METABOLIC EVALUATION OF KIDNEY STONES – a chance for the nephrologist to do good for patients

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What is metabolic evaluation (ME)?

- It is finding the reason (the metabolic defect) that is causing the kidney stones.
- The point of ME is to suggest dietary changes or start treatment that will correct the metabolic defect and thus minimize stone formation, leading to lower stone recurrence rates.

Why should we do ME?

- Kidney stones are a symptom of a disease not a disease in itself.
- Kidney stones tend to recur.
- Kidney stones are connected to a higher risk for CKD.
- Kidney stones are connected to a higher risk for adverse cardiovascular outcomes.
- Kidney stones may lead to osteoporosis.
- Kidney stones are painful and cause a significant lowering of quality of life.

Who needs ME?

- Recurrent stone formers
- First time stone formers:
  - Children and adolescents
  - Strong family history
  - Chronic bowel disorders: inflammatory bowel disease, post abdominal surgery (shortening of the bowel, bariatric surgery…)
  - Calcium phosphate, urate, struvite, cystine stones…

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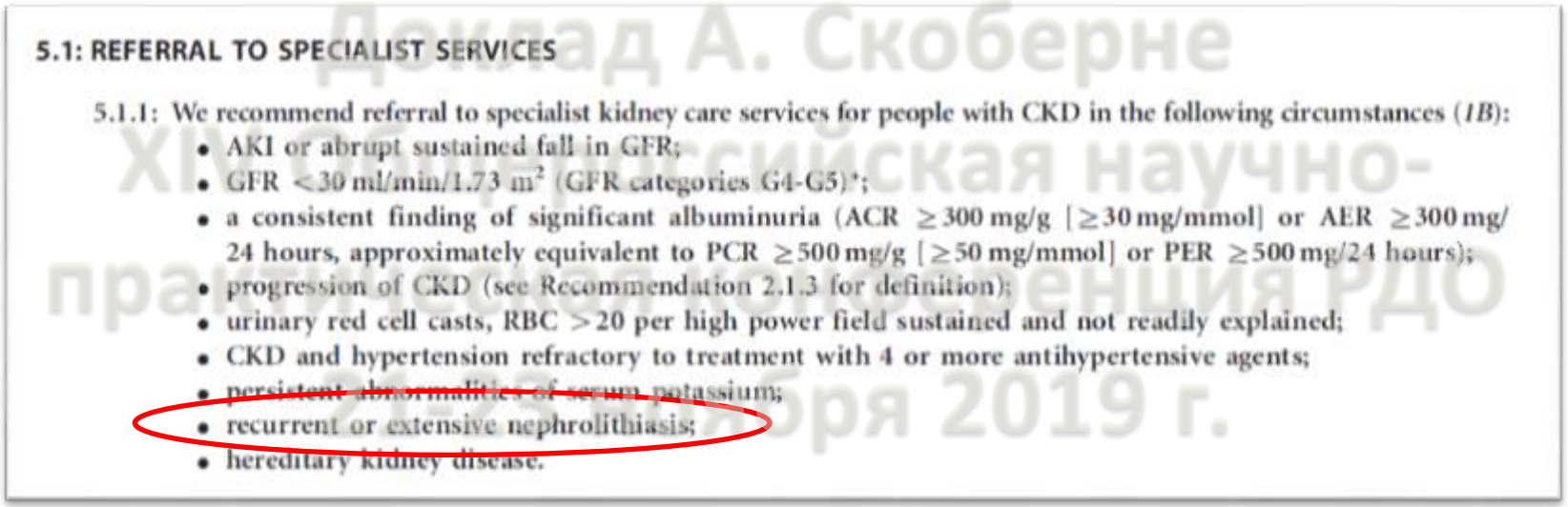
Who needs to do ME?

- UROLOGIST?
- NEPHROLOGIST?



5.1: REFERRAL TO SPECIALIST SERVICES

5.1.1: We recommend referral to specialist kidney care services for people with CKD in the following circumstances (*1B*):

- AKI or abrupt sustained fall in GFR;
- GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5)*;
- a consistent finding of significant albuminuria (ACR ≥300 mg/g [≥30 mg/mmol] or AER ≥300 mg/24 hours, approximately equivalent to PCR ≥500 mg/g [≥50 mg/mmol] or PER ≥500 mg/24 hours);
- progression of CKD (see Recommendation 2.1.3 for definition);
- urinary red cell casts, RBC >20 per high power field sustained and not readily explained;
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;
- persistent abnormalities of serum potassium;
- recurrent or extensive nephrolithiasis;
- hereditary kidney disease.

KDIGO Guidelines on Chronic Kidney Disease 2012

Myths about ME

~~– Nobody wants it.~~

88% of patients with a history if kidney stones want it![1]

~~It doesn't work.~~

More than 10 RCTs, several meta-analyses and guidelines would beg to differ[2]

~~It's to expensive.~~

Some evidence it is cost-effective[3]

1 Bensalah K et al. J Urol 2009; 182: 998-1004.
2 Fink HA et al. Ann Intern Med 2013; 152: 535-43.
3 Lotan Y et al. J Urol 2004; 172: 2275-81.

Major RCT in Ca stones

Table 1. Major clinical trials in pharmacotherapy of calcium nephrolithiasis

Author	Study Design	Enrollment Criteria (*n*)	Treatment	Duration, yr	Treatment/ Placebo, *n*	Recurrence Rate, %, Treated/Placebo	Relative Risk (95% CI) or *P* Value
Thiazide							
Borghi *et al.* (12)	RCT, DB	CaOx SF (75)	Indapamide 2.5 mg daily	3	43/14	15/43	$P<0.001$
Brocks *et al.* (78)	RCT, DB	CaSF (62)	Bendroflumethiazide 2.5 mg three times a day	1.6	33/29	24/16	$P=0.45$
Ettinger *et al.* (13)	RCT, DB	CaOx (73)	Chlorthalidone 25 or 50 mg daily	3	19/23/31	14/46	$P<0.01$
Fernández-Rodríguez *et al.* (77)	RCT	CaSF (100)	Hydrochlorothiazide 50 mg daily	3	50/50	NR	$P=0.003$
Laerum (14)	RCT, DB	CaSF (50)	Hydrochlorothiazide 25 mg twice a day	3	25/25	20/48	$P=0.04$
Mortensen *et al.* (80)	RCT, DB	CaSF (22)	Bendroflumethiazide 2.5 mg three times a day	2	12/10	40/40	$P=1.0$
Ohkawa *et al.* (15)	RCT	CaSF (175)	Triclormethiazide 4 mg daily	2.1–2.2	82/93	NR	$P<0.05$
Robertson *et al.* (76)	RCT, DB	CaSF (22)	Bendroflumethiazide 2.5 mg three times a day	3.0–5	13/9	NR	$P<0.01$
Scholz *et al.* (79)	RCT, DB	CaSF (51)	Hydrochlorothiazide 25 mg twice a day	1	25/26	24/23	$P=0.93$
Wilson *et al.* (75)	RCT	CaSF (44)	Hydrochlorothiazide 100 mg daily	2.8	23/21	21/44	0.48 (0.07 to 0.92)
Citrate							
Barcelo *et al.* (16)	RCT, DB	HypoCit CaSF (57)	Potassium citrate 30–60 mEq daily	3	18/20	28/80	$P<0.001$
Ettinger *et al.* (17)	RCT, DB	CaOx SF (64)	Potassium magnesium citrate 60 mEq daily	3	31/33	13/64	0.16 (0.05 to 0.46)
Hofbauer *et al.* (18)	RCT, DB	CaOx SF (50)	Sodium potassium citrate to keep urine pH at 7–7.2	3	25/25	69/73	$P=0.65$
Lojanapiwat *et al.* (83)	RCT	CaSF (76)	Potassium citrate 81 mEq daily	1	39/37	8/46	$P<0.01$
Soygür *et al.* (82)	RCT	CaOx SF (90)	Potassium citrate 50 mEq daily	1	46/44	0/32	$P<0.05$

95% CI, 95% confidence interval; RCT, randomized controlled trial; DB, double blind; CaOx, calcium oxalate; SF, stone former; CaSF, calcium stone former; HypoCit, hypocitraturic; NR, not reported.

Zisman AL. Clin J Am Soc Nephrol 2017; 12: 1699–1708.

The state of ME today (in Canada)

Metabolic evaluation guidelines in patients with nephrolithiasis: Are they being followed? Results of a national, multi-institutional, quality-assessment study

Sabrina S. Harmouch, MD[1]; Hiba Abou-Haidar, MD[1]; Hassan ElHawary, MD[2]; Thomas Grgic, MD[3]; Andrea G. Lantz, MD[4]; Jason Y. Lee, MD[5]; Ben H. Chew, MD[3]; Sero Andonian, MD[2]; Naeem Bhojani, MD[1]

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- 530 patients who came for ESWL
- 79,4 % had indication for ME:
  - 64,5% multiple/bilateral stones
  - 31,7% family history of stones
- 96,6% had indication or wished to have ME
- 41,8% received ME (among those who had an indication for ME)

Can Urol Assoc J. 2018 Oct;12(10):313-318.

How do you do ME?

- Stone analysis (necessary in every patient, even first time stone former)
- Blood: creatinine, Ca, iPTH,…
- 24-hour collection (1 or 2 collections?): volume, Ca, oxalate, citrate, urate, cystine, Mg, P,…

ME in CALCIUM stones

Metabolic defect	Therapy
U-Ca 5 - 8 mmol/day	Potassium citrate (9 – 12 g/day)
U-Ca > 8 mmol/day	Hydrochlorothiazide (25 – 50 mg/day) Chlorthalidone (25 mg/day) Indapamide (2,5 mg/day)
U-citrate < 1,8 mmol/day	Potassium citrate (9 – 12 g/day)
U-urate > 4 mmol/day	Potassium citrate (9 – 12 g/day) AND/OR Alopurinol (100 – 300 mg/day)
U-oxalate > 500 µmol/day	Secondary/enteric (500 – 1000 µmol/day): Calcium carbonate, Magnesium Primary (> 1000 µmol/day): Pyridoxin (5 – 20 mg/kg/day)
U-Mg < 3 mmol/day	Magnesium 200 – 400 mg/day

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ME in URATE stones

- Urinary alkalization!!!
  - Potassium citrate – titrate dosage to target pH:
    - Chemolytholisis phase: pH 6,5 – 7,2
    - Prevention phase: 6,2 – 6,8

- U-urate > 4 mmol/day OR patient has gout:
  - Alopurinol (100 – 300 mg/day)

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ME in INFECTION stones

- Surgery: complete stone and fragment removal
- Antibiotics after complete stone removal (culture of stone fragment)
- ?Urinary acidification: L-methionine 200 – 500 mg, 1 – 3 times/day?
- ?Urease inhibitor: Acetohydroxamic acid (15 mg/kg/day)?

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ME in CYSTINE stones

- Enhanced fluid intake: > 3.5 L/day
- Citrate (? g/day): maintain urine-pH 7.5 – 8.5
- Tiopronine (250 – 2000 mg/day) – possible severe side-effects

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Our experience with ME (2010 – 2018)

- 213 patients
- 52.6% females, 47.4% males
- Mean age 50.6 +/- 15.6 years
- Chronic kidney disease (CKD):
  - eGFR < 60 ml/min: 9%
  - Proteinuria: > 0.25 g/day 19.3%, > 0.5 g/day 9.9%
  - **CKD: 21.6%**

Metabolic evaluation in University Medical Centre Ljubljana (2010 – 2018)

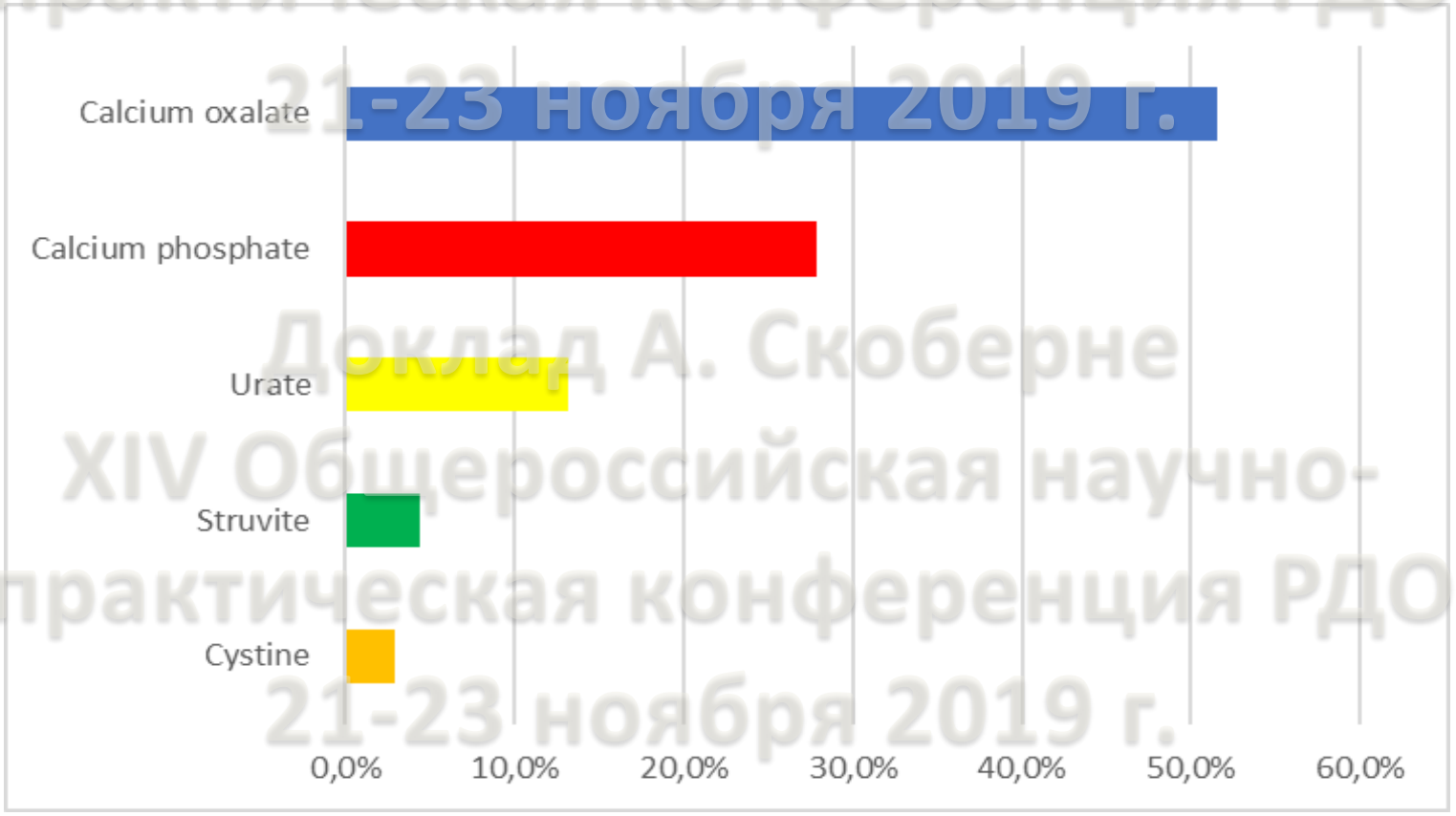
Causes of stone formation

Metabolic defect	Percentage
U-citrate < 1,8 mmol/day	51,9%
U-Ca > 5 mmol/day	46,8%
U-Ca > 8 mmol/day	20%
U-urate > 4 mmol/day	28%
U-Mg < 3 mmol/day	20,7%
U-cystine > 0,4 mmol/day	4,3%
U-volume < 1 L/day	3,6%
U-oxalate > 500 µmol/day	3,1%
No detectable metabolic defects	**6,2%**

Metabolic evaluation in University Medical Centre Ljubljana (2010 – 2018)

Stone analysis

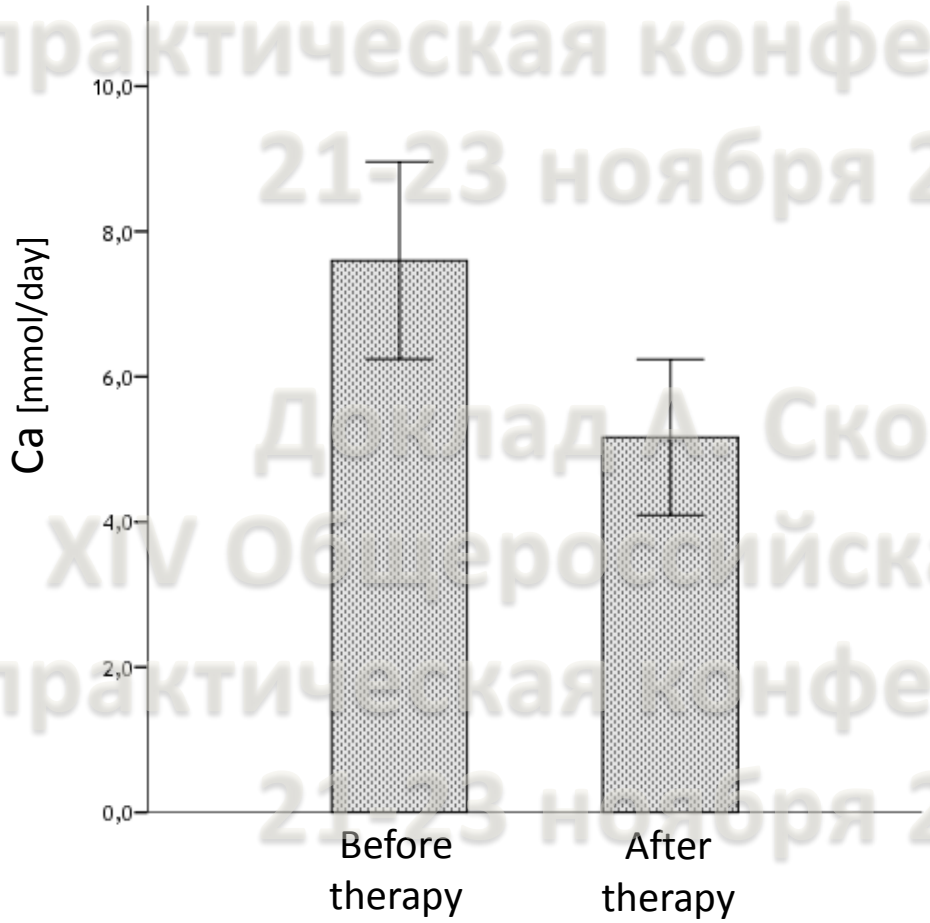
Done in 31.9% of patients



Metabolic evaluation in University Medical Centre Ljubljana (2010 – 2018)

Therapy – Indapamide

31 patients

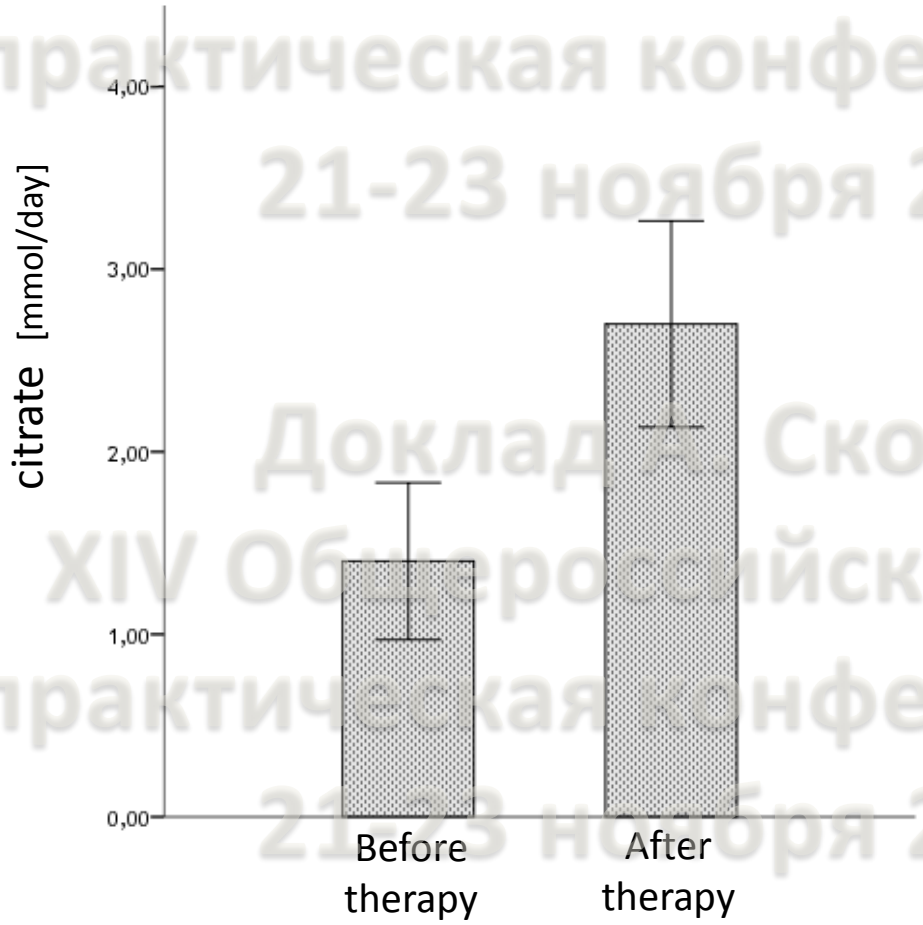


7.6 mmol/day
vs.
5.2 mmol/day
P = 0.009

Metabolic evaluation in University Medical Centre Ljubljana (2010 – 2018)

Therapy - Citrate

40 patients



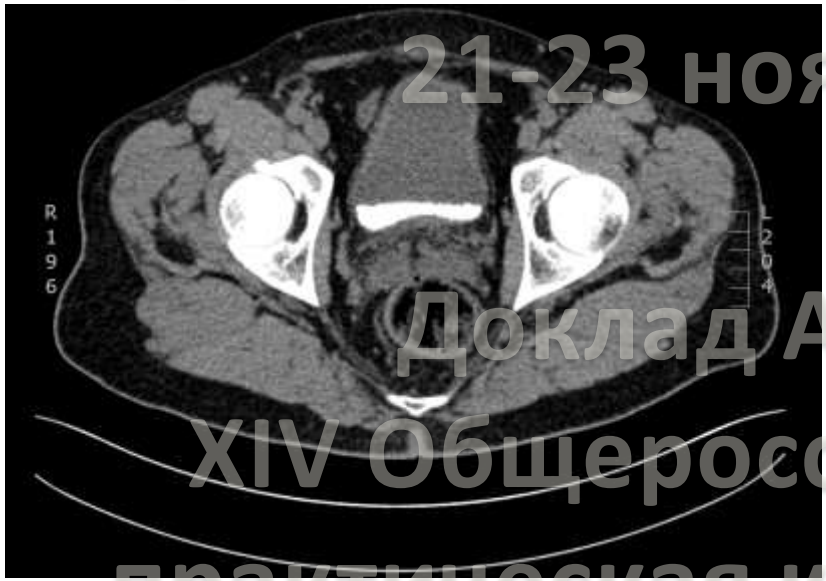
1.4 mmol/day
vs.
2.7 mmol/day
P < 0.001

Metabolic evaluation in University Medical Centre Ljubljana (2010 – 2018)

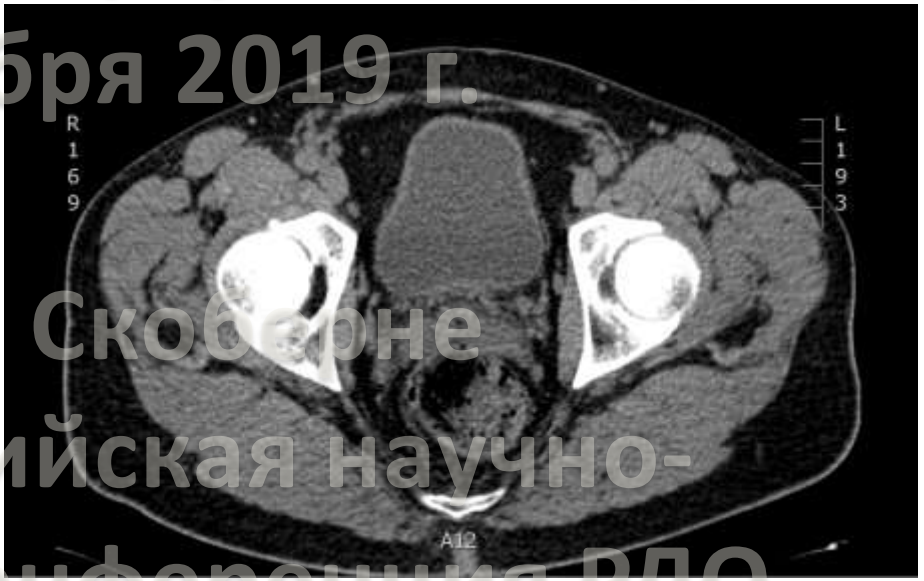
Patient

- Mr. Č. N., born 28.8.1953, exam.: 4.10.2017
  - Family history: father had stones
  - Past history: hyperlipidemia, arterial hypertension, one stone event 25 years ago
  - Current history: he brings into the office approximately **40 stones, approximately 1-2 mm in size, says this is probably 10% of all the stones he had passed in the past 6 months**

Patient



25.07.2017



04.10.2018

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21-23 ноября 2019 г.

Conclusions

- Metabolic evaluation is a useful and necessary diagnostic evaluation in patients with recurrent kidney stones or other risk factors for recurring stones.
- Metabolic evaluation identifies the causes of stone formation in the vast majority of patients.
- Treatment of metabolic defects can help prevent further stone formation and diminishes stone events.
- If you need me, here‘s my email: **andrej.skoberne@kclj.si**

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Taken from: https://www.lonelyplanet.com/slovenia/ljubljana