastroenterol Hepatol* 22:564–571

European Journal of Gastroenterology & Hepatology 2010, 22:564–571

Keywords: D-penicillamine, outcome, Wilson's disease

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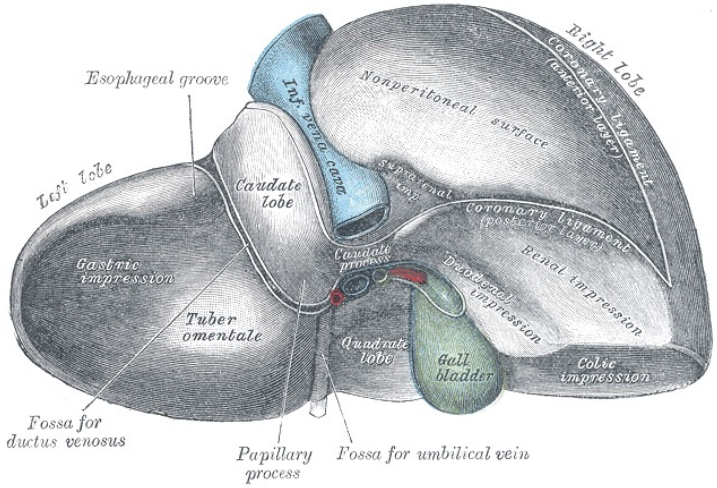
Outcome

11 complicated cirrhosis

- 6 recovered — **Reversal of cirrhosis!**
- 3 transplanted — **2 HCC, 1 SALF**
- 1 died
- 1 lost to FU



GASTROENTEROLOGY 2011;140:1189–1198

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease

KARL HEINZ WEISS,* DANIEL NILS GOTTHARDT,* DANIELA KLEMM,* UTA MERLE,* DANIELA FERENCI–FOERSTER,‡ MARK SCHAEFER,* PETER FERENCI,‡ and WOLFGANG STREMMEL*

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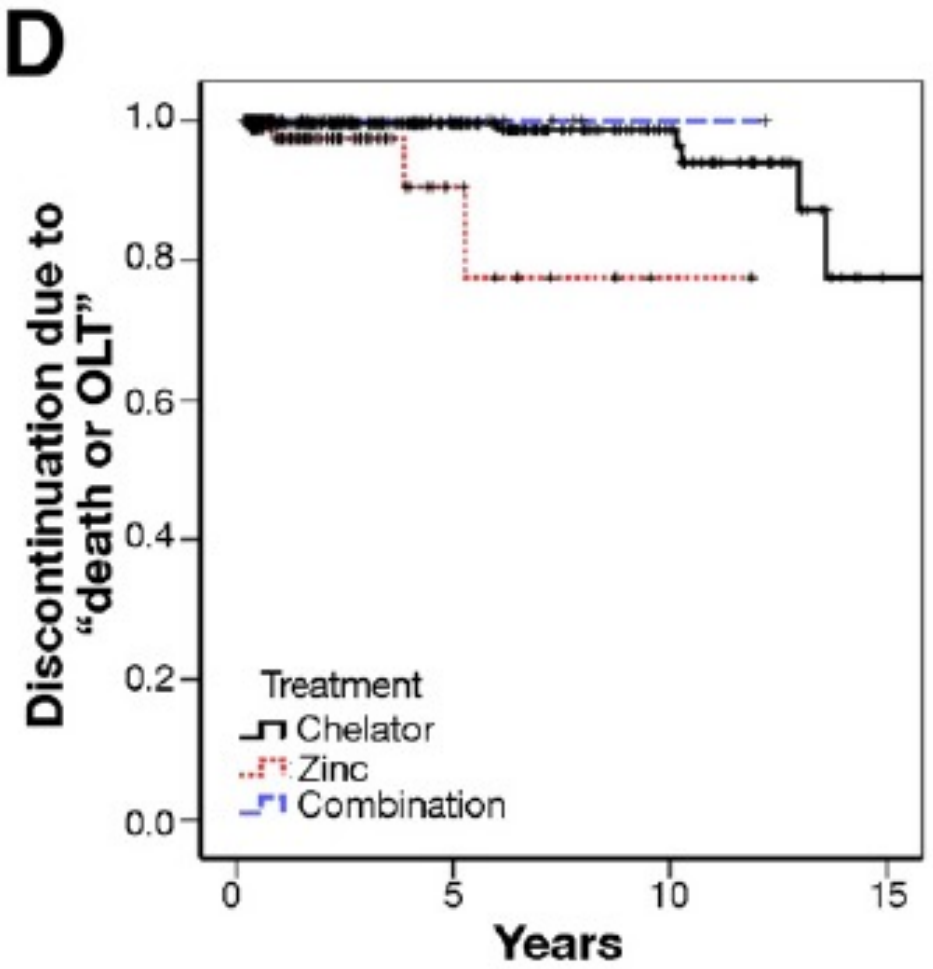
n = 288

Heidelberg and Vienna



Chelator vs. zinc	Chelator vs. combination	Zinc vs. combination
P<.001	*P*=.696	*P*=.140

Neurologic Deterioration Under Therapy

Neurologic worsening was observed within each treatment regimen, with 31 patients affected with chelator therapy (D-penicillamine, 22/243 [9.1%]; trientine, 9/102 [8.8%]), 9 patients with zinc therapy (9/95 [9.5%]), and 3 patients with combination therapy (3/41 [7.3%]); *P* values were not significant.

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Clin Transplant 2013: 27: 914–922 DOI: 10.1111/ctr.12259

Clinical Transplantation

Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease

Weiss KH, Schäfer M, Gotthardt DN, Angerer A, Mogler C, Schirmacher P, Schemmer P, Stremmel W, Sauer P. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease.

Karl Heinz Weiss[a]*, Mark Schäfer[a]*, Daniel Nils Gotthardt[a], Alexandra Angerer[a], Carolin Mogler[b], Peter Schirmacher[b],

Conclusion: Survival after OLT for Wilson disease with end-stage liver disease is excellent. Overall, neuropsychiatric symptoms improved after transplantation, substantiating arguments for widening of the indication for liver transplantation in symptomatic neurologic Wilson disease patients with stable liver function.

N=19

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:1028–1035

Efficacy and Safety of Oral Chelators in Treatment of Patients With Wilson Disease

KARL HEINZ WEISS,* FLORENTINE THURIK,‡ DANIEL NILS GOTTHARDT,* MARK SCHÄFER,* ULRIKE TEUFEL,§ FRANZISKA WIEGAND,* UTA MERLE,* DANIELA FERENCI-FOERSTER,‖ ANDREAS MAIERON,¶ RUDOLF STAUBER,# HEINZ ZOLLER,** HARTMUT H. SCHMIDT,‡‡ ULRIKE REUNER,§§ HARALD HEFTER,‖‖ JEAN MARC TROCELLO,¶¶ RODERICK H. J. HOUWEN,‡ PETER FERENCI,‖ and WOLFGANG STREMMEL,* for the EUROWILSON Consortium

- ±20% serious adverse effects (proteinuria, skin rash, hematotoxicity)
- Discontinuation due to adverse effects in 29% for D- penicillamine and 7% for Trientine
- Neurological worsening in 5-20% of patients

N = 405

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ORIGINAL ARTICLE

Hepatobiliary malignancies in Wilson disease

Jan Pfeiffenberger[1,2], Carolin Mogler[2,3], Daniel N. Gotthardt[1,2], Henning Schulze-Bergkamen[2,4], Thomasz Litwin[5], Ulrike Reuner[6], Harald Hefter[7], Dominik Huster[8], Peter Schemmer[2,9], Anna Członkowska[5,10], Peter Schirmacher[2,3], Wolfgang Stremmel[1,2], David Cassiman[11] and Karl Heinz Weiss[1,2]

Table 2. Wilson's disease cohorts of participating centres

Centre	Warsaw	Heidelberg	Duesseldorf	Dresden	Leuven	Total
Total number of WD patients	753	327	49	32	25	1186
Female [*n*] (%)	363 (48%)	198 (61%)	29 (59%)	17 (53%)	11 (44%)	618 (52%)
Patients with hepatic symptoms at diagnosis [*n*] (%)	446 (59%)	229 (70%)	12 (25%)	12 (38%)	17 (68%)	716 (60%)
Patients with neurological symptoms at diagnosis [*n*] (%)	400 (53%)	96 (29%)	16 (33%)	17 (53%)	6 (24%)	535 (45%)
Total patient years under surveillance since diagnosis of WD (y)	12 941	6392.41	1844.90	1013.08	391	22 582.39
Total patient years since birth (y)	32 442	12 880.49	2120.78	1611.84	1260	50 315.11
Number of HCC cases	2 (pat. 6; 7)	2 (pat. 4; 9)	1 (pat. 5)	1 (pat. 8)	2 (pat. 11; 12)	8
Number of ICC cases	–	4 (pat 1; 2; 3; 10)	–	–	2 (pat. 13; 14)	6

N=130 in The Netherlands. "No increased risk of HCC in cirrhosis due to Wilson disease."

van Meer S et al. JGH 2015;30:535-9.

Copper and bone

J Pediatr Gastroenterol Nutr. 1985 Aug;4(4):677-80.

Copper deficiency in infants with active celiac disease.

Goyens P, Brasseur D, Cadranel S.

Celiac disease was diagnosed in two unrelated infants aged 7 and 7.5 months with severe malnutrition. They showed typical clinical, biological, and histological signs of the disease. Moreover, accompanying copper deficiency was suggested by severe hypocupremia and persistent neutropenia; bone radiographs were also compatible with this diagnosis. Rapid and complete correction of these anomalies could only be obtained after addition of oral copper sulfate to the gluten-free diet. Mechanisms possibly involved in the development of copper deficiency in young infants with celiac disease are: chronic malabsorption; high copper needs in rapidly growing infants; and possibly increased biliary and digestive losses. It is therefore suggested that young children with severe celiac disease should be monitored for their copper status.

J Inherit Metab Dis
DOI 10.1007/s10545-015-9815-y

ORIGINAL ARTICLE

Bone demineralisation in a large cohort of Wilson disease patients

Karl Heinz Weiss · Mart Van de Moortele · Daniel Nils Gotthardt · Jan Pfeiffenberger · Jessica Seeßle · Elena Ullrich · Evelien Gielen · Herman Borghs · Els Adriaens · Wolfgang Stremmel · Wouter Meersseman · Steven Boonen · David Cassiman

Table 2 Prevalence of osteopenia and osteoporosis in WD patients and matched controls

Diagnosis	Control	WD
Normal (T-score >−1), *n* (%)	81 (54.7)	61 (41.2) [A]
Osteopenia (T-score >−2.5 and≤−1), *n* (%)	61 (41.2)	74 (50.0)
Osteoporosis (T-score ≤−2.5), *n* (%)	6 (4.1)	13 (8.8)

Significant difference in prevalence between the control and WD population (χ^2 =6.65, df=2, p =0.036), [A] WD patients with normal condition were under represented (less then expected, standardise residual=−2.33<−1.96)

N=148

Conclusions for the clinicians

Treat Wilson with Penicillamin or Tx

Screen Wilson patients for HCC and ICC

Wilson → osteoporosis: do BMD and treat