Dr. Fatheya Al Awadi

Welcome

ice2024

edec2024

21st International Congress of Endocrinology

in conjunction with the 14th Emirates Diabetes and Endocrine Congress

ise international society of endocrinology

Hosted by

edes EMIRATES DIABETES ENDOCRINE SOCIETY جمعية الإمارات للسكري والغدد الصماء

EMA

This is ICE 2024 for you!

Endocrinology of the Future
ICE 2024
21st International Congress of Endocrinology
1-3 March 2024 | Dubai, UAE

12 Plenary Sessions
68 Symposia
27 Meet the Professors
10 Regional Sessions
6 Workshops

408 Abstracts on Viewing
44 Oral Presentations
65 Poster Presentations

29 Corporate Partners
19 Industry Symposia
3 Product Theatres

+5,000 Attendees
98 Countries

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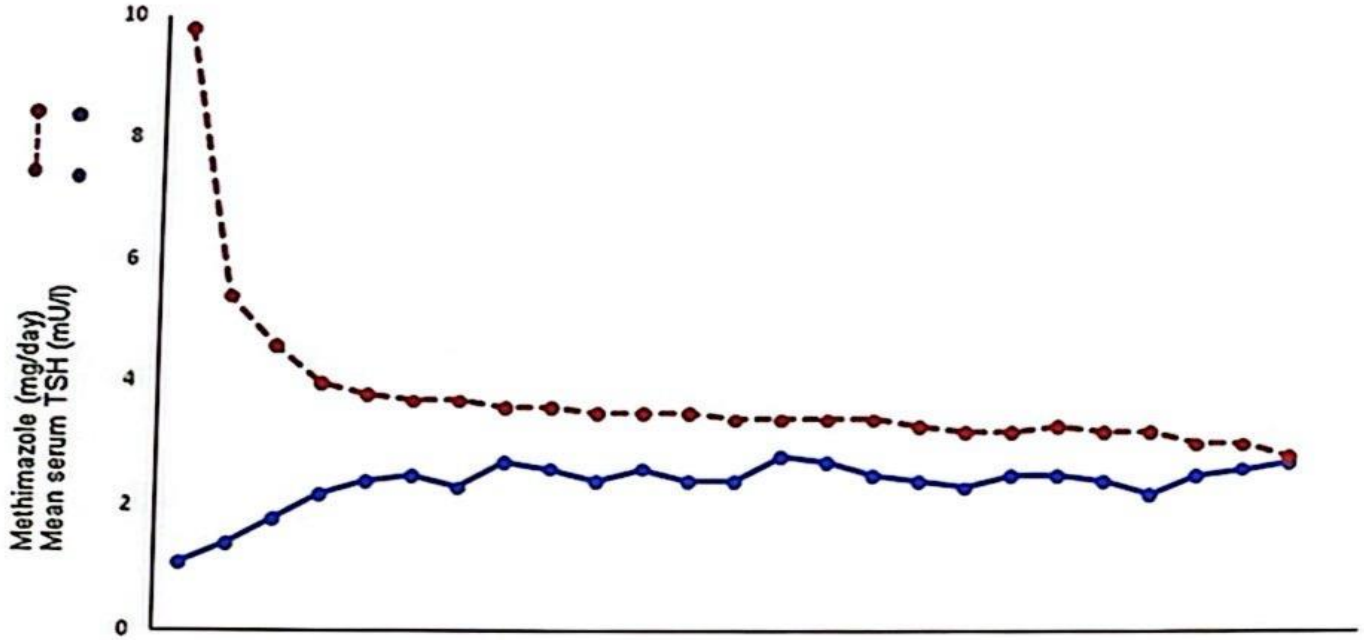
Control of Graves' hyperthyroidism with very long-term methimazole treatment: a clinical trial

Fereidoun Azizi [1], Hengameh Abdi [2], Atieh Amouzegar [3]

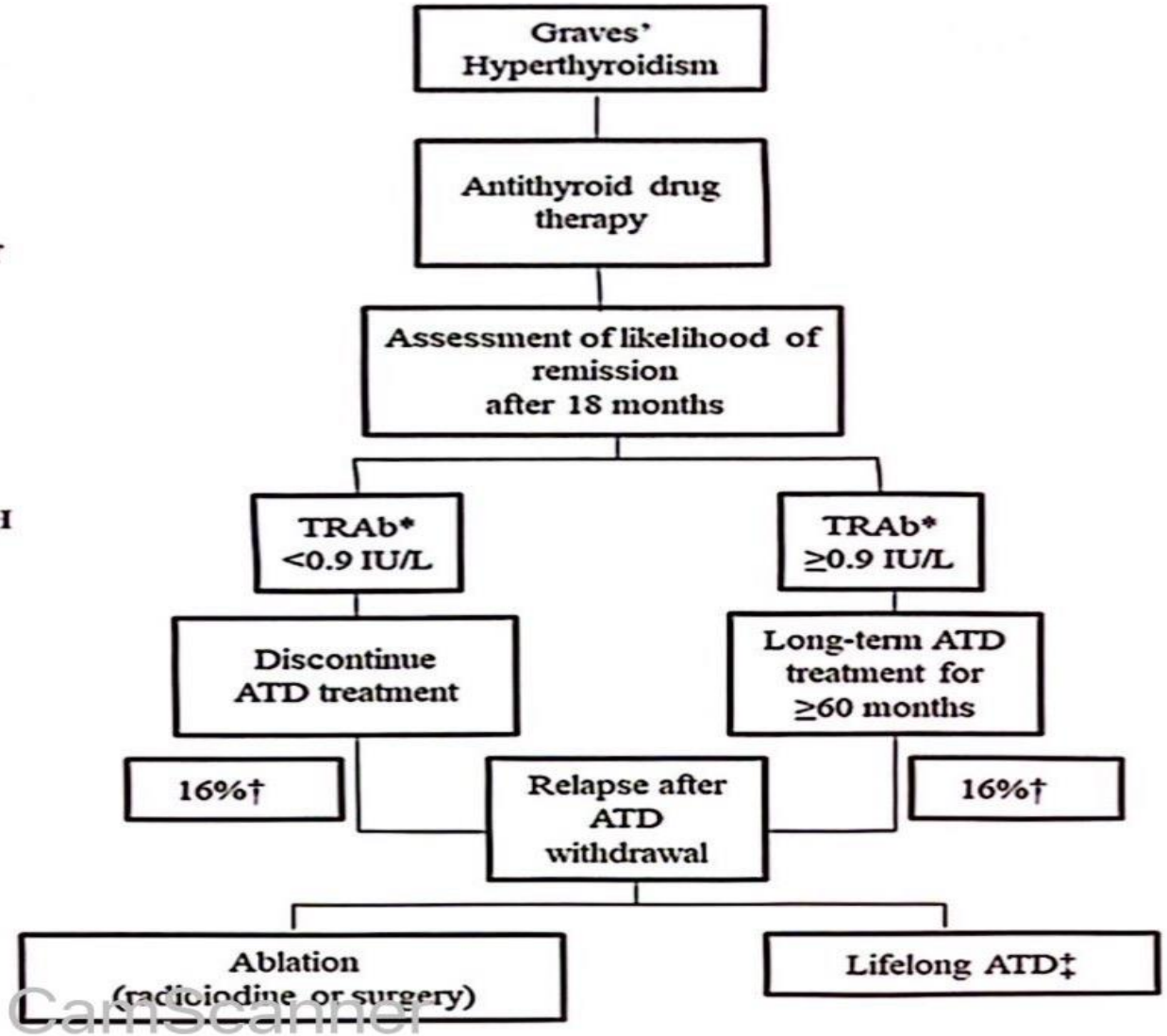
All 27 patients continued therapy for at least 15 years, 16 patients until 20 years and 11 patients until 24 years. Daily doses of methimazole to maintain euthyroidism decreased to mean of 3.4 ± 1.0 and 2.8 ± 1.7 mg daily, by 15 and 24 years of therapy; serum TRAb was normal in all patients during methimazole treatment



TSH<0.4mU/L No	12	11	5	2	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean serum TRAb (IU/ml)			1.2						1.1									1.0									0.9
Methimazole Mean mg/day	9.8	5.4	4.6	4	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.5	3.4	3.4	3.4	3.4	3.3	3.2	3.2	3.3	3.2	3.2	3.0	3.0	2.8
SD	1.0	1.6	1.5	1.2	1.1	1.0	1.1	1.0	0.9	1.1	1.2	1.1	1.0	1.1	1.1	1.0	1.1	1.1	1.1	1.3	1.1	1.1	1.7	1.6	1.7

Management and monitoring steps during long-term ATD treatment of Graves' disease

*Approximately 10% may have TRAb <0.9 IU/L after 12 months of ATD treatment.
†Equal chance of only 16% remission in each arm after discontinuation of ATD.
‡Yearly check of TRAb and discontinuation of ATD if TRAb would be <0.9 IU/L.
ATD, antithyroid drug; TRAb, TSH receptor antibodies



Azizi F, et al. J Endocrinol Invest 2022; 45: 1139-1150

Practice points

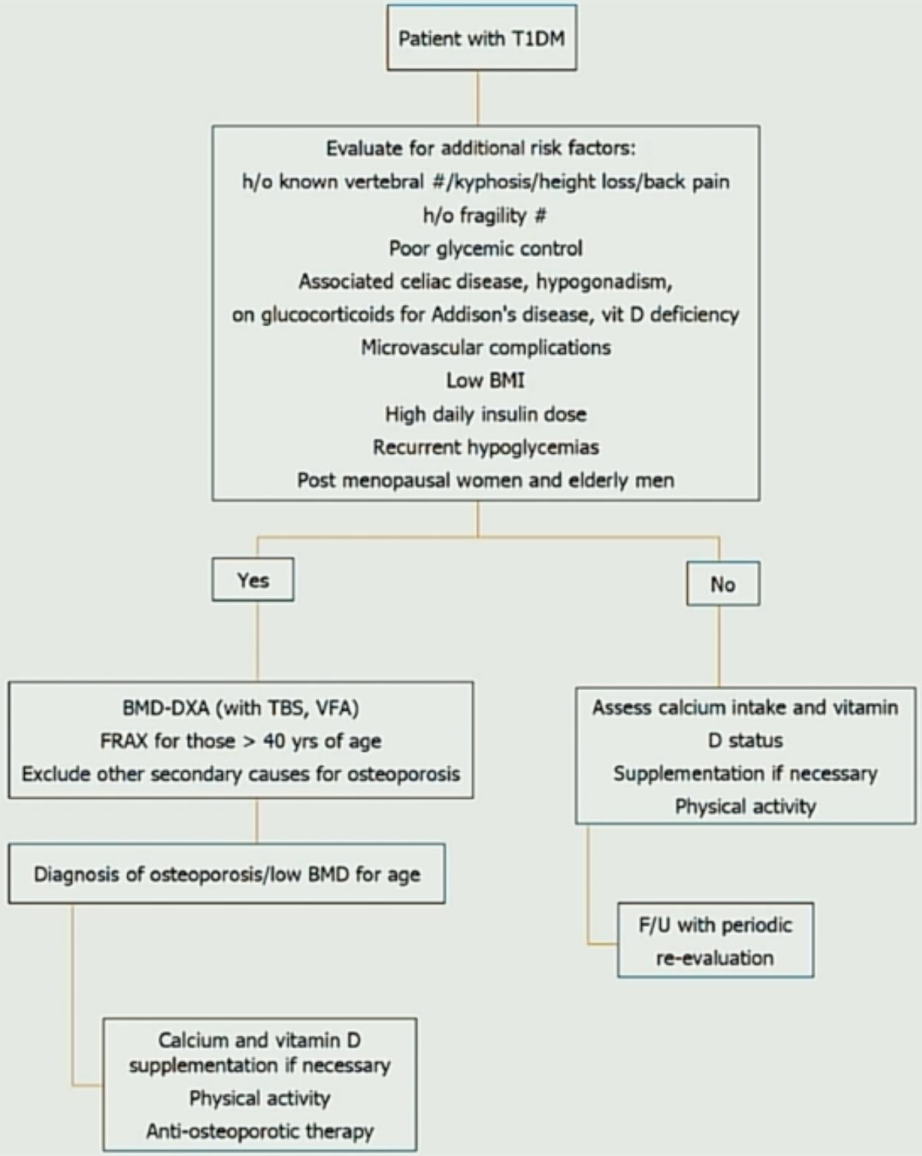
- **Antithyroid drugs are the treatment of choice for Graves' disease.**
- **To avoid relapse of hyperthyroidism, long-term (more than five years) treatment with antithyroid drugs are advised.**
- **The majority of patients with Graves' disease have less likelihood of relapse and benefit from long-term antithyroid drug treatment.**
- **Long-term methimazole therapy is associated with cure of hyperthyroidism in more than 80% of patients.**
- **Long-term therapy with methimazole in adults does not cause additional major adverse events.**

Azizi F et al. Best Pract Res Clin Endocrinol Metab 2022; 101631

Save thyroid, do not ablate

low dose MMI treatment may be prescribed effectively, even throughout the patients' life for those with Graves' hyperthyroidism who do not desire ablation treatment. Low cost, safe and effective drugs are prescribed as lifelong therapy for some specific diseases, such as epilepsy, inflammatory bowel disease and hypothyroidism and MMI may be added to the list of lifelong drugs for control of Graves' hyperthyroidism.

Azizi F et al. BMC Endocrine Disorders 2021; 21: 16



Algorithm for evaluation of bone health in type 1 diabetes mellitus

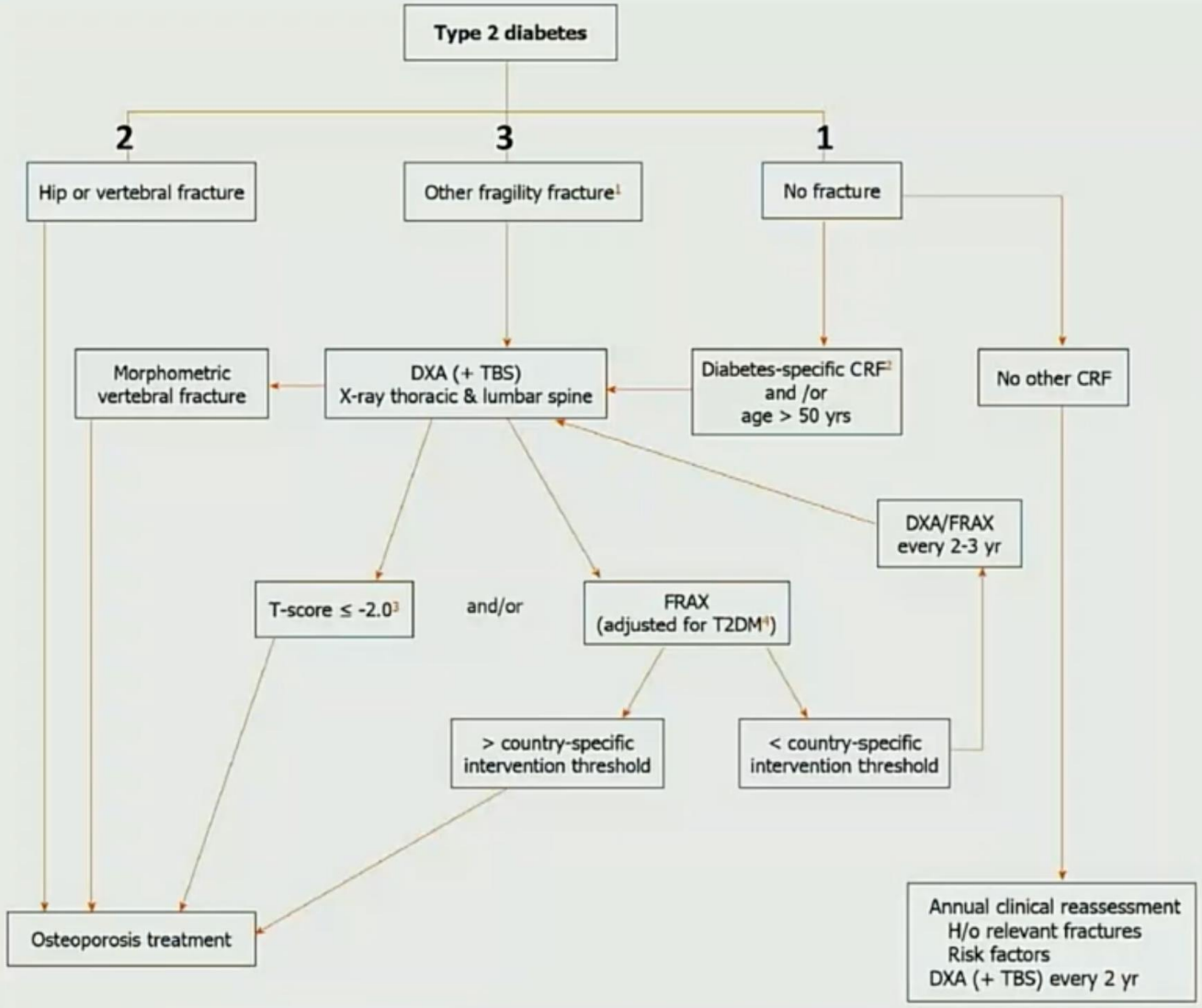
POINTS:

- In adult patients with T1DM, the first densitometry should be performed five years after the diagnosis of the diabetes mellitus and repeated every 2–5 years.
- The FRAX tool is not appropriate for assessing the fracture risk in **young patients** with T1DM.

BMI: Body mass index; BMD-DXA: Bone mineral density by dual energy X-ray absorptiometry; F/U: Follow up; FRAX: Fracture Risk Assessment Tool;
H/o: History of; T1DM: Type 1 diabetes mellitus; TBS: Trabecular bone score; VFA:Vertebral fracture assessment.

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus.
Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

Evaluation of fracture risk in patients with type 2 diabetes mellitus



1: ≥ 1 nonvertebral nonhip fragility fracture might be required to initiate therapy;
2: Diabetes-specific clinical risk factors (diabetes duration, antidiabetic medications,, hemoglobin A1c and microvascular complications);
3: In diabetes, fracture risk at T-score < -2 equivalent for nondiabetes at T-score < -2.5;
4: CRF: **Clinical risk factor**;
TBS: Trabecular bone score;
DXA: Dual energy X-ray absorptiometry; T2DM: Type 2 diabetes mellitus; FRAX: Fracture Risk Assessment Tool; H/o: History of.

Bone and Diabetes Working Group of IOF. Diagnosis and management of bone fragility in diabetes: an emerging challenge. ***Osteoporos Int*** **2018; 29:2585-2596.Copyright ©The Author(s) 2018. Published by Springer Nature.**
Modified from Ferrari *et al*: Ferrari SL, Abrahamsen B,Napoli N, Akesson K, Chandran M, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Suzuki A, Pierroz DD, Schwartz AV, Leslie WD;

Critical review of bone health, fracture risk and management of bone fragility in diabetes mellitus. Palui R, Pramanik S, Mondal S, Ray S. *World J Diabetes* 2021; 12(6): 706-729

May 09, 2023

New FRAXplus® (Beta version) illustrates potential of refined risk factor information entered to the world's most widely used fracture risk assessment tool

‹ PREVIOUS NEXT ›

A new, user-friendly platform for the freely available online FRAX® calculator now hosts the beta version of **FRAXplus®,** an optional extra that illustrates how fragility fracture risk probabilities can be modified for recency of prior fracture, exposure to higher dose oral glucocorticoids, duration of Type 2 diabetes mellitus, Trabecular Bone Score (TBS), recent falls history, concurrent data on lumbar spine BMD and Hip axis length.

FRAX® is the most widely used online fracture risk assessment tool to estimate the individualized probability of hip fracture and major osteoporotic fracture. It integrates well-validated risk factors for fragility fracture with or without the use of bone mineral density, calibrated according to the country-specific epidemiology of hip fracture and mortality. FRAX® is available for 78 countries or territories and in 35 languages, covering more than 80% of the world's population. It is incorporated into approximately 80 osteoporosis management guidelines worldwide.

Recency of osteoporotic fracture

Information on trabecular bone score (TBS)

High exposure to oral glucocorticoids

Falls history

Type 2 diabetes mellitus

Hip axis length

Concurrent data on lumbar spine BMD

Conclusions

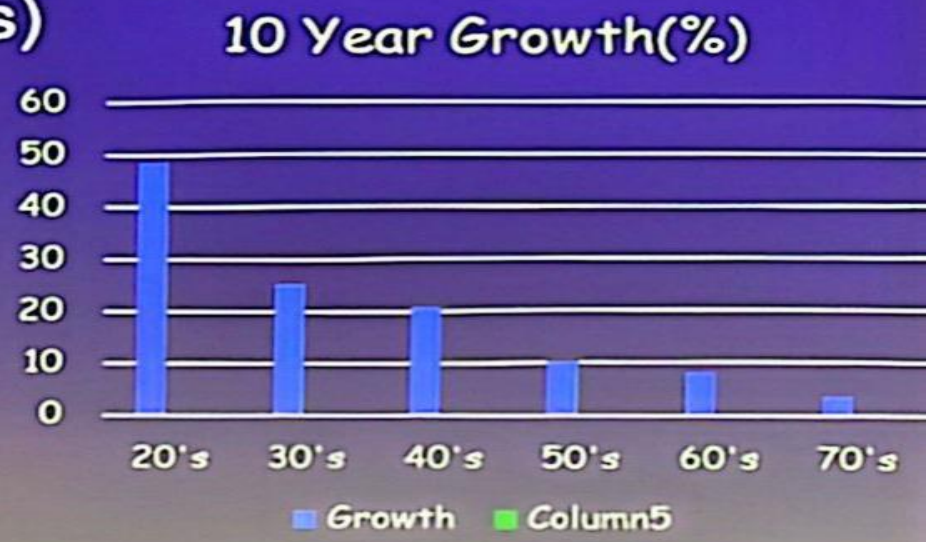
- Fragility fractures are another serious complication of diabetes

- Fracture risk evaluation in diabetics requires to integrate not only osteoporosis risk factors but also diabetes-related risk factors (HbA1c, hypoglycemia, type of Tx, complications,…)

- Osteoporosis drugs (AR and TPT) seem to work as efficiently in diabetics with osteoporosis as in osteoporotic subjects without diabetes, but data is limited

Active Surveillance in PTMC

- Active surveillance investigation by Drs Ito and Miyauchi at Kuma hospital initiated in 1993
  - 5 and 10 year growth >3 mm was 3% and 5.5%
    - Risk for growth is age related
  - 5 and 10 year node metastases was 0.9 and 1.1%
  - No distant metastases in 3 studies: 230/60 months; 1235/75 months; 219/25 months)



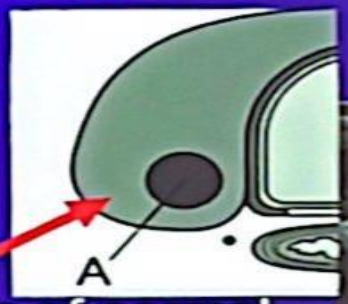
al World J Surg 2023;47:392; Miyauchi Surgery 2018;163:48; Ito and Miyauchi JES 2023

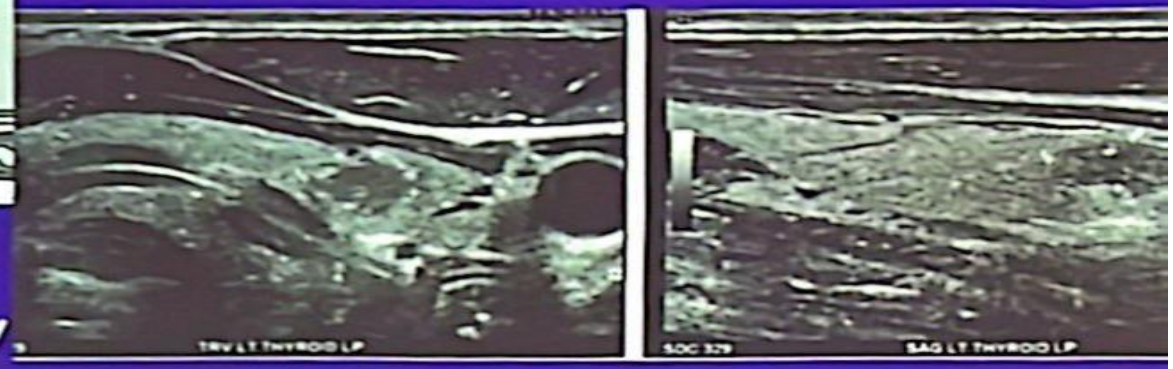
Appropriate Candidate for Active Surveillance

MAeSTro (Multicenter Prospective Cohort Study of Active Surveillance on PTMC)

Ideal for surveillance:

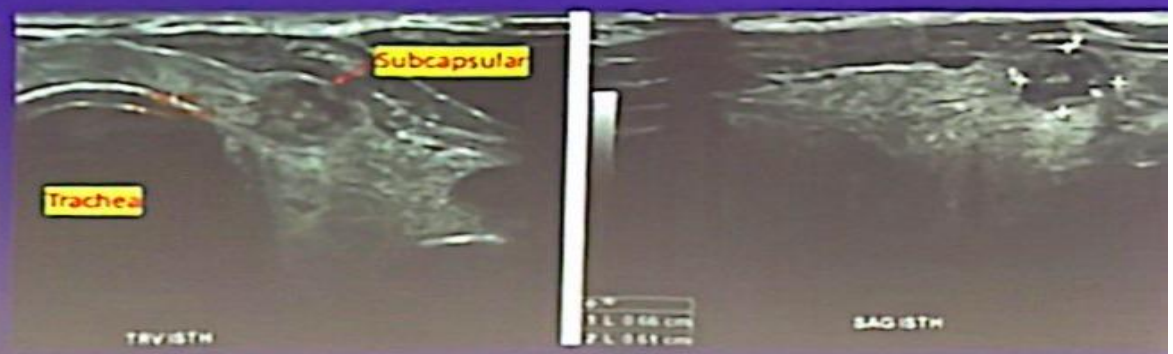
- Solitary
  - Older patient
  - ≤1.0 cm
  - Surrounded by ≥2 mm of normal thyroid tissue
  - No suspicious cervical adenopathy





Acceptable for surveillance:

- Multifoci microPTC
- PTC 1.0-1.5 cm
- Subcapsular
  - ≤1.0 cm
  - Not adjacent to any major structure (not posterior or medial)
  - No suspicious cervical adenopathy



Moon JH et al Endocrinol Meta (2018); Sugitani I et al. Thyroid (2

Follow-up Active Surveillance

- Ultrasound for nodule in remining lobe and nodes every 6 months for 1-2 years, then annually
- Significant progression and Indication for surgery
  - ↑ diameter ≥ 3 mm or ≥ 2 mm in 2 dimensions (~50% increase in volume)
    - Ito & Miyauchi: Surgery when 13 mm
  - Evidence of extrathyroid extension
  - Development of lymph node metastases
  - Development of other thyroid or parathyroid disease that requires surgery

Ito & Miyauchi J Endocrinol Soc (2023)

When do you Recommend a Completion Thyroidectomy after Lobectomy

- If PTC is > 4 cm on pathology
- If positive surgical margins
- If gross extrathyroidal extension
- If macroscopic LN metastases >#5 (>2 mm) or > 3 cm
- Confirmed contralateral disease > 1 cm
- If extensive (>4 vessel) vascular invasion
- If distant metastases
- If poorly diffentiated
- NOT minimal extrathyroidal extension
- NOT BRAFV600E mutation

NCCN 2022

What is New for Advanced Thyroid Cancer?

- US FDA approved 9 drugs or drug combintions

NO TARGETABLE MUTATION

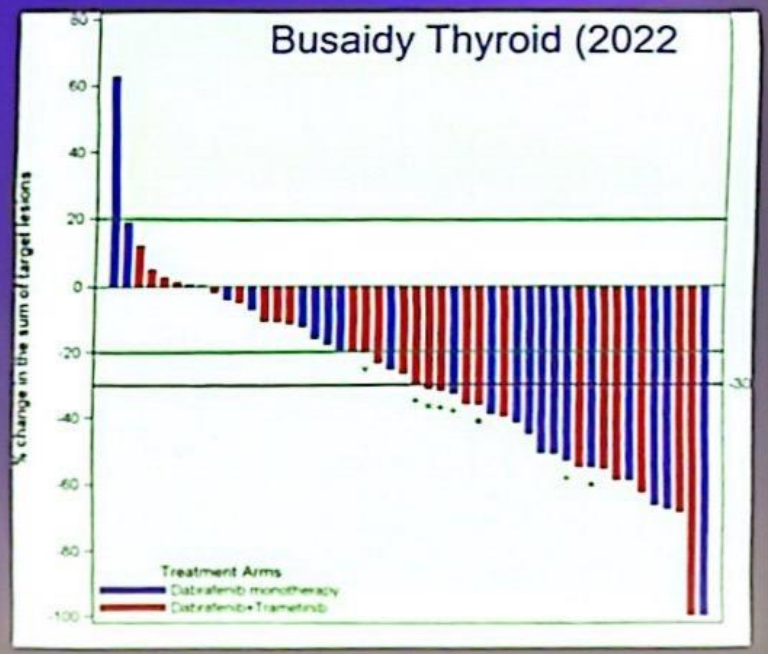
YES TARGETABLE MUTATION

Systemic treatments and their targets	Differentiated thyroid carcinoma (DTC)		Undifferentiated thyroid carcinoma
	Papillary, =84% Follicular, =4% Oncocytic, =2%	*More aggressive subtypes, =5%* High-grade differentiated Poorly differentiated	Anaplastic thyroid carcinoma (ATC), =1%
Antiangiogenic multikinase inhibitors			
Sorafenib - targets VEGFR, PDGFR, RET	▶ Radioactive iodine refractory (RAIR) DTC		
Lenvatinib - targets VEGFR, PDGFR, FGFR, RET	▶ RAIR DTC		
Vandetanib - targets VEGFR, PDGFR, RET			
Cabozantinib - targets VEGFR, RET, MET	▶ RAIR DTC (second line)		
Targeted inhibitors			
Dabrafenib/trametinib - targets BRAF/MEK			▶ BRAF mutation ATC
Dabrafenib - targets BRAF	▶ BRAF mutation RAIR DTC		
Larotrectinib - targets NTRK	▶ NTRK fusion DTC		▶ NTRK fusion ATC
Entrectinib - targets NTRK	▶ NTRK fusion DTC		▶ NTRK fusion ATC
Selpercatinib - targets RET	▶ RET fusion DTC		▶ RET fusion ATC
Pralsetinib - targets RET	▶ RET fusion DTC		▶ RET fusion ATC

Boucai JAMA (February 2024)

Emerging New Therapies

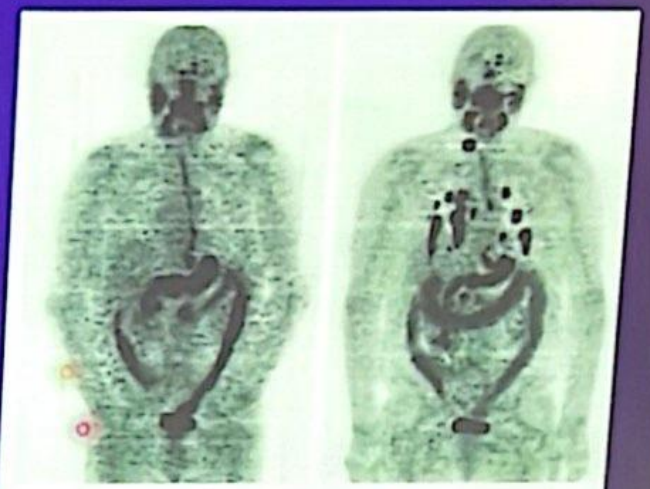
- Neoadjuvant therapy before surgery
  - Anaplastic thyroid CA with BRAFV600E mutation
  - Treated before surgery with BRAF/MEK inhibitors (dabrafenib and trametinib) often with a checkpoint inhibitor immunotherapy
  - 1 year survival 93.6%
  - Prospective studies being performed now
- Dabrafenib/trametinib may appears to be effective in advanced differentiated thyroid cancer with BRAFV600E mutation



Zhao Thyroid (2023); Busaidy Thyroid (2022); White Thyroid (2017)

Emerging New Therapies

- Redifferentiation therapy
  - Use of selective kinase inhibiros with RAI to restore RaI uptke in refractory patients
    - 8 case series or trials published with some selected favorable results
      - First case series by Ho in 2013
    - Prospective redifferentiation clinical trial with selective MEk and RET inhibitors are underway



Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

Boucai JAMA (February 2024); Ho NEJM 2013

Conclusions

- Changes in the management of thyroid cancer has lead to less aggressive treatment
  - Active surveillance is acceptable for <1.5 cm PTC with a rim of normal tissue
  - No extrathyroidal invasion, no metastatic nodes
- Lobectomy is a acceptable for <4 cm PTC
  - No extrathyroidal invasion, no metastatic nodes
  - Thyroglobulin levels rise over time and cannot be used for tumor recurrence
  - Recurrence of tumor occurs in about 14% of patient but >50% after 10 years

dd

Conclusions

- Advances therapies are actively under investigation
  - Genomic characterization is necessary to determine appropriate targeted treatment
  - BRAFV600E adfanced tumors respond to BRAF/MEK inhibition and can used as adjuvant therapy before surgery
  - Redifferentiation therapy to restore RAI avidity are active being studied

dd

Efmody: a new MR hydrocortisone therapy

Cross section of an Efmody granule

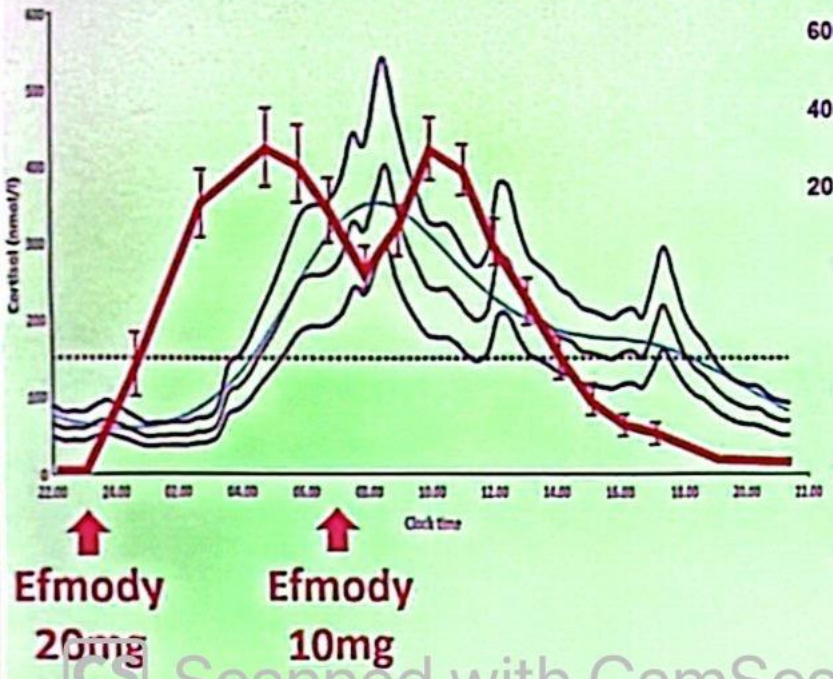
- Approved by EMA in 2021 for the treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12+ and adults
- Available in dose strengths of 5mg and 10mg

- Given in a twice a day regimen. The total daily dose should be split with 2/3 to 3/4 of the dose given in the evening at bedtime and the rest given in the morning

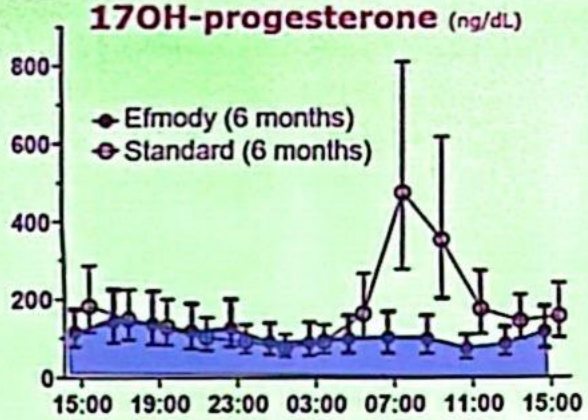
- Hydrocortisone is protected by a pH-resistant coating that prevents its release in the stomach.[2]
- On reaching the small bowel, the enteric coating dissolves at pH 6.8.[2]
- The hydrocortisone is released approximately 4.5 hours post-dose.[1]

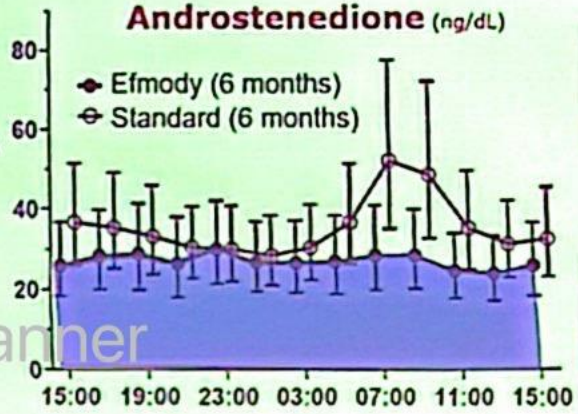
Diurnal NEUROCRINE BIOSCIENCES

Physiological cortisol profile & CAH control



Debono M, et al. JCEM, 2009





80% of subjects maintained good disease control at 3 years (vs. 46% at baseline)

The median hydrocortisone-equivalent dose was 20mg at 3 years (vs. 30mg at baseline)

Patients on Efmody required less stress dosing and had fewer adrenal crises

Events of therapeutic benefit:

- Menstrual improvement
- Pregnancies
- Improved sperm count

HYPERPARATHYROIDISM: FROM BENCH TO BEDSIDE

Matthew T. Drake MD, Ph.D

Mayo Clinic College of Medicine

International Congress of Endocrinology

March 1, 2024

SURGERY FOR PRIMARY HYPERPARATHYROIDISM
FIFTH INTERNATIONAL WORKSHOP

- Age < 50 years
- Serum calcium > 1 mg/dL (0.25 mM) ULN corrected for albumin
- Overt Complication (Stones/Bones)
  - Includes radiographic stones (imaging recommended)
  - Hypercalciuria
    - > 300 mg/day (men) or > 250 mg/day (women)
  - Calculated creatinine clearance <60 ml/min
  - BMD with T-score ≤ 2.5
  - Vertebral fracture (morphometric) or fragility fracture
- If no guidelines are met, parathyroidectomy is still an option with concurrence of the patient and physician, if no contraindications

HEREDITARY STATES OF HYPERPARATHYROIDISM

Disorder	Responsible gene	Pathogenic mechanism	Associated clinical features
MEN type 1*	*MEN1, CDKN1B*	Loss-of-function mutation	Pituitary and gastroenteropancreatic tumors; less frequently, adrenal tumor, facial angiofibroma, collagenoma and lipoma
MEN type 2A	*RET*	Gain-of-function mutation	Medullary thyroid cancer, pheochromocytoma, cutaneous lichen amyloidosis
Hyperparathyroidism – jaw tumor syndrome	*CDC73* (formerly known as *HRPT2*)	Loss-of-function mutation	Fibromas in mandible or maxilla, renal and uterine tumors, ↑ rate of parathyroid carcinomas (15-20%)
Familial hypocalciuric hypercalcemia	*CASR*	Loss-of-function mutation	Rare pancreatitis, relative hypocalciuria (24-hr urinary calcium:creatinine ratio <0.01)
Neonatal severe primary hyperparathyroidism	*CASR*	Loss-of-function mutation	Life-threatening condition with marked hypercalcemia, hypotonia and respiratory distress
Familial isolated hyperparathyroidism	*MEN1, CDC73, CASR, GCM2*	Loss-of-function mutation	Lack of specific features of other syndromic forms

Marcocci and Cetanin. N Engl J Med. (2011) 365:2389

NON-SURGICAL TREATMENT OF PHPT

	BMD	Serum calcium	PTH	Turnover markers
Alendronate	↑	0	0	↓
Estrogen	↑	↓	0	↓
Raloxifene	No data	↓	0	↓
Denosumab	↑	0	↑	↓
Cinacalcet	0	↓	↓/0	↑/0
Cinacalcet + Denosumab	↑	↓	↑	↓
Cinacalcet + Alendronate	↑	↓	↓/0	↓

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21st International Congress of Endocrinology in conjunction with
14th Emirates Diabetes & Endocrine Congress 1-3 March | Dubai

Hypoparathyroidism: New Treatment Options

Sihoon Lee, M.D., Ph.D.

Lab. Genomicae et MedicinaeTranslationis

Gachon University College of Medicine

Saturday, March 2, 2024

Dubai International Convention Center

가천대학교 의과대학
Gachon University College of Medicine

가천대길병원
Gachon University Gil Medical Center

Drawbacks to HypoPT on conventional therapy

Hazard ratio (95% confidence interval)

	Postsurgical	Non-surgical
Renal insufficiency	3.10 (1.73 - 5.55)*	6.01 (2.45 - 14.75)*
Nephrolithiasis	4.02 (1.64 - 9.90)*	0.80 (0.17 - 3.85)
Ischemic heart disease	1.09 (0.83 - 1.45)	2.01 (1.31 - 3.09)*
Seizures	3.8 (2.2 - 6.8)*	10.1 (5.4 - 18.7)*
Cataract	1.17 (0.66 - 2.09)	4.21 (2.13 - 8.34)*
Neuropsychiatric	2.01 (1.16 - 3.50)*	2.45 (1.78 - 3.35)*
Infections	1.42 (1.20 - 1.67)*	1.94 (1.55 - 2.44)*

* Significantly different from control population

Conventional therapy

Unknown whether complications are

- due to the **disease itself**

  or

- the **result of treatment** with calcium and activated vitamin D?

  (often causing fluctuation in calcium levels, high levels of phosphorous and hypercalciuria)

HypoPT is the last of the major hormone deficiency states, which is usually not treated by substitution with the missing hormone

New treatments

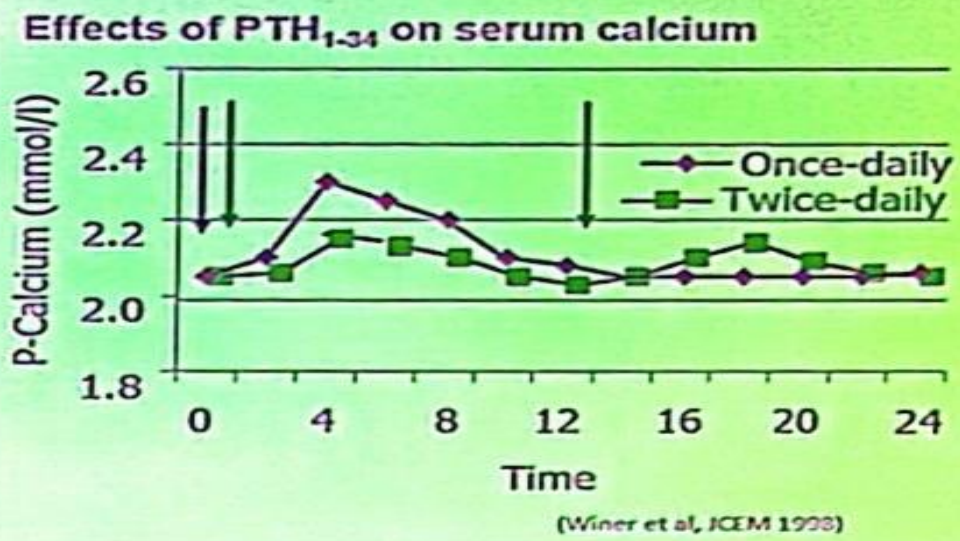
PTH replacement therapy

rhPTH$_{1\text{-}84}$ (Natpar®) has been marketed for the treatment of HypoPT used in several countries – including USA, Europe, Japan

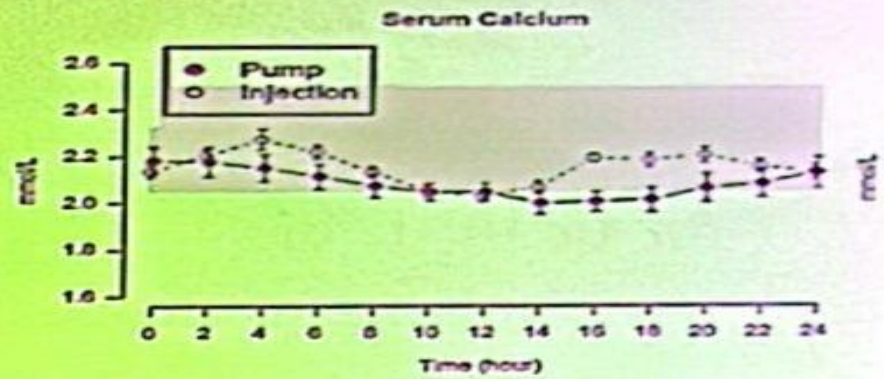
Available as once-a-day subcutaneous injection in different dosages

25 mcg, 50 mcg, 75 mcg, and 100 mcg/d

PTH(1-34) twice a day or by pump delivery



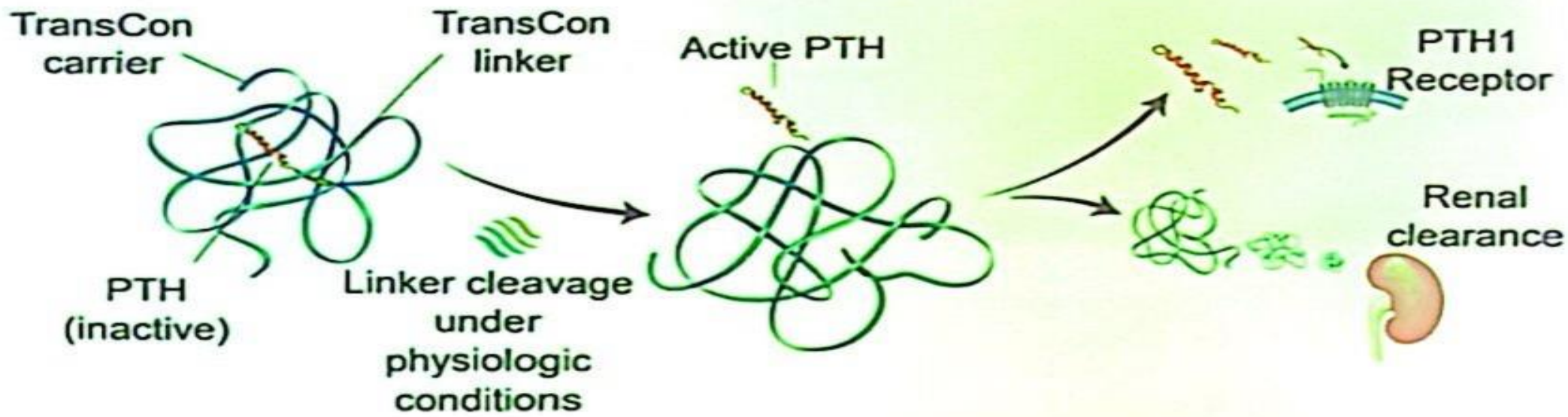
(Winer et al, JCEM 1998)



(Winer et al, JCEM 2012)

TransCon® PTH (palopegteriparatide)

TransCon: transient conjugation



subcutaneously once daily, active PTH is released sustainedly, PTH levels in the physiological range for 24 hours.

Karpf DB, et al J Bone Miner Res 35(8):1430-1440, 2020

Palopegteriparatide (TransCon) PTH

PaTH Forward Phase 2 trial:

Clinical Research Article

PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism

Aliya A. Khan,[1] Lars Rejnmark,[2] Mishaela Rubin,[3] Peter Schwarz,[4] Tamara Vokes,[5] Bart Clarke,[6] Intekhab Ahmed,[7] Lorenz Hofbauer,[8] Claudio Marcocci,[9] Uberto Pagotto,[10] Andrea Palermo,[11] Erik Eriksen,[12] Meryl Brod,[13] Denka Markova,[14] Alden Smith,[14] Susanne Pihl,[15] Sanchita Mourya,[14] David B. Karpf,[15] and Aimee D. Shu[14]

PaTHway Phase 3 trial:

CLINICAL TRIAL

JBMR®

Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial

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Palopegteriparatide (TransCon) PTH

Overall

Treatment with palopegteriparatide seems to address some of the issues in the treatment of HypoPT

- provides stable serum calcium levels
- decreases renal calcium excretion
- improves HR-QoL

Is in the process of being approved by the regulatory authorities

Eneboparatide

Long-Acting PTH Analog (LA-PTH)

- An agonist of parathyroid hormone receptor
  - .... produces a prolonged calcemic response
  - .... being developed for treatment of chronic HypoPT

Phase 2b study

Included 14 patients (10 F) – aged 52 (11) years - 79% post-surgical

- well tolerated with no serious adverse event
- >90% of patients were off active vitD and oral Ca (≤500mg/d)
- In 6 of 7 patients with hypercalciuria at baseline, urinary calcium was normalized

Calcilytics: Encaleret

Autosomal Dominant Hypocalcemia (ADH)

A disease caused by activating variants in the calcium-sensing receptor gene
→ causes the receptor to believe calcium levels are higher than they are
Consequently:

- PTH secretion is suppressed causing hypocalcemia
- In the kidney: high renal calcium excretion

Encaleret

- An oral treatment of ADH
- Acts by resetting the set-point of the calcium-sensing receptor – causing:
  - increased PTH levels
  - normocalcemia
  - normalization of urinary calcium

Conclusion
– to the next level....

Substitution with the missing hormone is needed

Once-a-day injections with short acting PTH-analogues is not feasible

PTH-analogues with a long duration of action is currently being develop

- Seems to be promising
- Still must await long-term effects (complications etc.)
- Specific oral treatment of ADH (calcilytics) is being tested

Overall – in the upcoming years treatment of HypoPT is likely to improve!

Several Challenges in PCOS

- ❑ Complex etiology
- ❑ Heterogeneous clinical presentation
- ❑ Reproductive, metabolic and psychological features
- ❑ Diagnostic difficulties in adolescence
- ❑ Management challenges

Natural History of PCOS

Fetal androgen excess
? Maternal GDM

SGA → Rapid catch-up growth
LGA → Sustained adiposity

Premature adrenarche
Precocious puberty

Adrenal/ ovarian hyperandrogenism
Insulin resistance

Subfertility
Hyperandrogenism
Metabolic syndrome
DM, HTN, Dyslipidemia
Cardiovascular disease

PCOS: an Evolving Definition

1990 NIH criteria:

- ✓ Ovulatory dysfunction ***and***
- ✓ Clinical ***or*** biochemical hyperandrogenism

2003 Rotterdam criteria: (2 out of 3)

- ✓ Ovulatory dysfunction
- ✓ Clinical or biochemical hyperandrogenism
- ✓ Polycystic ovary appearance on ultrasound

2006 Androgen Excess Society criteria:

- ✓ Androgen excess is a must for diagnosis

- Exclusion of other causes of hyperandrogenism is a must for all criteria

Zawadzki J. in Dunaif A et al (eds):PCOS.1992; Fertil Steril 2004; J Clin Endocrinol Metab 2006

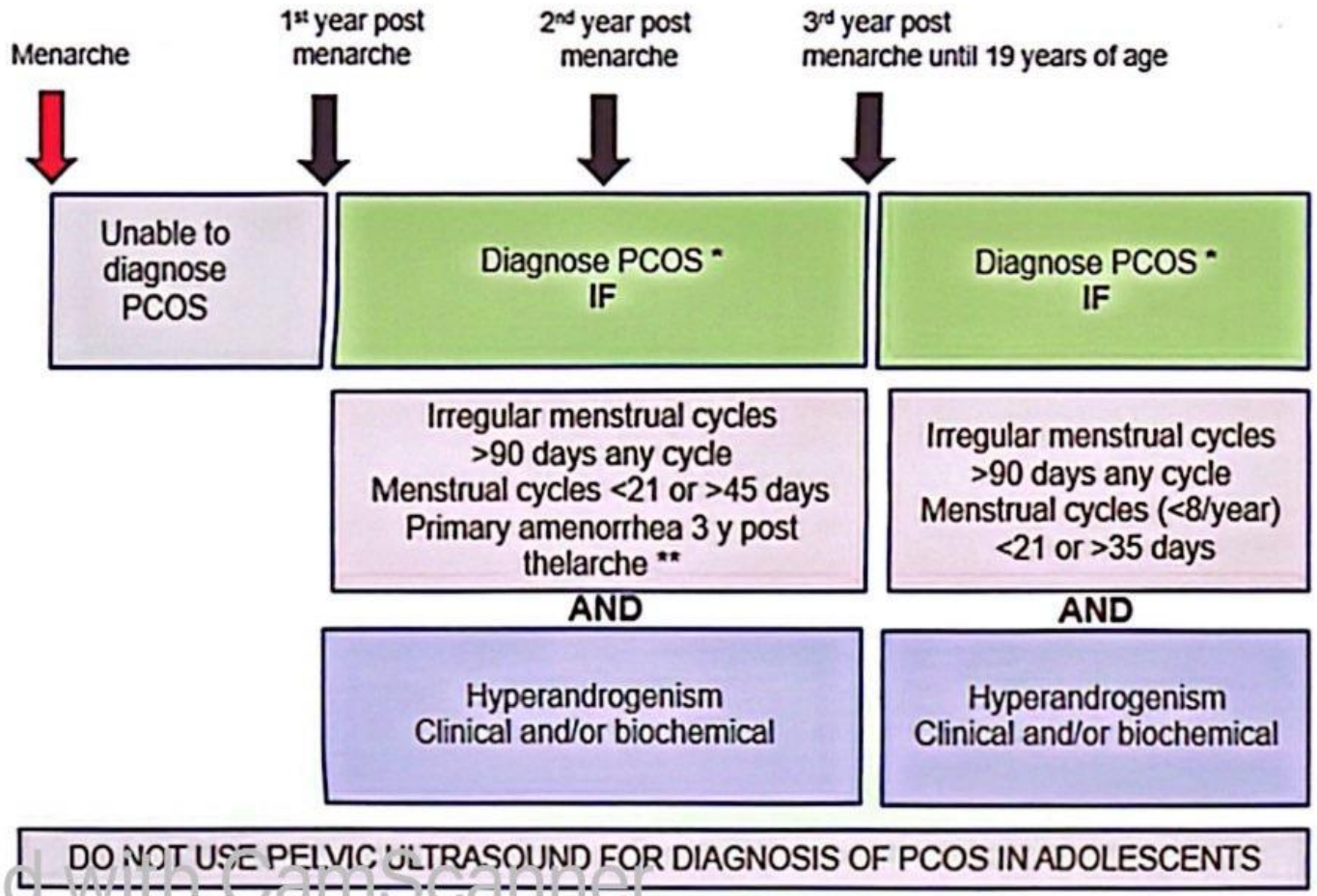
What Constitutes Menstrual Irregularities in Adolescents

Menstrual irregularities defined by time from menarche

Less than 1 year post menarche	Irregular menstrual cycles are normal pubertal transition
> 1 to < 3 years post menarche	< 21 or > 45 days
> 3 years post menarche	< 21 or > 35 days or < 8 cycles per year
More than 1 year post menarche	> 90 days for any one cycle

Adapted from Peña A.S. BMC Med 2020

Adolescent PCOS diagnosis according to time post-menarche



*After exclusion of other causes that may mimic PCOS

**Further investigation may be needed to evaluate primary amenorrhea

Peña A.S. BMC Med 2020

Key messages: PCOS in Adolescents

PCOS phenotypes

- **Lean** PCOS seem to have **worse hyperandrogenic profile**
- **Both obese and lean** have a degree of **insulin resistance**, but this is **more pronounced among obese**
- Among obese adolescents with PCOS, there are varying degrees of insulin resistance/hormonal abnormalities
- Evaluation and management should consider the different phenotypes

ice2024 | edec2024

21st International Congress of Endocrinology in conjunction with
14th Emirates Diabetes & Endocrine Congress 1-3 March | Dubai

Update on Guidelines for Acromegaly Diagnosis and Treatment Follow up

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Pituitary
https://doi.org/10.1007/s11102-023-01360-1

Consensus on criteria for acromegaly diagnosis and remission

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Accepted: 17 October 2023

Diagnosis criteria - 14th Acromegaly Consensus

Focus on IGF-I!!

Characteristic clinical signs and symptoms of disease

IGF-I > 1.3 × ULN for age

Giustina et al. *Pituitary* 2023

And for equivocal results?

1.0 < IGF-I < 1.3: repeat IGF-I

OGTT might be useful

Giustina et al. *Pituitary* 2023

OGTT: only if baseline levels of GH and IGF-I are not enough for the diagnosis

BMI-based GH nadir cutoffs: < 0.4 µg/L for BMI < 25 kg/m^2 and < 0.2 µg/L for BMI ≥ 25 kg/m^2

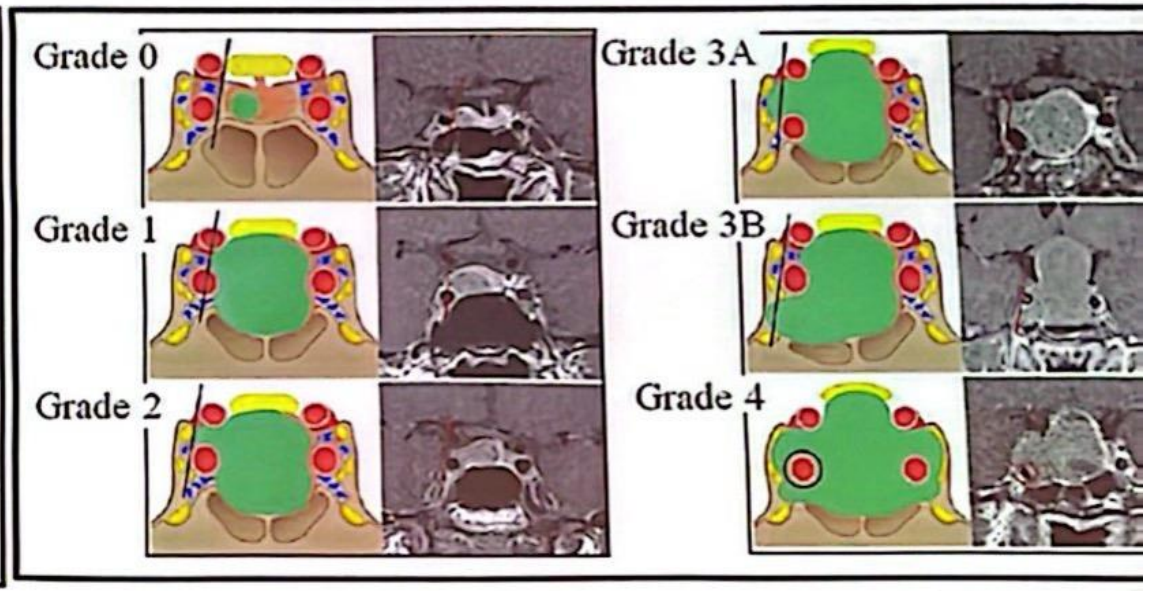
Cessation of oral estrogen therapy for 4 weeks and repeat IGF-I prior to OGTT

Up to one third of patients with acromegaly may show a paradoxical increase in GH following OGTT

Giustina et al. *Pituitary* 2023

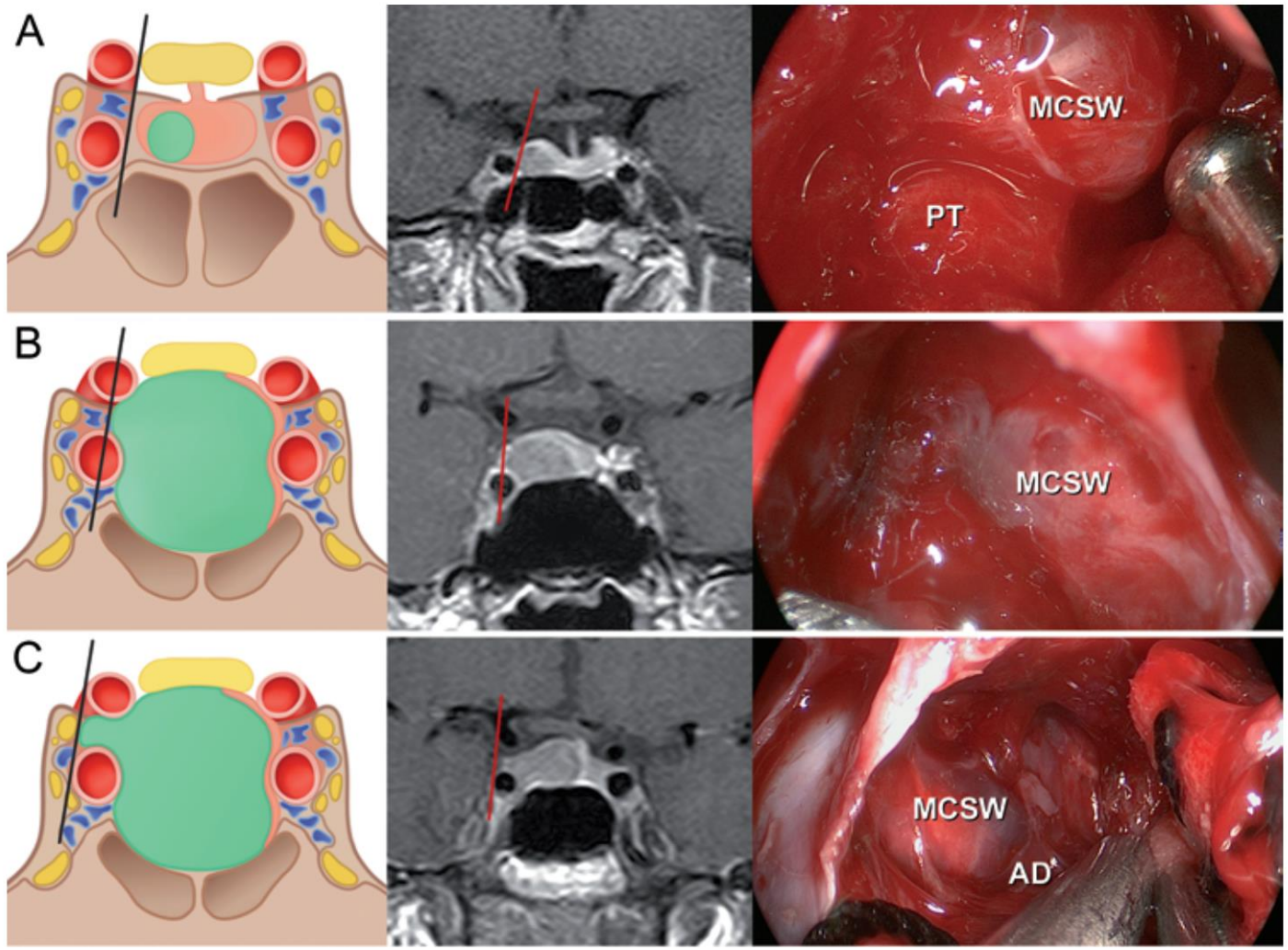
Diagnosis: Imaging
Gd-enhanced MRI

Reporting should be standardized
High-resolution, 1.5T or 3T scanners
T1- and T2-weighted sequences
Coronal and sagittal planes
2–3 mm slice thickness
No or minimal spacing



Gadelha et al. *JCEM* 2022

Micko et al., Journal of Neurosurgery, 2015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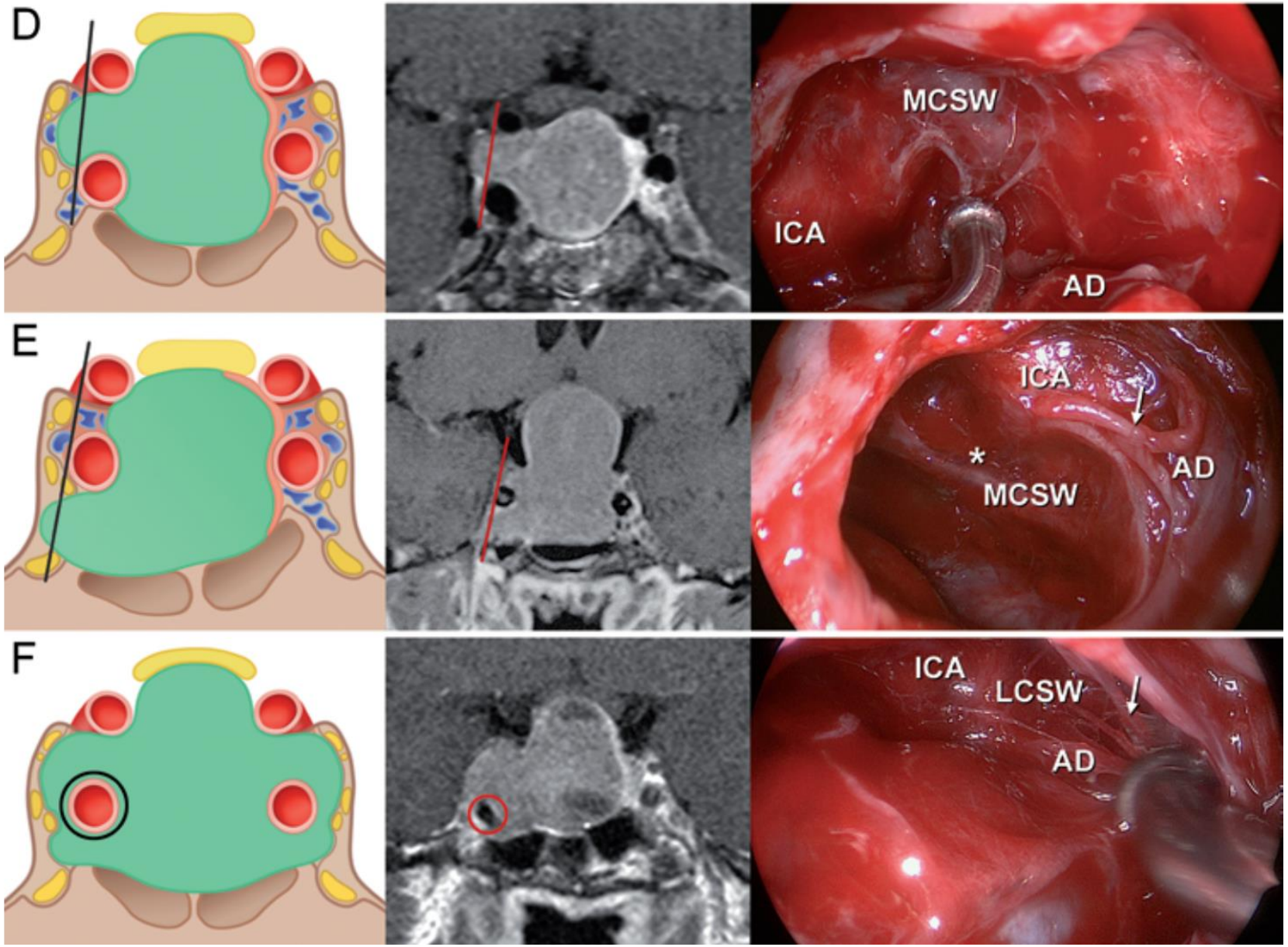
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Diagnosis – Pathology
7 types of adenomas are associated with acromegaly

Standard reporting should include HE, IHC for pituitary hormones, LMWK and transcription factors (PIT-1; ER; GA

Densely granulated somatotroph adenoma

Sparsely granulated somatotroph adenoma

Mammosomatotroph adenoma

Mature plurihormonal PIT-1 lineage adenoma

Immature PIT-1 lineage adenoma

Acidophil stem cell adenoma

Mixed somatotroph and lactotroph adenoma

Proliferation markers: Ki-67, mitosis (risk of progression)

SST expression, *AIP* mutation (molecular diagnosis): identification of patients responsive to SRLs

Giustina et al. *Pituitary* 2023

- Clinicopathologic classification of pituitary adenomas that considers adenoma invasiveness using Knosp grade and sphenoid sinus invasion as well as proliferation by Ki-67 and mitoses can distinguish adenomas with potentially more aggressive behavior and thus identify patients at increased risk for progression.
- Somatostatin receptor immunopositivity, granulation pattern, and *AIP* mutation status have been reported to identify patients less likely to respond to somatostatin receptor ligand (SRL) ther- apy .

Postoperative biochemical remission

IGF-I normalized for age 12 weeks after surgery: surgical success

SRL preoperative treatment: *carryover effect*

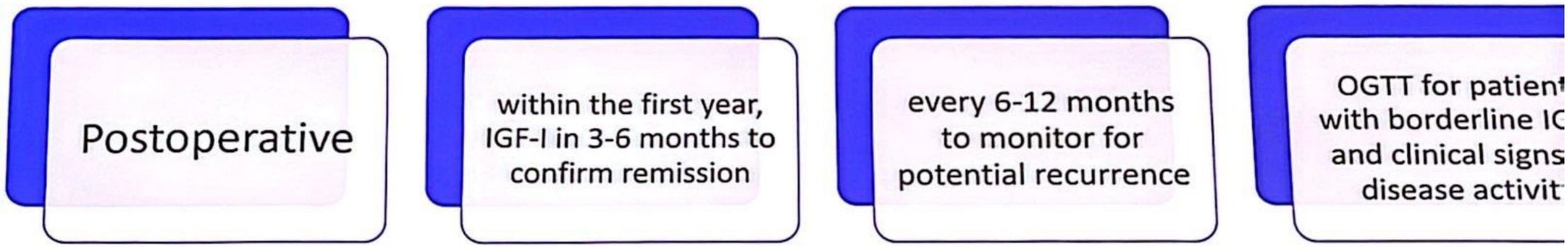
OGTT: nadir < 0.4 µg/L at 2–5 days and at 3–6 months correlated better with remissic than did < 1 µg/L; low random GH on day 1 or 2 post surgery

GH <1.6 µg/L 48 h after surgery was able to predict remission with 93% sensitivity and 86% specificity

Antunes X et al. *Endocrine* 2018

Giustina et al. *Pituitary* 2023

Follow up – biochemical assessment



Giustina et al. *Pituitary* 2023

Follow up - imaging (MRI)

3-6 months postoperatively (baseline for further assessments)

Not every year for patients in remission! Only upon signs of biochemical or clinical disease progression

Individualized approach: pegvisomant, genetic syndromes and aggressive disease

Giustina et al. *Pituitary* 2023

The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, e1571–e1579
https://doi.org/10.1210/clinem/dgad378
Advance access publication 26 June 2023
Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

Long-term Efficacy and Safety of Pasireotide in Patients With Acromegaly: 14 Years of Single-Center Real-World Experience

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Nov 2008 – Jun 2022 (n=50 patients)
IGF-I < ULN
Safety

Pasireotide LAR

20mg, 40mg and 60mg

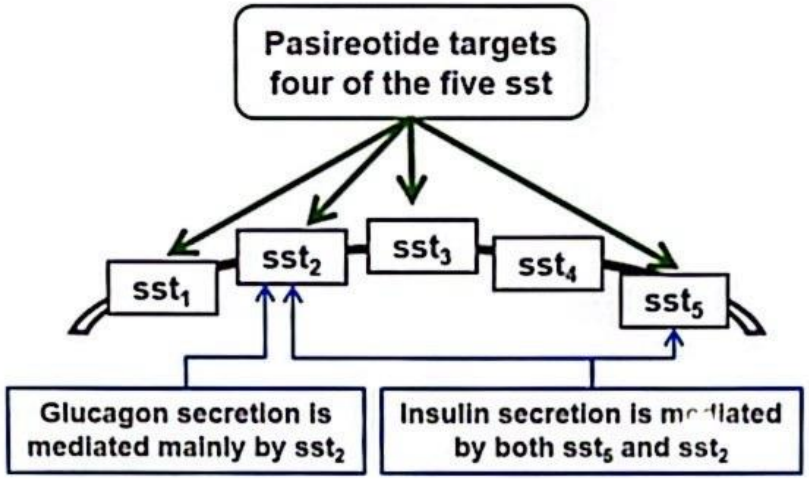
20G (0,9mm)

0.9mm x 30mm

- Patients who switch to pasireotide report less discomfort on administration
- Less presence of nodules
- Easier preparation, no risk of clogging

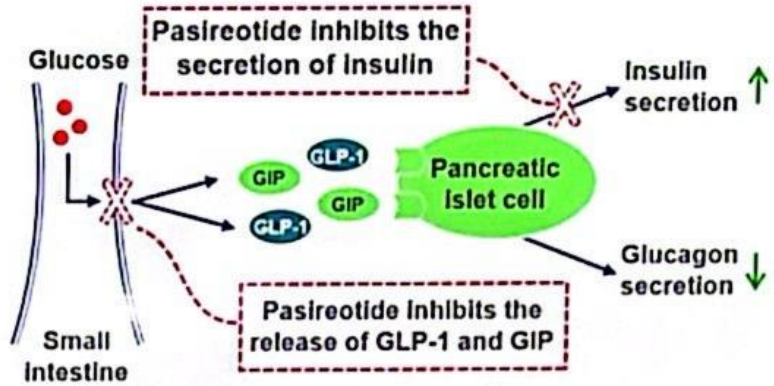
Mechanism of hyperglycaemia related to pasireotide

- sst_2 and sst_5 play important roles in blood glucose regulation



- The higher binding affinity of pasireotide to sst_5 than to sst_2 may lead to unequal regulation of insulin and glucagon

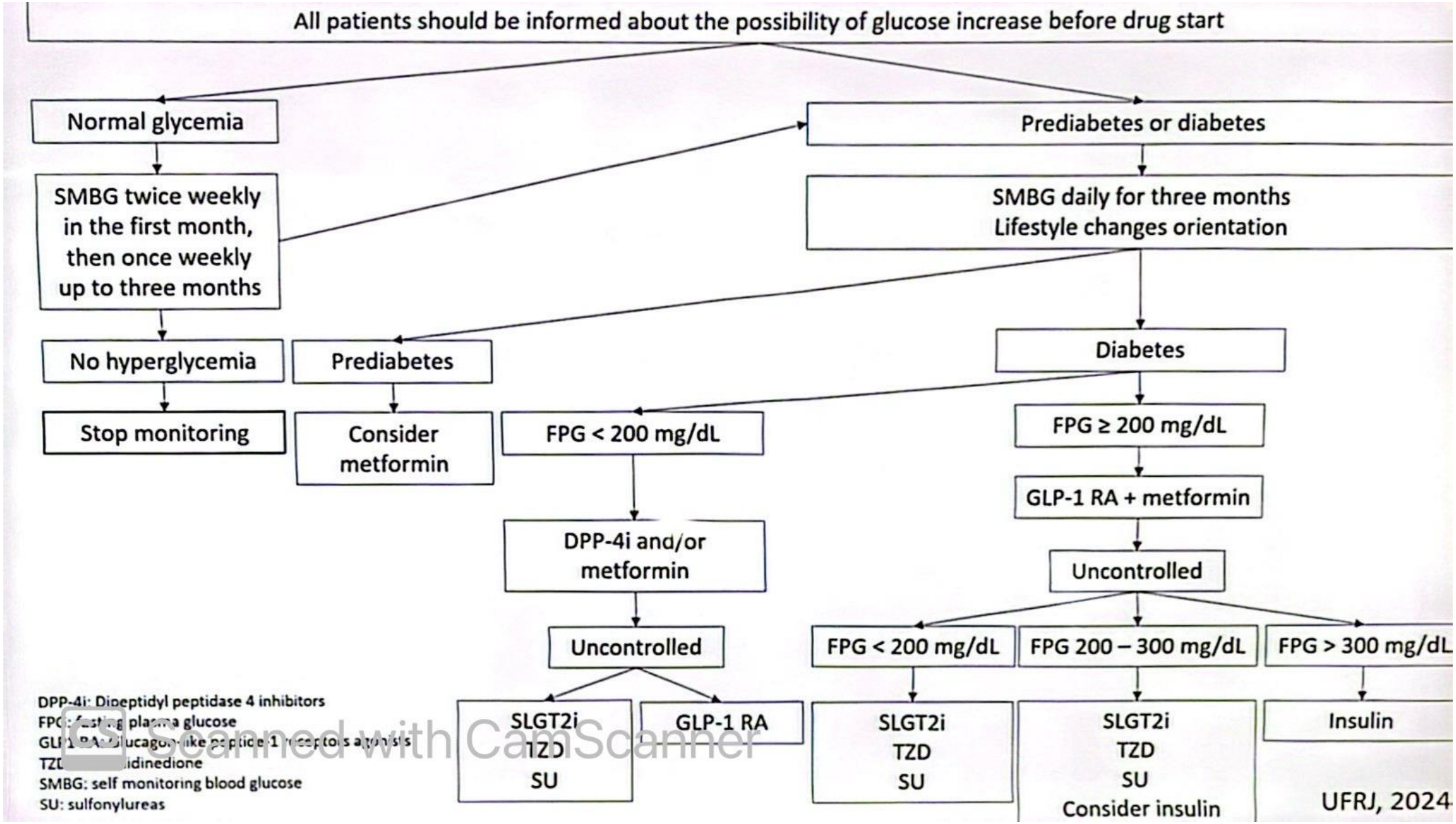
- GLP-1 and GIP stimulate insulin secretion and decrease glucagon secretion from the pancreas



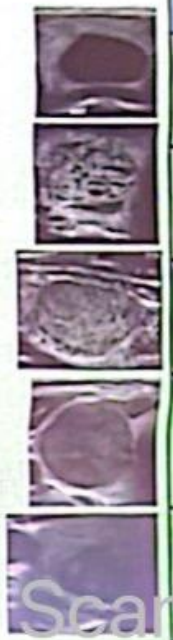
- Pasireotide inhibits the secretion of GLP-1 and GIP

Henry RR *et al. JCEM* 2013

GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1



Size Thresholds for FNA Recommendation



American Thyroid Association (ATA) 2016 — Pattern based		ATA 2024 *draft* — Pattern based		American College of Radiology (ACR) — Sum of points assigned to features	
Benign	No FNA	Benign	No FNA	TR1 Benign	No FNA
Ve	No FNA or ≥2cm	*Very Low Sus*	*No FNA*	TR2 Not Su	No FNA
Low Suspici	≥1.5cm	Low Suspi	≥1.5-2.5cm	TR3 *Mildly*	≥2.5cm
Intermediate Suspicion	≥1cm	Intermediate Suspicion	≥1-2cm	TR4 Moderately Suspicious	≥1.5cm
High Suspicion	≥1cm*	High Suspicion	≥1-1.5cm*	TR5 Highly Suspicious	≥1cm *

*FNA if 5-9mm under certain circumstances (ALL evaluate cervical LNs)

Follow up for BENIGN CYTOLOGY NODULES

ATA 2024 *draft*

ATA Sonographic pattern at FNA	US follow up	Repeat FNA	Strength of Recommendation	Quality of Evidence
High ROM >50%	Within 12months	Repeat FNA for all nodules	Strong	Moderate
Intermediate ROM >20%-50%	18months-3 years	Repeat FNA if change to more suspicious pattern*	Conditional	Low
Low ROM 3% -20%	3-5 years	Repeat FNA if change to more suspicious pattern*	Conditional	Low
Very low ROM <3%	No for cancer surveillance	NA	Strong	Moderate

*Repe[illegible] FNA is not recommended for growth alone

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Insulin Resistance

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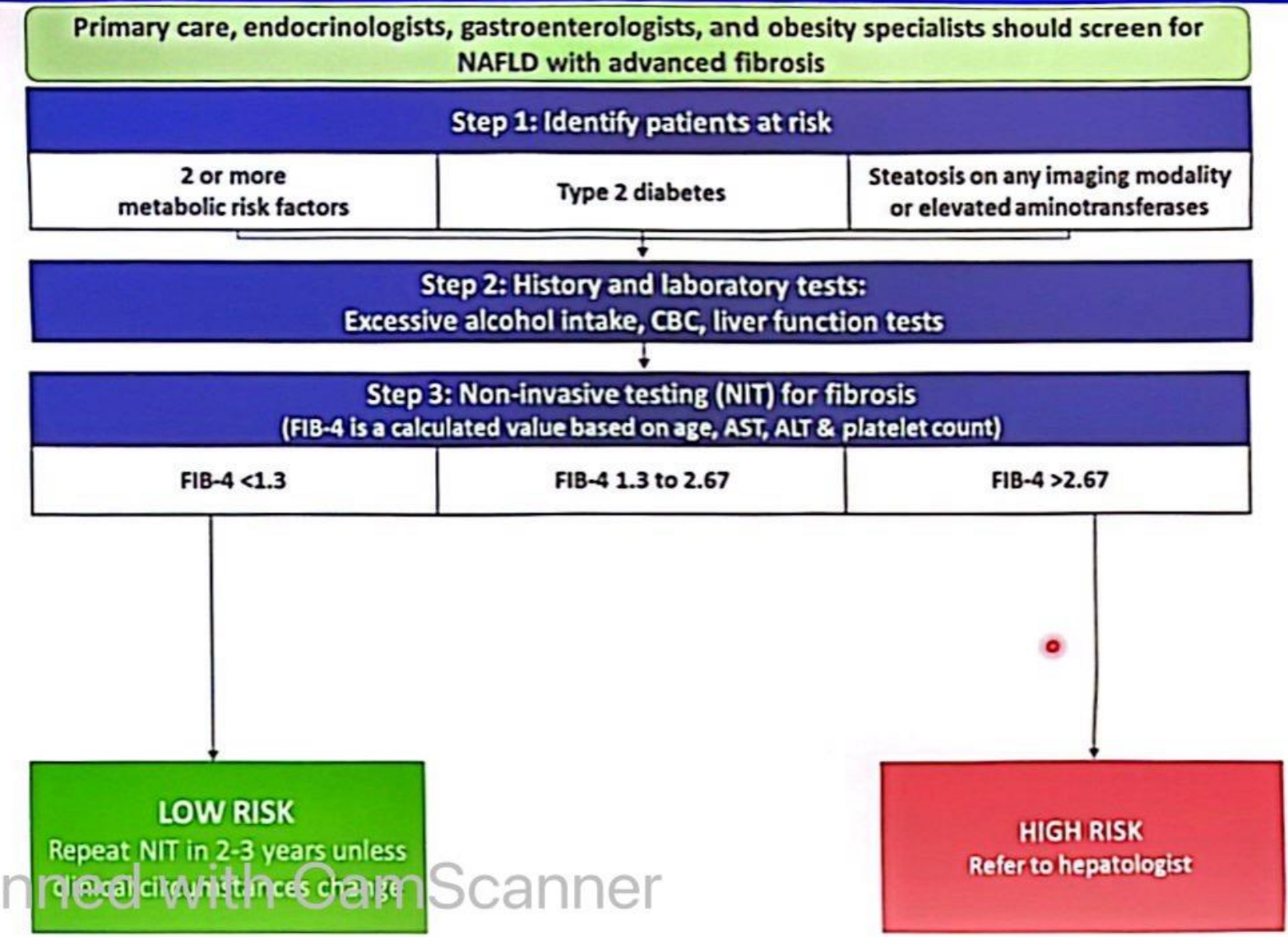
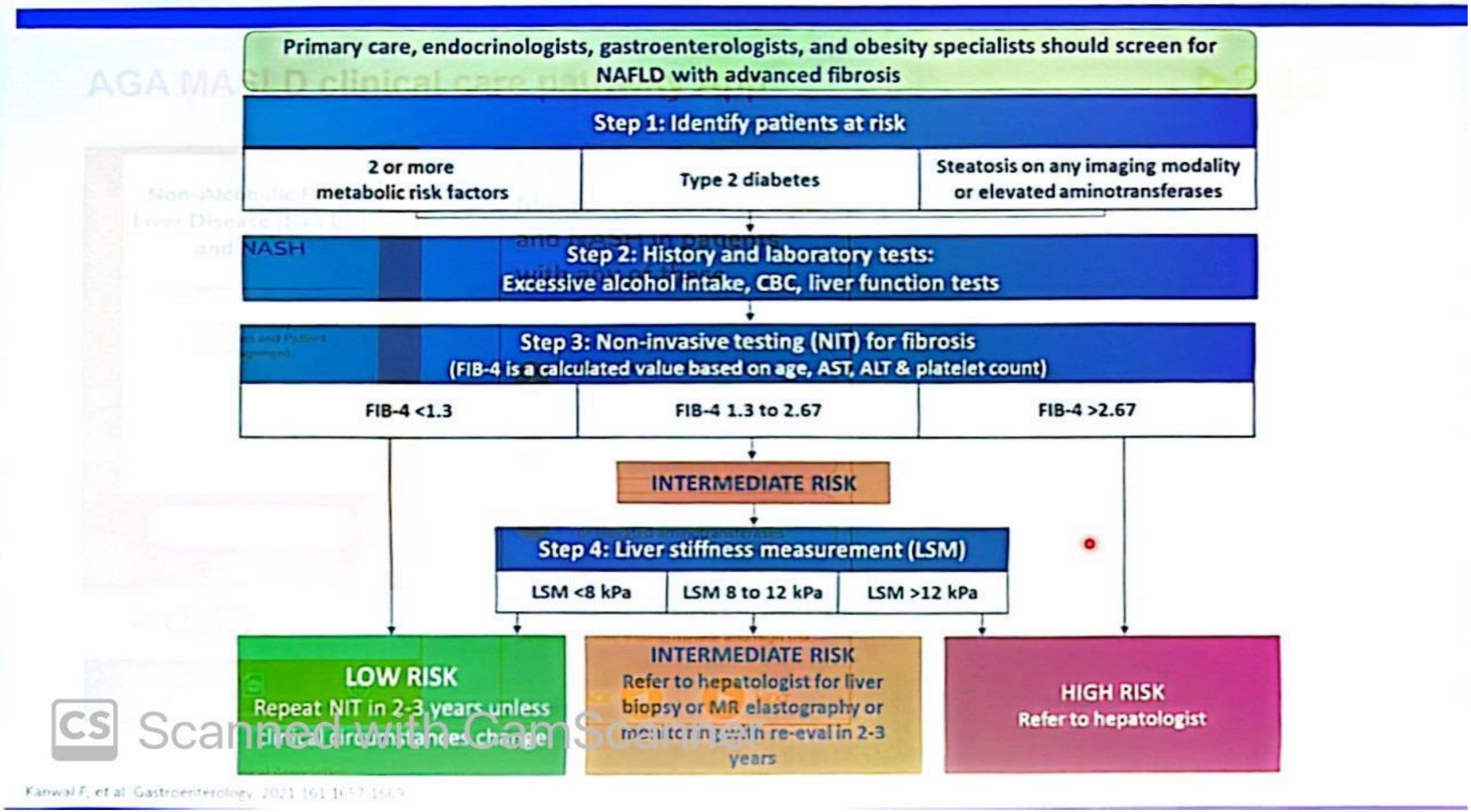


Kanwal F, et al. Gastroenterology. 2021;161:1657-1669.



Kanwal F, et al. Gastroenterology. 2021;161:1657-1669.

American Diabetes Association

Standard of Medical Care in Diabetes - 2022

Table 4.6—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFLD	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonist[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. [a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. [b]Among glucagon-like peptide 1 (GLP-1) receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. [c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution. Adapted from "Preparing for the NASH Epidemic: A Call to Action" (62).

Comprehensive medical evaluation and assessment of comorbidities. Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45(Suppl. 1):S46–S59

Emerging therapies for MASH

- **Resmetirom** (selective thyroid hormone receptor β agonist)
- **Pegozafermin and efruxifermin** (FGF-21 analog)
- **Semaglutide** (selective GLP-1 receptor agonist)
- **Tirzepatide** (dual GIP/GLP-1 receptor agonist)
- **Pemvidutide, Survodutide** (dual GLP-1/Glucagon receptor agonist)
- **Retatrutide** (triple GIP/GLP-1/Glucagon receptor agonist)