CAROLINAS CHAPTER/AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

2016 Annual Meeting

HILTON HEAD ISLAND

SATURDAY HANDOUTS

September 9-11, 2016 ~ Sonesta Resort ~ Hilton Head Island, SC

This continuing medical education activity is jointly provided by the
Carolinas Chapter, AACE and Southern Regional Area Health Education Center

8.25 CME Credits!

2015 ATA Treatment Guidelines for Differentiated Thyroid Cancer

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Objectives

- 1. Learn new nomenclature FVPTC
- 2. Review 2015 ATA guidelines for use I 131
- 3. To describe the proper selection of patients for ablation and/or adjuvant therapy.

The Genetic Basis for Thyroid Cancer
Applying genetics to FVPTC

Follicular thyroid epithelial cell

- Papillary thyroid cancer
  - *BRAFV600E*
  - *RET/PTC fusions*
- Follicular thyroid cancer
  - *RAS*
  - *PAX8-PPARγ*

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

- The most common mutation in PTC is BRAFV600E
  - Follicular adenomas and FTC do not harbor BRAF
- The common mut. follicular adeno. & FTC are RAS mutation
  - RAS mutations are virtually never found in PTC.
  - depends upon the presence/absence capsular/vascular invasion
- The ***infiltrative FVPTC*** often have BRAF mutation
- The ***encapsulated FVPTC*** most commonly have RAS mutations.
- These observations lend further support to the distinction between PTC-like FVPTC and follicular tumor–like FVPTC.

Yuri E. Nikiforov, MD, et.al. *JAMA Oncol*. 2016.0386 Published online April 14, 2016.
Gilbert H. Daniels, (Thyroid Unit Harvard Medical School), Follicular Variant of Papillary Thyroid Carcinoma: Hybrid or Mixture? Thyroid. June 2016.
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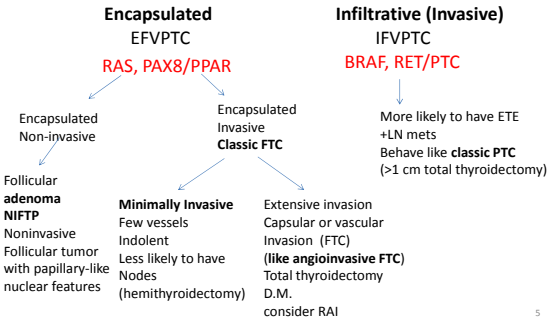
AUS/FLUS

FVPTC = 85% of all follicular patterned thyroid cancer



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Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance [AUS/FLUS] or follicular neoplasm cytopathology

- Noninvasive follicular tumor with papillary-like nuclear features: ***acronym NIFTP.***
- Encapsulated FVPTC without capsular or vascular invasion behave like follicular adenomas.
- NIFTP: a benign condition: reduces the incidence of malignancy in the Indeterminate FNA Categories.
- Rare cases of encapsulated FVPTC (and even tumors called benign follicular adenomas) that subsequently present with metastatic disease, estimated incidence 0.6% of encapsulated noninvasive FVPTC

Gilbert H. Daniels, (Thyroid Unit Harvard Medical School), Follicular Variant of Papillary Thyroid Carcinoma: Hybrid or Mixture? Thyroid. June 2016.
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2016 Paradigm Shift FVPTC

- Reclassification reduces the risk of malignancy (pre-test probability) across Bethesda categories (AUS/FLUS, FN/SFN, SM)
- Total thyroidectomy for a *BRAFV600E* or *RET/PTC* positive FNA specimen from nodules >1.5cm
- Hemi-thyroidectomy reasonable for many *RAS*-mutant nodules. A majority of these prove to be encapsulated FVPTCs.

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Risk Stratification

- 2009 ATA: Tumor type, size, margins, LN involvement, distant metastasis
- 2015 ATA: ALL THE ABOVE, PLUS:
  - Histologic variants of Thyroid cancer
  - **Vascular invasion with number of invaded vessels**
  - Multifocality
  - Number of LN examined and involved
  - **Size of largest metastatic focus to the LN**
  - Extranodal extension
  - **Consideration of genetic markers**

Eric Alexander, Endo ATA 6/20/14, Cooper et al, ATA guidelines 2015

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National Thyroid Cancer Treatment Cooperative Study Gp ATA Guidelines, Mayo Clinic Rochester

- National Thyroid Cancer Treatment Cooperative Study Group 2001, 2936 patients, 2 decades of data the concluded that "no treatment modality, including radioactive iodine, was associated with altered survival in stage I patients.
- ATA guidelines recommend **judicial use of I131 in low-risk patients**: (most low-risk patients continue to receive I131 -Guidelines do not translate into outpatient practices due to lack of confidence, fear, need to rid Tg)
- Mayo Clinic Rochester: post/op recurrences were in regional nodes, especially in those who presented with metastatic neck nodes. 636 node-neg vs 527 **node-positive cases**: no statistically significant differences in 20-year outcomes (cause-specific mortality and tumor recurrence) observed between those having surgery alone vs those given postoperative RRA*
- **European consensus report 2005 (12 European countries) advised that "remnant ablation should be restricted to patients with incomplete surgical excision or poor prognostic factors for recurrence or death."**

*Hay ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. *J Surg Oncol*. 2006;94:692-700.

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Case 2

- 52 yo female referred for incidental 2 cm thyroid nodule on routine exam.
  - No FMHx or Hx radiation, TSH 1.5 mU/L.
  - Neck US – 1.7 cm hypoechoic, solid L nodule w/o other suspicious features, no LAD, right lobe pristine
- FNA – suspicious for papillary thyroid cancer

- Total thyroidectomy and CLND
  - 1.7 cm PTC, 0/6 LN
  - Stage 1 (T1N0MX)

- Radioiodine?

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Prediction of Cause-Specific Mortality in 4,138 Adult PTCs Treated 1935-2014 MACIS Scores, as of April 2016

- Based on **M**etastasis, **A**ge, **C**ompleteness of surgery, **I**nvasion and **S**ize
- 20-yr rates for CSM in low risk (scores <6) of 0.7% and in high risk (scores 6+) of 27.6%, for 20-yr mortality ratio of 39

Ian Hay, Mayo data

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www.thyroid.org, calculators, thyroid cancer staging calculator

Age at diagnosis (years)	52
Gender	F
Size of primary tumor (cm)	2.3 cm
Invasion (Any)	N
Invasion (RLN, Larynx, Trachea, Eo	N
Invasion (Posterior cervical f./ ves.	N
Complete surgical resection	y
Nodes (Region VI – central)	N
Nodes (Regions I – V, or VII)	N
Distant metastases	N
pTNM	pT2N0M0
Stage	II
MACIS	4.85 LOW RISK
AGES(≤4 low risk; >4 high risk)	3.06 LOW RISK
AMES	LOW RISK

ATA Events

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Prognostic Indicators and Therapeutic Implication

- Knowledge of appropriate prognostic factors at the time of initial treatment should permit **accurate prediction of likely postoperative outcome**
- Risk group assignment (**scoring/staging systems**) allows:
  - a "selective approach" to therapy,
  - avoiding unnecessarily aggressive treatment in the low-risk majority
  - Avoiding inadequate therapy for the high-risk minority

Ian Hay, Mayo data

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Tg Changes Following Thyroidectomy

- Stimulated Tg good accurate estimate of response to initial therapy
- Tg Nadir after Thyroidectomy depends on
  - Size of remnant thyroid
  - Presence of residual tumor
  - Metastatic disease that is meaningful
  - 2 w PO non suppressed Tg <2ng/ml, great sign patient is surgically cured (excellent initial therapy) *

Hands, KE EIGHT YEAR FOLLOW-UP OF 378 CONSECUTIVE LOW-INTERMEDIATE RISK DIFFERENTIATED THYROID CANCER PATIENTS WITHOUT I131 ABLATION IN A COMMUNITY BASED SETTING, presented at AACE 5/15/15

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BE A THOUGHTFUL ENDOCRINOLOGIST
Golden Rules for Managing PTC: right team

- Carefully choose your pathologist (+/- Local)
- Expert US scanning; pre op assessment vital.
- Know skills/limitations of your thyroid surgeon
- Use TNM stages and apply prognostic scoring (risk assessment)
- Permit tolerance of 'detectable' Tg levels
- Use I-131 therapy "selectively"

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RAI use 2015 ATA Guidelines

ATA recurrence risk TNM staging	Description	Post surgical RAI recommendation (ROR)
Low risk (no aggressive histo) T1a/N0,NX/M0, MX	T<1cm unifocal or multifocal	NO (~2%)
Low risk T1b, T2/N0,Nx/M0, MX	T1b 1- 2cm T2 2-4	NO, not routine (~2%) (multifocal PTMC 4-6%)
Low- indeterminate risk T3/N0,Nx/M0,MX	T>4 cm or microscopic invasion	NO, not routine (p/o Tg?) unless adverse features
Low- indeterminate risk T1-3/N1a/M0,MX	CLN mets present	NO , if ≤ 5, (<0.2cm) (~5%) Consider size and number
Indeterminate risk Any T1-3/N1b/M0,MX	Lateral nodes present pT3 minor ETE (3-8%)	Consider size and number NO unless large, >5LN (~20%)
High risk T4/and N/any M	Gross ETE (BRAF 10%)	YES (10-40%) (VE 15-30%, ETE BRAF 10-40%)
High risk M1 (any T, any N)	Distant mets, ENE extranodal extension 40%	YES (30-55%) TERT >40%,

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Intermediate Risk

- Microscopic invasion perithyroidal tissue
- Aggressive histology (tall cell, hobnail variant, columnar cell
- PTC with vascular invasion
- Clinical N1 or >5 pathologic <3cm
- Multifocal PMTC with ETE and BRAF

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ATA High Risk

- Macroscopic invasion (gross ETE)
- Incomplete tumor resection
- Distant mets
- P/O Tg suggestive of distant mets
- Pathologic N1 nodes >3 cm
- FTC with extensive vascular invasion (>4 foci)
- Only stage/risk where I 131 has shown disease specific survival and improves disease –free survival

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2015 ATA Recommendation

- In addition to the basic tumor features for AJCC/UICC thyroid cancer staging, pathology reports should include information helpful for risk assessment.
  - Presence of vascular invasion/number of vessels invaded
  - Number of LN examined and involved with tumor
  - Size of the largest metastatic foci to the LN
  - Presence of extranodal extension of the metastatic tumor. **(strong recommendation, moderate quality evidence)**

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"Selective use of RAI for ablation/adjuvant therapy after total thyroidectomy for DTC:
A Practical Approach to Clinical Decision Making"

- 2015 ATA guidelines call for a risk adapted approach to the selection of patients for post-operative RAI treatment.
- Utilizing pre-operative, intra-operative, and post-operative clinico-pathologic factors accurately identifies patients most likely to benefit from RAI.
- "Risk Adapted approach ensures that patients most likely to experience a clinical benefit are selected for RAI ablation while avoiding unnecessary exposure to ionizing radiation in the majority of low to intermediate risk thyroid cancer patients."

R. Michael Tuttle, Mona M. Sabra, Oral Oncology 4/13

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Impact on Overall Survival of Radioactive Iodine in Low-Risk DTC Patients

- **Objectives:** to assess the survival benefit of RAI for DTC.
- **Design:** 1298 DTC low risk patients, treated between 1975-2005. compared overall survival (OS) vs disease-free survival (DFS)
- **Results:** Median follow-up was 10.3 yr.
  - 911received RAI after surgery *vs.* 387 without RAI after surgery.
  - 10-yr OS no RAI was 95.8% *vs.* 94.6% in RAI after surgery ($P = 0.006$)
  - 10-yr DFS no RAI was 93.1% *vs.* 88.7% ($P = 0.001$).
- **RAI was neither significantly nor independently associated with OS ($P = 0.243$) and DFS ($P = 0.2659$).**
- **DFS did not differ ($P = 0.48$) with a stratified univariate hazard ratio of 1.11 (95% confidence interval 0.73–1.70).**
- **Conclusion: long-term follow-up (10.3 yr), failed to prove any survival benefit of RAI after surgery in a large cohort of low-risk DTC patients.**

Schwartz, C. et.al., (France) JCEM 1, 2012

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Major factors impacting decision making in RAI ablation: Much more than TNM.

- Need pre-op assessment, surgical report, P/O Tg
- Are they high risk: large nodes, dist. Mets, ETE, VI
- Is the patient at significant risk of recurrence?
- Is the patient at significant risk of having non-RAI avid distant metastases? (Inappropriate Tg, BRAF+)
- Is RAI ablation required to facilitate follow up?
- P/O serum Tg level (excellent for prognostication)
- Are anti-Tg antibodies present? (Watch them fall!!)

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2015 ATA and NCCN guideline recommendations

- **DO NOT recommend RAI ablation for all patients with locoregional lymph node metastases.**
- ATA surgical affairs committee:
  - risk of recurrence in N1 disease is related to the number and size of involved lymph nodes
  - ≤5 microscopic LN metastases in the clinical N0 neck carries a risk of recurrence <5% (similar to multifocal papillary microcarcinoma).

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Recommended observation rather than immediate RAI ablation:
Very unlikely to obtain substantial benefit
from an initial empiric dose of RAI after thyroidectomy

- **Papillary microcarcinoma (<1 cm), intrathyroidal, unifocal or multifocal, with normal post-operative Tg**
  - Very low risk of recurrence, very low risk of distant metastases, RAI of unproven benefit with regard to recurrence or mortality, neck US and serum Tg likely to identify the few cases of recurrence in a timely manner
- **Papillary thyroid cancer, intrathyroidal, 1–4 cm, with normal postoperative Tg**
  - Low risk of recurrence, low risk of distant metastases, RAI of unproven benefit with regard to recurrence or mortality, neck US and serum Tg likely to identify the few cases of recurrence in a timely manner

R.M. Tuttle, M.M. Sabra / Oral Oncology 49 (2013) 676–683

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Therapeutic Outcomes

- **Excellent: complete remission**
  - No biochemical, structural or clinical evidence of disease
  - Best response to initial therapy (total thyroidectomy)
- **Acceptable: minimal residual disease**
  - Have biochemical or clinical evidence of small-volume disease with no evidence progression
  - Most can undergo FU with observation alone
  - Additional Tx reserved for evidence progression
  - Show meaningful effect of additional Tx before subjecting relatively low risk pt to potential SE of surgery RAI, EBRT, chemo
- **Incomplete: persistent disease**
  - Clinically important failure of initial therapy
  - Usually offered further/additional Tx
  - Observation alone will likely lead to clinically significant disease
  - Additional therapy reasonable: benefit may outweigh the risks of therapy

Tuttle, RM, Risk-Adapted Management of Thyroid Cancer, Endocrine Practice, 2008

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Clinical scenarios selected for **observation** rather than immediate RAI ablation.

- **Small volume cervical lymph node metastases, with normal postoperative Tg**
  - Low risk of recurrence, low risk of distant metastases, conflicting data with regard to benefit on recurrence or mortality, neck US and serum Tg likely to identify the few cases of recurrence in a timely manner (serial US and Tg)
- **Minor extrathyroidal extension identified only on pathology examination, with normal post-operative Tg**
  - Low risk of recurrence, low risk of distant metastases, inadequate data with regard to benefit on recurrence or mortality, neck US and serum Tg likely to identify the few cases of recurrence in a timely manner (serial US and Tg)

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Conclusions

- Learn to perform/or refer for pre-op neck surveillance US to recommend appropriate initial surgery for complete resection.
- Know the skills and/or limitations of your thyroid surgeon (should never take pt to OR without appropriate pre-op neck US).
- Define risk assessment: minimal disease, requires minimal treatment. MACIS <6, 20 year survival 99% without RAI
- In a community based setting, low and intermediate risk stage I and II DTC can be managed safely, effectively and confidently **without** RAI using a 2wPONSTg <2ng/ml.
- A low, detectable and stable Tg is an easy tool to follow patients without RAI.
- Neck ultrasound and careful observation for any rising **TREND** of serum Tg concentrations, will routinely detect structural disease amenable to surgery.

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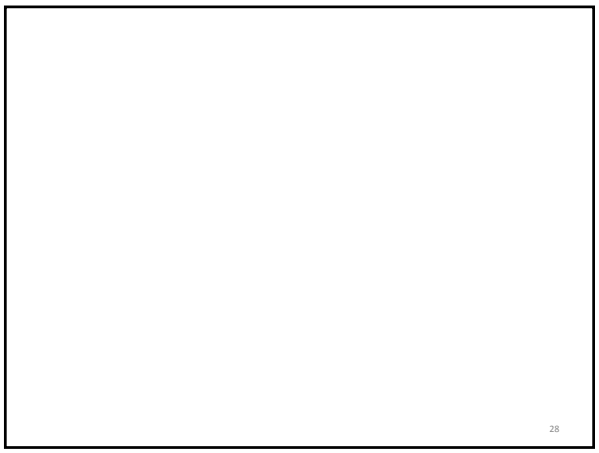
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Male Hypogonadism and Infertility: An Endocrine Perspective

Jerald Marifke, MD, FACE
Prevea Health
Green Bay, WI

Objectives

- Review the diagnosis, treatment and monitoring of male hypogonadism
- Review currently revised clinical practice guidelines
- Discuss endocrine evaluation and treatment of male infertility

Male Hypogonadism

What is male hypogonadism?

- A decrease in one or both major functions of the testes
  - Sperm production
  - Testosterone production

Who should be screened?

- Clinical manifestations
- Signs and symptoms reported
- Certain clinical disorders

Clinical Manifestations

Incomplete or delayed sexual development	Small or "shrinking" testes
Decreased libido	Infertility
Erectile dysfunction	Height loss, low trauma fracture or low bone mass
Gynecomastia	Hot flushes, sweats
Loss of body hair (decreased shaving)	

Signs and Symptoms Reported

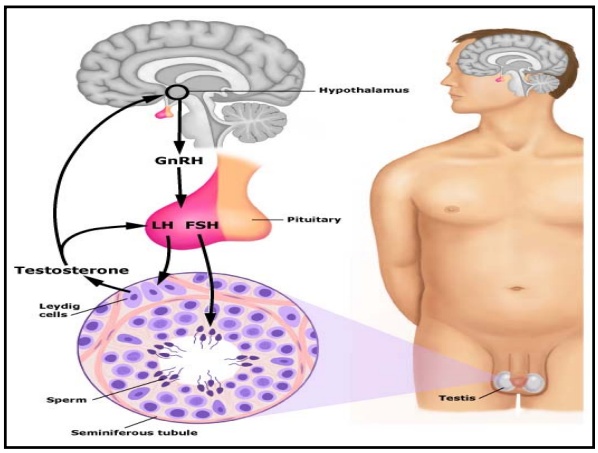
Decreased energy, motivation, initiative and self-confidence	Depression, feeling sad
Poor concentration, memory	Sleep disturbance, increased sleepiness
Anemia	Reduced muscle strength, bulk
Increased body fat, BMI	Decreased physical or work performance

Clinical Disorders

Sellar mass, sellar radiation or other sellar disease*	Medications (glucocorticoids, opioids)*
HIV associated weight loss*	ESRD and hemodialysis
COPD (moderate to severe)	Infertility*
Metabolic bone disease or osteoporosis*	Type 2 DM

Primary vs. Secondary

- Primary hypogonadism
  - Disease of the testes
  - Testosterone and/or sperm count are low with serum LH and FSH above normal
- Secondary hypogonadism
  - Disease of the pituitary or hypothalamus
  - Testosterone and/or sperm count are low with serum FSH and LH normal or below normal



Erectile Dysfunction

Primary and secondary hypogonadism:
Second most common cause

- Medication effect
- Psychogenic
- Primary hypogonadism
- Secondary hypogonadism
- Diabetes mellitus
- Neurologic
- Unknown
- Hypothyroidism
- Urologic
- Hyperprolactinemia
- Miscellaneous
- Hyperthyroidism

Combined Primary and Secondary

- Variable gonadotropin levels depending on whether primary or secondary testicular failure predominates
- Occurs with

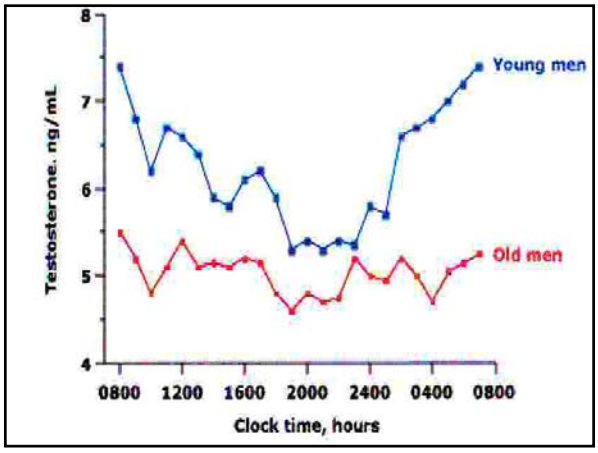
Hemochromatosis	Sickle cell disease
Thalassemia	Glucocorticoid therapy
Alcoholism	DAX-1 mutation
Older men	

Diagnosis

- Signs and symptoms
- Unequivocally low serum testosterone levels

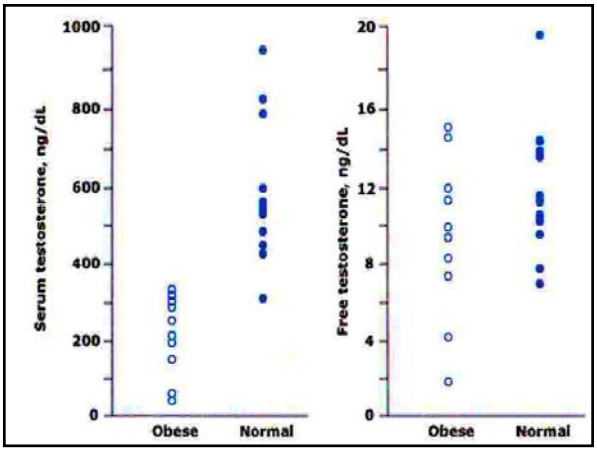
Diagnosis

- Morning total testosterone level
- Repeat
- Free or bioavailable level if total value in lower limit of normal or suspected alteration of SHBG
- Do not make diagnosis during acute or subacute illness



Conditions with ↓ SHBG

Morbid Obesity
Nephrotic Syndrome
Glucocorticoids, progestins, anabolic steroids
Diabetes mellitus
Hypothyroidism
Acromegaly



Conditions with ↑ SHBG

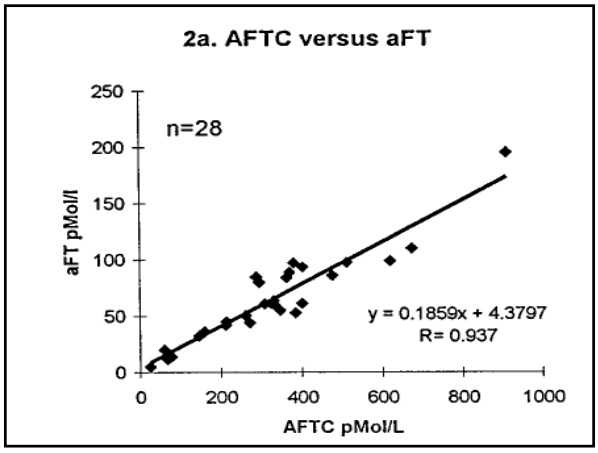
Aging
Hepatic cirrhosis and hepatitis
Anticonvulsant use
Hyperthyroidism
Estrogen use
HIV disease

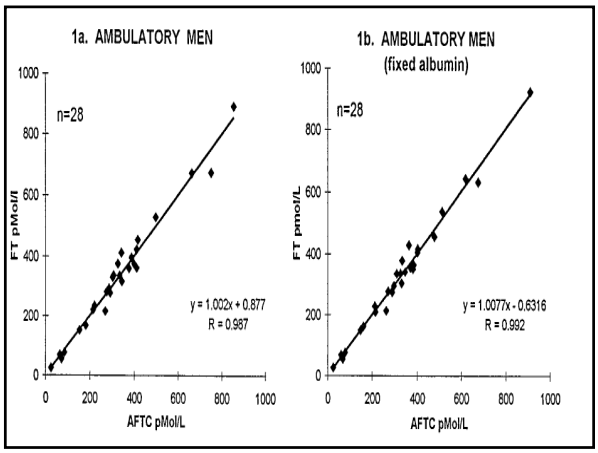
Testosterone Assays

- Liquid chromatography/tandem mass spectrometry (LC/TMS) is the gold standard
- Most labs use platform immunoassay or radioimmunoassay (RIA) often termed automated assay
- Lab should make sure there assay is accurately reflecting LC/TMS

Reliable free testosterone assay

- Free testosterone immunoassays that directly measure testosterone are not considered reliable
- Options include
  - Lab assay that incorporates SHBG
    - Testosterone, free and weakly bound
    - Bioavailable testosterone
  - Free testosterone by calculation
  - Free testosterone by equilibrium dialysis





Concentration Testosterone = FT(free) + Alb-bound-T + [SHBG]-bound-T

Testosterone = [S] + $[S_A]$ + [SP]

· ***Albumin***

$[S_A]$ = constant = $K_A \times C_{conc.}^{Alb} = 3.6 \times 10^4 \times \frac{43 g/1}{69000} = 22.4$

[S]

69000 =(molecular weight alb.)

$K_A = 3.6 \times 10^4$

for an average albumin conc. of 4.3 g/dL

or $[S_A] = 22.43\ [S]$

$[S] + [S_A] = (1 + 22.43)[S] = 23.43\ [S]$ (1)

· ***SHBG***

[P] = free SHBG

[SP] = steroid bound SHBG

$K = 10^9$ M

[S] +[P] « [SP] or $[S] = \frac{[SP]}{[P]\,[K]}$ (2)

[P] + [SP] = [SHBG] **or [P] = [SHBG] –[SP]** (3)

· ***Bioavailable***

[Bio T] = [S] + [SA]

Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole
approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakl
affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone i

Albumin	4.0	g/dL	Calculate	Explana
SHBG	36	nmol/L		
Testosterone	500	ng/dL		

Free Testosterone	10.4 ng/dL = 2.08 %
Bioavailable Testosterone	227 ng/dL = 45.5 %

Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole me
approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly b
affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone incl

Albumin	4.0	g/dL	Calculate Explanatio
SHBG	90	nmol/L	
Testosterone	500	ng/dL	

Free Testosterone	5.10 ng/dL = 1.02 %
Bioavailable Testosterone	112 ng/dL = 22.3 %

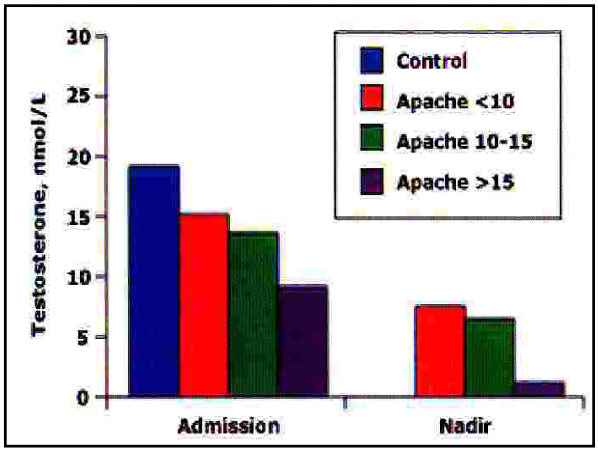
Free & Bioavailable Testosterone calculator

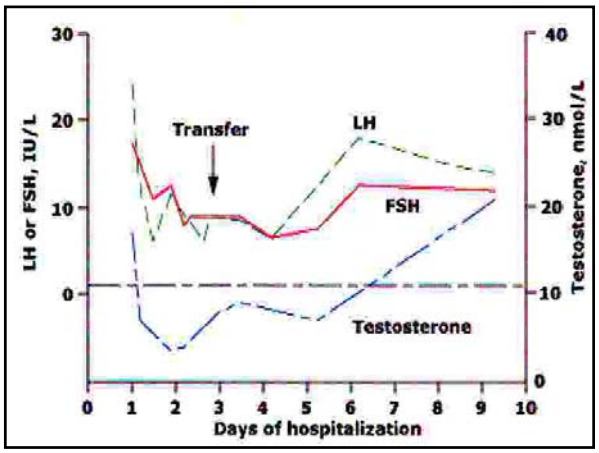
These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

Albumin	4.0	g/dL	Calculate	Explanation and examples
SHBG	2	nmol/L		
Testosterone	500	ng/dL		

Free Testosterone	21.7 ng/dL = 4.35 %
Bioavailable Testosterone	476 ng/dL = 95.1 %

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/ circumstances without the prior consultation of experts or professional persons. No responsability whatsoever is assumed for its





Evaluation

- Check LH and FSH
- If normal or low – secondary hypogonadism
  - Prolactin
  - Iron saturation
  - Pituitary function assessment
  - Sellar MRI

Evaluation

- If elevated – primary hypogonadism
  - Karyotype (especially if testes < 6 mL)
- BMD if severe androgen deficiency or low trauma fracture

Treatment

- Goals
  - Induce and maintain secondary sexual characteristics
  - Improve sexual function and sense of well being
  - Improve and maintain bone mineral density
  - Testosterone mid-normal range

Treatment

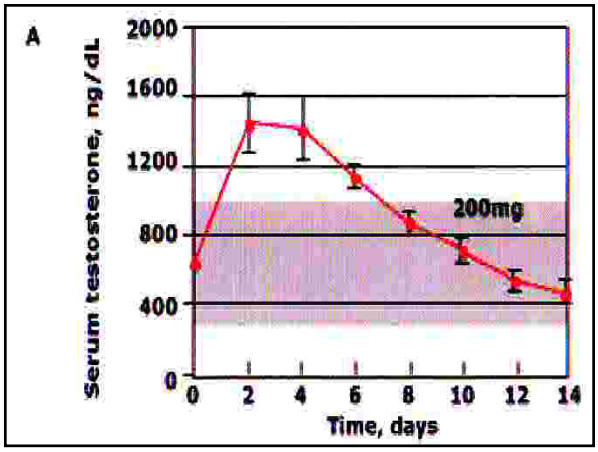
- Contraindications
  - Breast or prostate cancer
  - Hematocrit > 50%
  - OSA
  - Lower urinary tract symptoms (severe)
  - CHF
  - Fertility desired

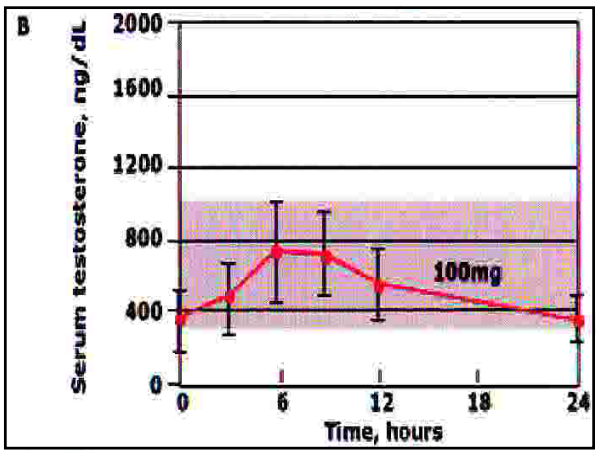
Prostate

- If > 40 years of age baseline PSA, if > 0.6 check DRE prior to initiating treatment
- Repeat PSA, DRE at 3 or 6 months after initiating treatment then per age and race recommended guidelines
- Do not initiate therapy without further urologic evaluation if palpable prostate nodule or PSA > 4 ng/ml or > 3 ng/ml if high risk patient

Testosterone formulations

- Enanthate or cypionate (IM)
- Androgel, testim, axiron, fortesta, and natesto (gel/solution/cream)
- Androderm (body patch)
- Striant (buccal patch)
- Testopel (pellets)
- 17-α methyl (oral – not recommended due to association with liver toxicity)





Adverse Events

- Evidence of association
  - Erythrocytosis
  - Acne and oily skin
  - Detection of subclinical prostate cancer
  - Growth of metastatic prostate cancer
  - Reduced sperm production and fertility

Adverse Events

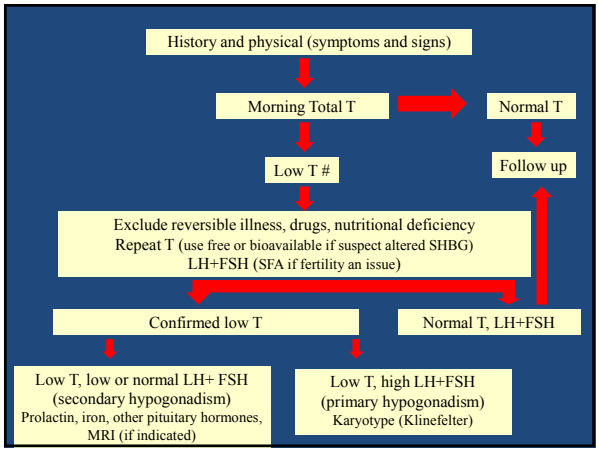
- Weak evidence of association
  - Gynecomastia
  - Male pattern balding
  - Growth of breast cancer
  - Induction or worsening of OSA

Monitoring

- Evaluate at minimum 3 to 6 months on therapy and annually
- Check testosterone at first evaluation
- Check hematocrit at first evaluation then annually
- BMD after 1 to 2 years of therapy with osteoporosis or low trauma fracture

Monitoring

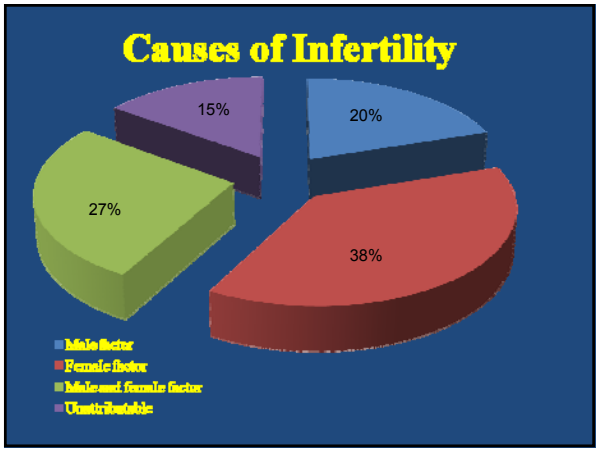
- Urologic evaluation if
  - Increase in PSA > 1.4 ng/ml in any 12 month period
  - PSA velocity > 0.4 ng/ml/yr using PSA level at 6 months as baseline (must have 2 years of data)
  - DRE abnormality
  - AUA/IPSS prostate symptom score > 19

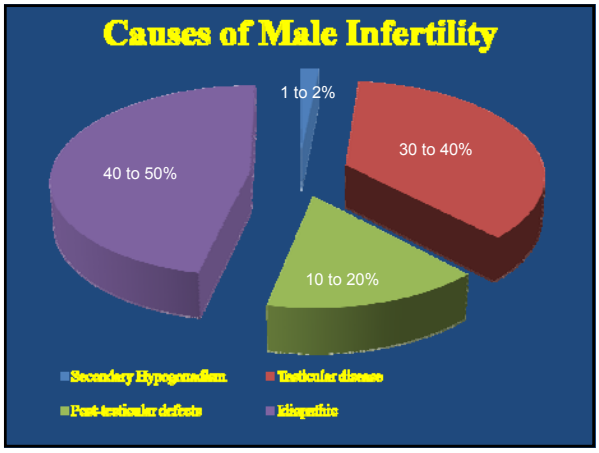


Male Infertility

Definitions

- Infertility - inability to achieve conception despite one year of frequent unprotected intercourse
- Oligospermia – decrease in number of sperm cells in ejaculate compared to normal
- Azoospermia – no sperm cells in ejaculate
- Asthenospermia – low sperm with decreased motility
- Teratozoospermia – decrease in motility and morphology





Semen Analysis

- Collect after 2 to 7 days of sexual abstinence
- Collect ideally at office or lab, but can be collected with condoms without chemical additives and delivered within one hour of collection
- At least two samples 1 to 2 weeks apart due to variability

Semen Analysis

- Volume
- pH
- Agglutination
- Concentration
- Motility
- Morphology
- Leukocyte count
- Immature germ cells

Semen Volume

- 2 to 5 mL
- Low volume with no or severely low sperm count suggests genital tract obstruction

Sperm Concentration

- > 20 million/mL
- < 20 million/mL can be associated with normal fertility
- < 10 million/mL when looking at in vitro fertilization
- If no spermatozoa seen need to centrifuge and examine pellet before diagnosing azoospermia

Sperm Concentration

- Any sperm in pellet allow ICSI (intracytoplasmic sperm injection) rather than testicular aspiration
- Immature germ cells suggest disorders of spermatogenesis
- Leukocytes > 1 million suggest infection
- Agglutination suggests autoimmunity which should be confirmed with sperm surface antibody testing

Sperm Motility

- Rapid progressive
- Slow progressive
- Non-progressive
- Non-motile
- 50% should be motile with 25% rapidly progressive
- Distinction between living, non-motile and dead sperm important for type of ART (assisted reproductive technology) used

Sperm Morphology

- Shape
- Length
- Width
- Width ratio
- Area occupied by acrosome
- Neck and tail defects

Semen Analysis

- Lack of sperm in ejaculate does not indicate absence of testicular sperm production
- A home kit is available, but reliability in question

Specialized Testing

- Sperm autoantibodies
- Semen biochemistry
  - Fructose
- Semen culture
- Sperm-cervical mucus interaction
- Sperm functions tests

Semen Analysis

		Collected Date	06/25/2014
		Collected Time	09:15:00
Procedure	**Units**	**Ref Range**	
Semen Appearance		[Mod Turbid]	Mod Turbid
Semen Color			Gray-white
Sperm Count	Million/mL	[60-200]	73
Semen Volume	mL	[2.5-5.0]	2.0 L
Semen pH		[7.2-8.9]	8.0
Initial Motility	%	[60-100]	66
Semen Comment			See Below @

06/25/2014 09:15:00 Semen Comment

Sperm Morphology Panel
Normal Morphology, % % normal >=30

30% of the sperm is normal by WHO 3rd standards.
The WHO 3rd normal is Normal >30%

14% of the sperm is normal by Strict/WHO 4th Standards
The Strict/WHO 4th normal is Normal >14%

W.H.O Criteria, 1992, 3rd

Head Def,%	96	%
Midpiece Defect, %	7	%
Tailpiece Defect, %	13	%

Component	Value	Flag	Range	Units	Status
COMPLETE SPECIMEN	unknown				Final
TIME RECEIVED	748				Final
TIME EXAMINED	754				Final
LAB NUMBER	650-14				Final
DAYS OF ABSTINENCE	4				Final
SEMEN APPEARANCE	cloudy		Cloudy		Final
SEMEN VOLUME	1.5	(A)	2	ml	Final
SEMEN pH	8.0		7.2		Final
SEMEN COLOR	white		Grey/Yellow		Final
LIQUEFACTION	complete		complete	</= 60 minutes	Final
VISCOSITY	normal		normal		Final
AGGLUTINATION	none		scant,moderate		Final
SPERM CONCENTRATION	120		20	M/ml	Final
TOTAL MOTILITY	50		50 - 100	%	Final
PROGRESSIVE MOTILITY	42		25 - 100	%@grade3	Final
TOTAL PROG MOTILE/EJACULATE	75		10	M	Final
TOTAL MOTILE SPERM/EJAC	90		20		Final
TOTAL SPERM IN THE EJACULATE	180		40	M	Final
PARTNER NAME					
PARTNER DOB					

Specialized Testing

- Genetics
  - Microdeletions of Y chromosome
  - Karyotype

Disorders of Sperm Transport

- Epididymis
  - Absence
  - Dysfunction
    - Intrauterine estrogen exposure
    - Medication
      - Triptolide
    - Toxin
      - Chlorhydrin
  - Obstruction

Disorders of Sperm Transport

- Vas Deferens
  - Acquired
    - Bilateral obstruction
      - Infection (gonorrhea, chlamydia, tuberculosis)
    - Ligation
    - Altered peristalsis
  - Congenital
    - Absence
      - CFTR gene
- Defective ejaculation

Treatment

- Should always involve concomitant evaluation of the couple
- Assisted reproductive techniques can be complex, invasive, expensive, and often unsuccessful
- Reports are misleading due to use of semen quality rather than pregnancy as criterion for success and failure to include a control group

Limited Available Treatment

- Variety of causes of irreversible infertility for which no treatment is available with the following exception:
  - Azoospermia when sperm can be extracted from the seminiferous tubules
  - Reports of success in Klinefelter syndrome, but important genetic implications to this

Specific Treatment Available

- Hyperprolactinemia
  - In medication associated discontinue medication if possible
  - In adenoma treat with dopaminergic agonist
  - Normal spermatogenesis takes 3 months therefore it can take 3 to 6 months after prolactin and testosterone have returned to normal to see a normal sperm count
  - If macroadenoma and testosterone not normal by 6 months after prolactin normalized likely permanent damage to gonadotroph cells, then consider gonadotropin treatment

Specific Treatment Available

- Hypogonadotropic hypogonadism
  - All men can be treated with gonadotropins, but only men with hypothalamic disease will respond to GnRH (gonadotropin releasing hormone)
  - Diagnosis of secondary hypogonadism must be firmly established before treatment is initiated

Specific Treatment Available

- Factors predictive of success
  - Development of hypogonadism after puberty rather than before
  - Partial hypogonadism
    - Less severe abnormalities of testicular size, FSH levels, inhibin, and testosterone
  - Descent of both testes into scrotum by birth or one year of age

Specific Treatment Available

- Appearance of sperm in ejaculate occurs in up to 90% of men, but rarely to normal
- Even if spontaneous pregnancy does not occur there is usually enough sperm for assisted reproductive technique

Specific Treatment Available

- Human chorionic gonadotropin (HCG)
  - Biologic activity of LH, but longer half-life
  - Approved by the FDA for fertility treatment in secondary hypogonadism
  - No theoretical reason to use recombinant human LH due to decreased half life and therefore less efficacy

Specific Treatment Available

- Always replace HCG prior to FSH/HMG (human menopausal gonadotropin)
  - HCG stimulates Leydig cells to produce testosterone with an intratesticular concentration 100X that in the peripheral circulation, a concentration essential to spermatogenesis
  - HCG alone may be sufficient for spermatogenesis, but FSH alone is not effective
  - HCG costs $3,000 – 11,000/year while FSH (recombinant or HMG) costs $26,000 to $52,000 per year, even more for human recombinant

Specific Treatment Available

- Administer HCG (after stopping testosterone therapy if necessary)
  - Teach patient technique of IM injection in thigh (recombinant preparation which is dosed differently can be injected subcutaneously)
  - Initial dose 2,000 IU 3 times weekly
  - Measure serum testosterone level every 1 to 2 months with goal of 400 to 900 ng/dl
  - Adjust dose accordingly if not up to goal by 3 to 4 months
  - Dose varies from 500 to 10,000 IU 3 times weekly

Specific Treatment Available

- Rarely testosterone fails to respond thought to be due to antibodies to HCG
- Measure sperm count every 2 to 4 weeks, but value not used to adjust dose
- Most reach goal of normal sperm count after 6 months, but can take 12 to 24 months
- Add HMG if don't reach ½ normal count by 12 to 24 months
- Less than normal number of sperm usually restores fertility due to all sperm qualitatively normal
- Side effects similar to testosterone (except > gynecomastia

Specific Treatment Available

- HMG
  - If necessary to add to HCG therapy give 75 IU 3 times a week most conveniently administered in same syringe as HCG
  - Measure sperm count every 2 to 4 weeks (frequency of measurement due to variability in specimens require this to detect a trend)
  - Maximum count usually seen in 3 to 24 months
  - Increase to 150 IU if does not reach ½ normal after 6 months

Specific Treatment Available

- Discontinue HMG once pregnancy occurs due to high cost
- Continue HCG if couple considering future pregnancies
- Monotherapy will maintain testosterone and possibly sperm count, but if not HMG can be added when next pregnancy is desired
- When fertility no longer an issue can continue HCG or switch to testosterone

Specific Treatment Available

- GnRH
  - Administered in a pulsatile fashion via a pump and syringe that is programmed to deliver a bolus of GnRH every 2 hours and is connected via a subcutaneous needle and worn continuously
  - Dose 25 ng/kg and increase as necessary to normalize testosterone
  - Can need doses as high as 600 ng/kg in rare cases
  - Sperm may be seen in 12 months, but more often 3 or more years of therapy are required

Specific Treatment Available

- Similar efficacy to gonadotropin treatment
- GnRH currently not available in the United States

- If pregnancy does not occur spontaneously after a year or more of combined treatment an assisted reproductive technique should be strongly considered

Treatment of Uncertain Efficacy

- Genital infections
  - If leukospermia documented one or two courses of antibiotics may be tried
- Sperm autoimmunity
  - Glucocorticoids continuous or intermittent high dose (prednisone 40 to 80 mg/day) for up to 6 months
  - Usually poorly tolerated by patients

Treatment of Uncertain Efficacy

- Retrograde ejaculation
  - Intrauterine insemination (IUI) using sperm collected after alkalinization of the urine and extensive washing of the sperm
- Varicocele
  - Controversial, but may be beneficial in large varicocele
- Obstructive azoospermia
  - Surgical repair

Empiric Therapy

- Clomiphene citrate
- Anastrozole
- Recombinant FSH
- Vitamins
- Kallikrein
  - None of the above have been shown effective in idiopathic oligospermia or azoospermia in randomized placebo controlled clinical trials

Assisted Reproductive Techniques

- Intrauterine insemination
  - Washing an ejaculated semen specimen to remove prostaglandins, concentrating the sperm in a small volume of culture media and injecting the sperm suspension directly into the upper uterine cavity using a small catheter threaded through the cervix
- In vitro fertilization
  - Pregnancy rates very low with oligospermia

Assisted Reproductive Techniques

- Intracytoplasmic sperm injection
  - Direct injection of a single sperm into the cytoplasm of an egg
  - Overall 60% fertilization rate
  - Clinical pregnancy rate per cycle is 20%
- Retrieval of sperm from the testis
- Artificial insemination with donor sperm

The Future

- Germ cell transplantation
- Cultured testicular stem cells
- Early diagnosis and treatment of causes

Summary

Summary

- Firmly establish the diagnosis of male hypogonadism in appropriate patients prior to considering treatment
- Evaluate appropriately especially for secondary hypogonadism and consider long term goals of patient (fertility)
- Attempt to tailor treatment options to those which are most physiologic and meet patient's lifestyle needs

Summary

- Monitor therapy appropriately to achieve goals, but also detect adverse events
- Although a minority of men will have a hormonally mediated cause of their infertility, it can be treated quite successfully in many of these patients

Questions

Vitamin D:
How much is enough & How much is too much?
Implications for Skeletal & Non-skeletal Effects
Old Questions & New Answers?

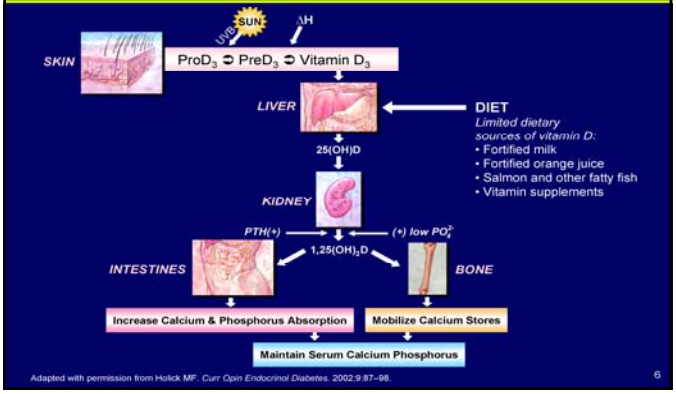
Carolinas AACE Annual Meeting
September 10, 2016

D. Sudhaker Rao, M.B;B.S., FACP, FACE
Section Head, Bone & Mineral Metabolism
Director, Bone & Mineral Research Laboratory
Tel:313-916-2369; Fax: 313-916-8343
Cell phone: 313-971-4984; srao1@hfhs.org

Objectives

- Review of vitamin D production, metabolism & functions
- Current "State of Vitamin D Nutrition" in populations
- Role of vitamin D in Bone & Mineral Disorders
  - Osteoporosis
  - Muscle strength, falls & fractures
  - Parathyroid gland growth & Disease expression
  - Vitamin D Nutrition in CKD
- Role of vitamin D in Non-Skeletal Health
  - Diabetes, CVD, Cancer, Autoimmunity & Others
- Assessment of vitamin D nutrition
  - Which test (s), how often, and how to monitor adequacy?
- Vitamin D toxicity
  - Does it occur or how much is safe?
- Vitamin D repletion strategies
- Conclusions

Vitamin D: Production and Metabolism



Adapted with permission from Holick MF. *Curr Opin Endocrinol Diabetes.* 2002;9:87–98.

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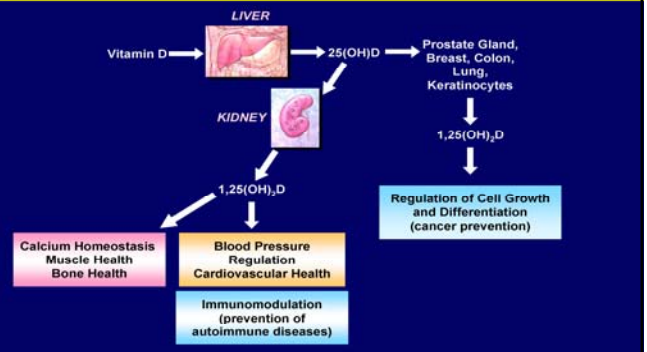
Vitamin D: Biologic Functions



Adapted with permission by the *American Journal of Clinical Nutrition*. © *Am J Clin Nutr*. American Society for Clinical Nutrition. 2004;80(suppl):1678S–1688S.

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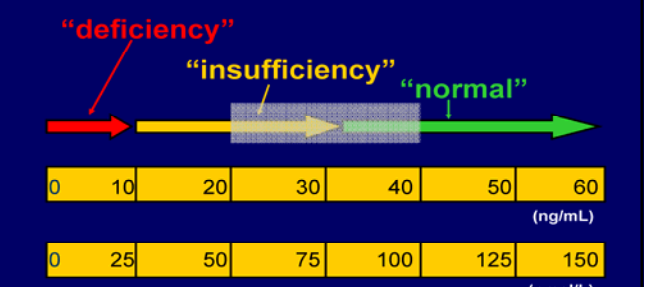
The 25(OH)D Continuum Controversy



1. Boonen S et al. *Osteoporos Int*. 2004;15:511–519.
2. Lips P. *Endocr Rev*. 2001;22:477–501.
3. Heaney RP. *Osteoporos Int*. 2000;11:553–555.
4. Heaney RP. *Am J Clin Nutr*. 2004;80(suppl):1706S-1709S.
5. Thomas MK. *N Engl J Med*. 1998;338:777–783.

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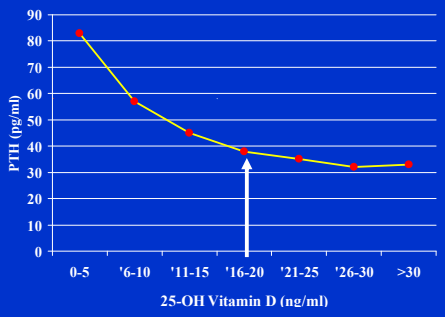
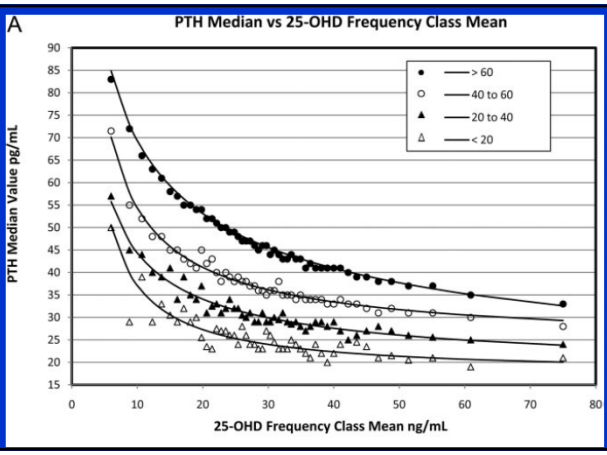
Biologic Correlates of Vitamin D Nutritional Adequacy

Relationship Between 25-OHD & PTH

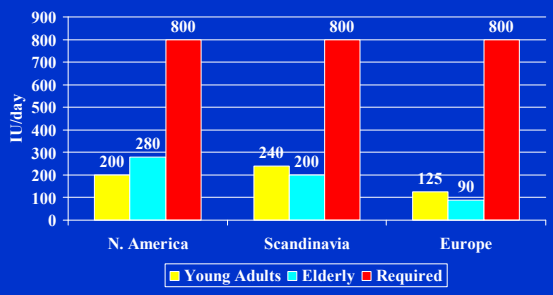




Vitamin D Nutrition
In Different Populations

Daily Oral Vitamin D Intake (Actual *vs.* Optimal)

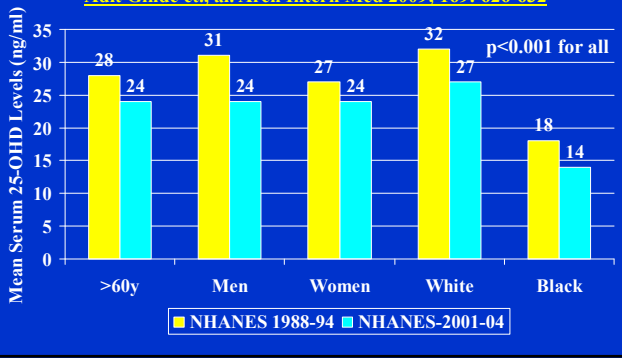
D.S. Rao, 2003, after McKenna, Am J Med, 1992; 93:69



Mean Serum 25-OHD Levels (ng/ml)

(NHANES 1988-1994 Vs. 2001-2004)

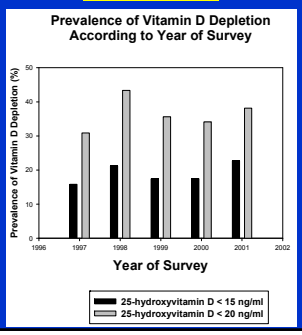
Adit Ginde et., al. Arch Intern Med 2009; 169: 626-632



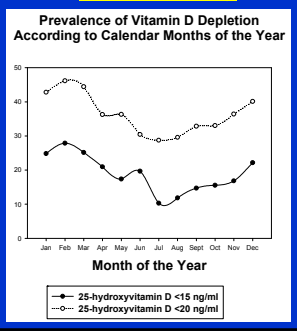
Prevalence of Vitamin D Depletion According to Definition & Season (1997-2002)

Guardia et al, Osteoporosis International 2008

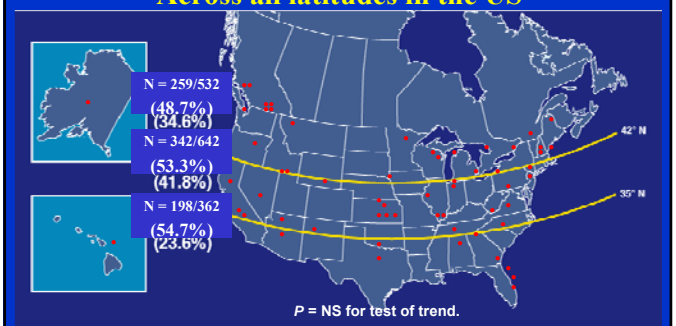
Year of Study



Season of Study



25-OHD <30 ng/mL are prevalent in PM Women Receiving Therapy for OP Across all latitudes in the US



Holick MF et al. *J Clin Endocrinol Metab.* 2005;90:3215–3224.

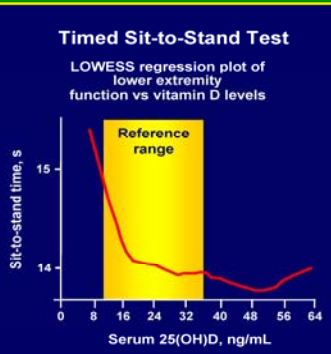
Conclusions

- Vitamin D depletion appears to be on the rise again especially among patients seeking advise about osteoporosis, and particularly among African Americans.
- Since a combination of vitamin D depletion & high PTH contributes to osteoporotic fractures, and since poor vitamin D nutrition may directly affect osteoblast function and perhaps response to specific osteoporotic therapy, greater attention to vitamin D nutrition in addition to calcium is ***both necessary & essential.***

Role of Vitamin D Nutrition in Muscle Strength & Function

Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test



LOWESS = locally weighted regression plot.
Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL).
N = 4,100; *P*<0.001.

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Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

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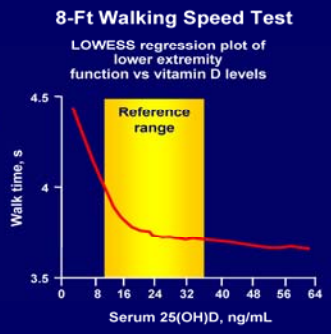

LOWESS = locally weighted regression plot.
Reference range of 9.0–37.7 ng/mL(22.5–94.0 nmol/L).
N = 4,100; *P*<0.001.

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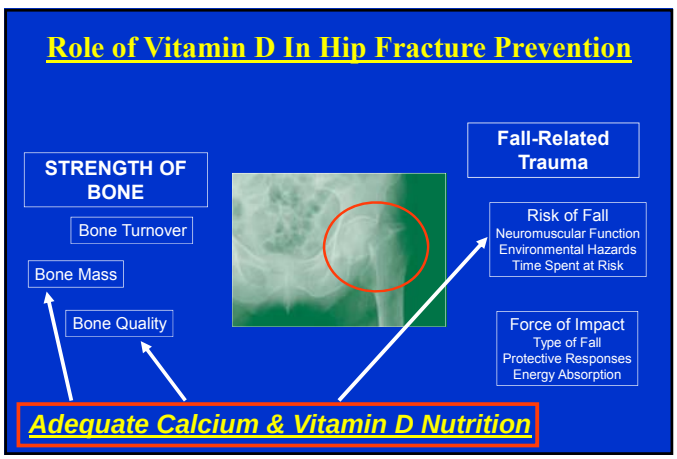
Role of Vitamin D In Hip Fracture Prevention



IOM & Endocrine Society Controversy 20ng/ml Vs. 30ng/ml

- Global health (IOM) versus select populations (TES)
- Effect on PTH & Bone (TES)
- Effect on bone mineralization (Priemal Paper; TES)
- Potential non-skeletal benefits (TES)
  - DM, Cancer, Fall risk etc
- Concerns about accuracy 25-hydroxyvitamin D assays
  - ICMA versus LC-MS/MS (IOM & TES)
- Who to screen? (IOM & USPSTF)
- High risk populations (IOM & USPSTF)

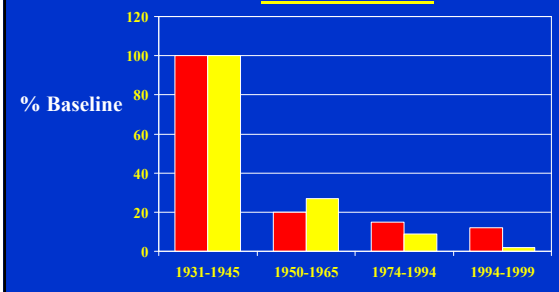
Role of Vitamin D Nutrition in

Parathyroid Tumoriqenesis & Disease Expression

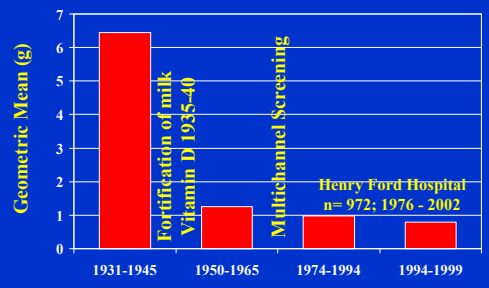
Role of Vitamin D in Parathyroid Function/Growth

- **Role of Calcium (?D) Nutrition, Fuller Albright, 1945**
- **Parathyroid function in Vitamin D deficiency and Vitamin D deficiency in PHPT (Stanbury, Am J Med, 1974)**
- **? Vitamin D Nutrition: Kleeman 1985; Rao, Delhi, 1991**
- **Vitamin D Nutrition & Adenoma Weight**
  - **Rao, et, al. J Clin Endo Metab, 2000**
- **Vitamin D Nutrition & BMD: Silverberg et, al 1999**
- **Reduced VDR & CaSR, and VDR mRNA**
  - **Rao, Clin Endo, 2000; Carling, JCEM, May 2000**
- **Prevalence of vitamin D Deficiency in PHPT**
  - **Rao, et., al. ASBMR Annual Meeting, 2005**

Temporal Relationship Between Declining Tumor Weights & Prevalence of OFC *Within the USA*



Potential Reasons for Changes in Parathyroid Adenoma Weights in the US



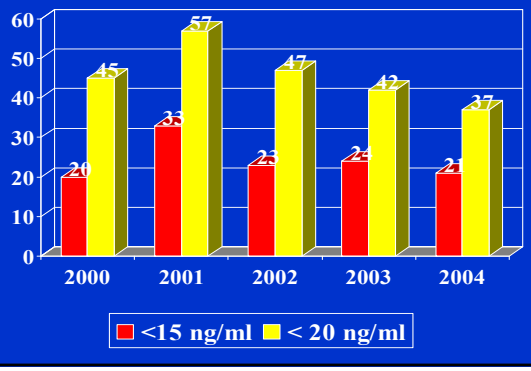
Influence of VDN on Disease Expression In Patients with Primary Hyperparathyroidism

N. Parikh, T. Eskridge, J. Hill, A. Bhan, M. Honasoge and D. Sudhaker Rao
Bone & Mineral Research Laboratory
Henry Ford Hospital, Detroit, MI, USA

Partly supported by the NIH/NIDDK & NIAMS

Prevalence (%) of Vitamin D Depletion in PHPT

(Parikh et al ASBMR Annual Meeting, Cincinnati, 2005)



Effect of Vitamin D Depletion on Biochemical Findings

Silverberg et al. Am J Med 1999;107-561-567

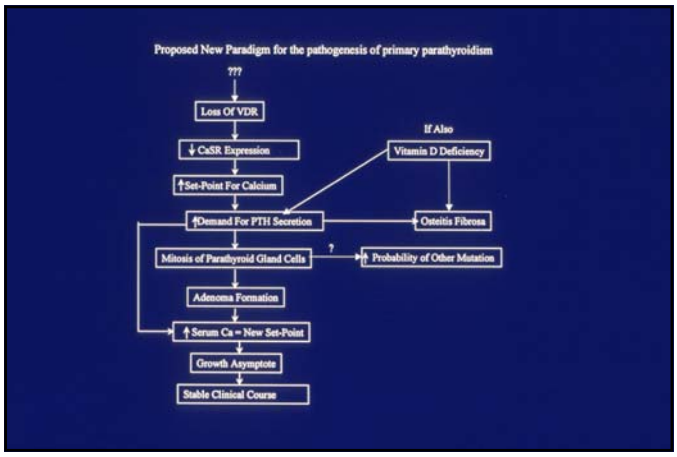
Variable	Lowest Tertile	Highest Tertile
PTH	158 ± 66	103 ± 62
AP	114 ± 48	91 ± 35
Phosphate	2.7 ± 0.4	3.0 ± 0.4
BMD (Spine)	0.94 ± .03	0.83 ± 0.03

Is More Severe Disease in the East Related to Delay in Dx/Rx?

Country	Age	PTH	Duration
Brazil	36	14X	3.0
China	37	20X	---
India (Delhi)	32	14X	3.2
India (Lucknow)	35	15X	2.8
Pakistan	38	10X	3.0
US (NY)	55	2	---
US (Detroit)	61	1.5	4.0

Conclusions

- Differences in vitamin D nutrition explains the differences in the manifestations and presentation of PHPT both ***within*** & ***between*** populations/ethnic groups.
- Improved VDN is partly, and perhaps largely, responsible for the historical changes in disease severity and manner of presentation over the past 50 years in the US and the West.



Vitamin D Nutrition in CKD

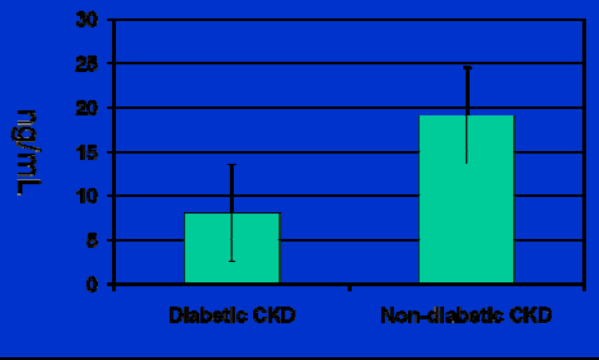
Vitamin D Deficiency in Diabetic Chronic Kidney Disease Patients Response to Replacement Therapy
Lina Yassine, MD; Gary Zasuwa; D. Sudhaker Rao, MD; Jerry Yee, MD; Nizar Attallah, MD

Relevant Biochemical Data (mean ± SD) and Prevalence of Vitamin D Depletion (%)

	Diabetic CKD patients (n=164)	Non-diabetic CKD patients (n=110)	P value
Calcium (mg/dl) *	9.6 ± 0.8	9.4 ± 0.7	0.396
Phosphorus (mg/dl) *	4.6 ± 0.6	5.0 ± 0.4	0.106
Calcium (mg/dl)¶	9.9 ± 0.7	9.8 ± 0.6	0.427
Phosphorus (mg/dl) ¶	4.5 ± 0.7	4.8 ± 0.5	0.249
Vitamin D Depletion (n & %) *	137 (83.5)	76 (69.1)	**0.041**
Vitamin D Depletion (n & %) ¶	67 (40.9)	25 (22.7)	**0.021**

	Odds Ratio	95% CI	p value
Multivariate Analysis			
Age > 50 (for every 10 years)	1.55	1.20-1.85	**0.036**
Diabetes status	2.1	1.8-2.7	**0.027**
Protcinuria>1 g/d (for every 1 g/d)	2.4	1.95-2.90	**0.017**
GFR<60 ml/min (for every 10 ml/min)	1.9	1.6-2.2	**0.021**
Univariate Analysis			
Diabetes status	1.9	1.6-2.4	**0.033**
Protcinuria>1 g/d (for every 1 g/d)	2.1	1.8-2.7	**0.026**
GFR<60 ml/min (for every 10 ml/min)	1.7	1.4-2.0	**0.041**

Change in Serum 25-OHD Levels



Role of Vitamin D in Non-Skeletal Health

- Autoimmunity
  - Type 1 DM
  - Rheumatoid Arthritis (*50,000 IU/day)
  - Childhood allergy & asthma, bronchitis etc
- Cardiovascular
  - Myocyte apoptosis, Hypertension, Cholesterol
- Diabetes
  - Insulin secretion & insulin resistance
  - Risk of developing DM; both Type 1 & 2
- Cancer
  - Breast, Prostate, Colon, Lung, Leukemia etc.
- Multiple sclerosis
- Psoriasis
- Tuberculosis

Role of Vitamin D in DM

25-OHD Levels in T1DM & NDNS

Cooper et al. Diabetes. 2011; 60:1624

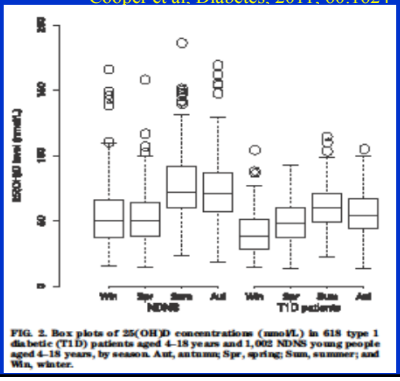
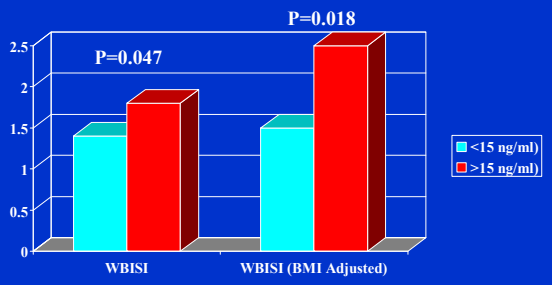


FIG. 2. Box plots of 25(OH)D concentrations (nmol/L) in 618 type 1 diabetic (T1D) patients aged 4–18 years and 1,002 NDNS young people aged 4–18 years, by season. Aut, autumn; Spr, spring; Sum, summer; and Win, winter.

Whole Body Insulin Sensitivity Index (WBISI) in Blacks (Higher the better)

Ambika Ashraf et., al. J Clin Endocrinol Metab 94: 3200-3206; 2009



25-OHD level, Ca Intake & Insulin Resistance

Gagnon et al, Diabetes Care, 2011;34:1133

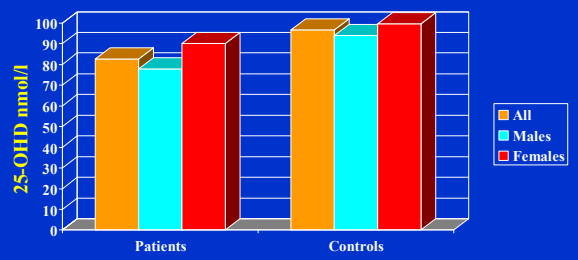
Table 3—*Association between serum 25OHD level and dietary calcium intake with insulin sensitivity (HOMA-S)*

Log insulin sensitivity (HOMA-S)		Outcome per 25 nmol/L increase in serum 25OHD	Outcome per 200 mg/day increase in dietary calcium‖
Model 1*	B (95% CI)	0.083 (0.068–0.099)	0.003 (−0.007 to 0.014)
	P value	<0.001	0.53
	Adjusted R^2	0.31	0.29
Model 2†	B (95% CI)	0.063 (0.048–0.078)	0.001 (−0.010 to 0.011)
	P value	<0.001	0.88
	Adjusted R^2	0.34	0.33
Model 3‡	B (95% CI)	0.060 (0.045–0.075)	−0.008 (−0.019 to 0.003)
	P value	<0.001	0.13
	Adjusted R^2	0.35	0.34
Model 4§	B (95% CI)	0.063 (0.048–0.078)	0.000 (−0.011 to 0.010)
	P value	<0.001	0.97
	Adjusted R^2	0.35	0.34

B, β coefficient. *Model 1: adjusted for age, ethnicity, WC, family history of diabetes, smoking status, and PA (and season and latitude for serum 25OHD). †Model 2: model 1 plus hypertension and serum triglycerides. ‡Model 3: model 2 plus energy-adjusted magnesium intake. §Model 4: model 2 plus FPG. ‖Energy-adjusted calcium intake.

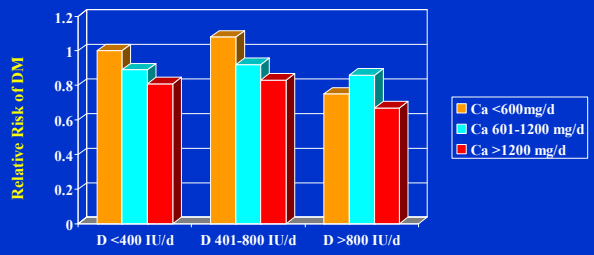
Serum 25-OHD Levels in Type 1 DM

Diabetes Incidence Study in Sweden (DISS)
Diabetalogia, 2006; 49:2847



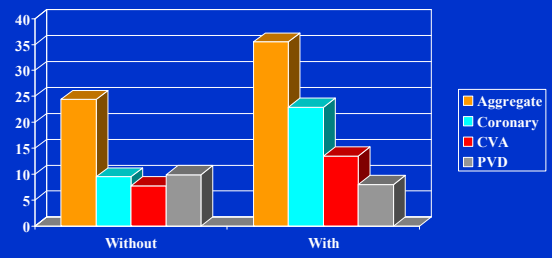
RR of Type 2 DM Based on Ca & D Intakes

Nurses Health Prospective Observational Study
Pittas et., al. Diabetes Care, 2006; 29:650



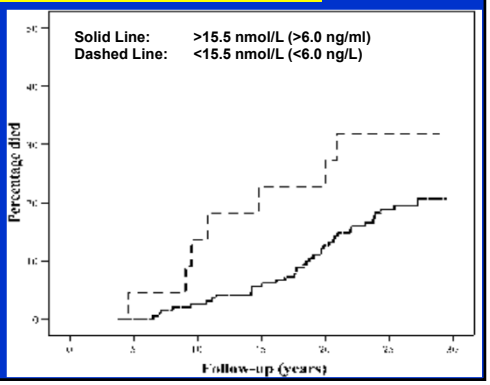
"Effect of VDN" on Events

25-OHD & Cardiovascular disease among Type 2 DM patients
Cigolini et. al, Diabetes Care; 2006; 29:722

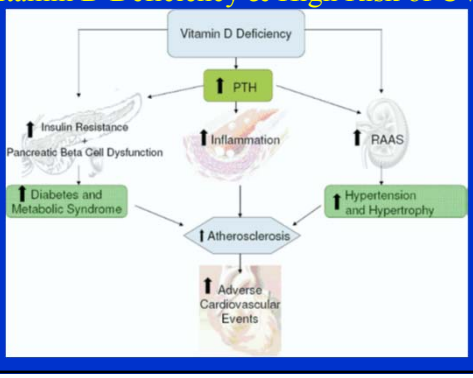


25-OHD Levels & Mortality

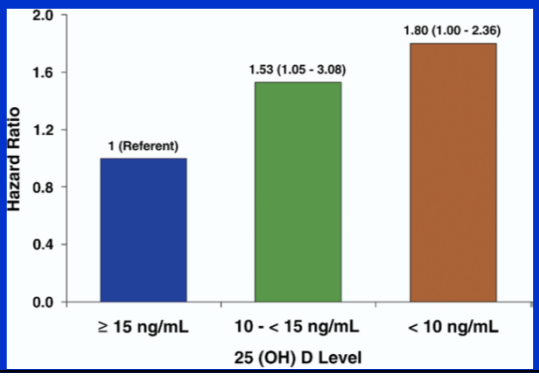
Joergensen et al; Diabetes Care, 2011; 34:1081



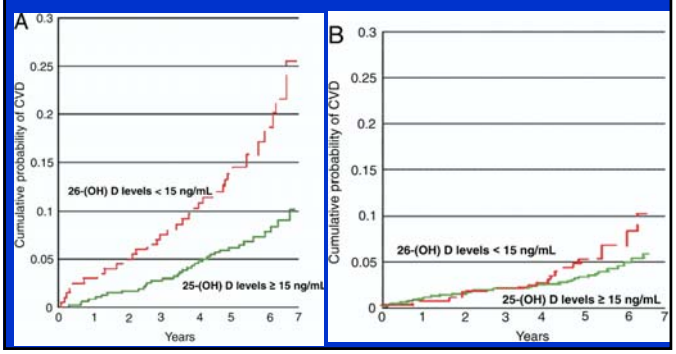
Potential Mechanism for Vitamin D Deficiency & High Risk of CVD



Vitamin D Deficiency & Risk of CVD



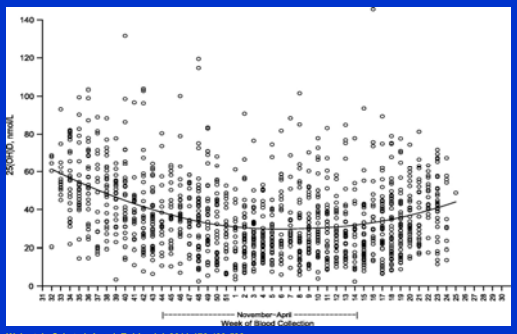
Vitamin D & Risk of CVD (In Patients With & Without Hypertension)



Role of Vitamin D in Cancer

- Cancer
  - Breast; Prostate; Colon, Leukemia, Lung, ?others
- All express VDRs
- Vitamin D is involved in
  - Antiproliferation
  - Terminal differentiation
  - Cell-cycle protein regulation
    - p27, p21, p17, ?p53
- Ecologic/observational studies

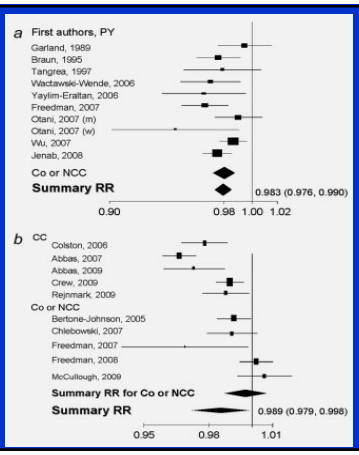
Serum 25-hydroxyvitamin D (25(OH)D) concentrations according to calendar week of blood collection in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, Finland, 1985–2005.



Weinstein S J et al. Am. J. Epidemiol. 2011;173:499-508

American Journal of EPIDEMIOLOGY

Meta-Analysis
VDN & Cancer Risk
Gandini et al
Int J Cancer. 2011; 128:1414-24



"Dose-Response"

Disease	Units of increase	Summary relative risk	95% CI	Heterogeneity χ^2 *p*-value	I^2
Colorectal cancer					
All studies	10 ng/ml	0.85	0.79; 0.91	0.004	55
NCC and cohort studies[1]	10 ng/ml	0.85	0.79; 0.92	0.002	59
Breast cancer					
All studies	10 ng/ml	0.89	0.81; 0.98	<0.001	88
NCC and cohort studies	10 ng/ml	0.97	0.92; 1.03	0.07	54
Prostate cancer					
All studies[2]	10 ng/ml	0.99	0.95; 1.03	0.11	37

[1]All studies were prospective cohorts, but Yaylim-Eraltan *et al.*[15] [2]All studies were prospective cohort. Abbreviation: NCC, nested case-control study.

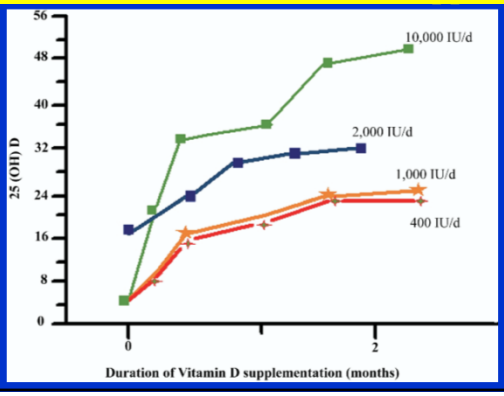
How to assess & what's optimal vitamin D nutritional status?

- The best available index of vitamin D nutrition is measurement of serum 25-hydroxyvitamin D
- The latest IOM recommends a minimal optimal level of >20 ng/ml or 50 nmol/L
  - Some are challenging this & heated debate continues
  - IOM position:
    - Inconclusive with regard to causality & insufficient to inform nutritional requirement
- Circulating 1,25-DHCC levels are of dubious clinical relevance

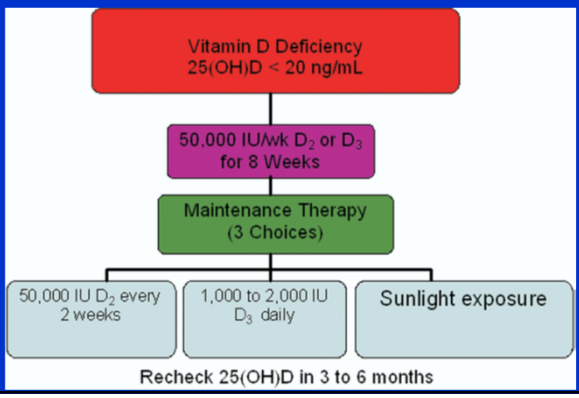
Vitamin D Repletion How much is too much?

- Vitamin D (D2 or D3) 50,000 IU
  - Once week for 8 -12 weeks
  - Followed by once a month forever?
- Is adequate exposure to sunlight really enough?
  - What is the evidence in population based studies?
- Role of body fat in vitamin D nutrition/economy
  - Need more data

25-OHD Rise with Vitamin D Supplemts



Vitamin D Replenishment



Vitamin D Toxicity; Does it occur?

- Probably not...
- Large latitude between optimal & toxic levels
  - 30 ng/ml & >150 ng/ml
  - Cumulative input of >1,000,000 IU
- Cases of vitamin D toxicity have been reported with >10,000/day for at least >1 month
- However, no toxic effects with 4000 IU/day for 5 months
- Critical control step ~ product-substrate feedback
- Redundant catabolic pathway ~ inert metabolites

Conclusions

- We need to rethink "one nutrient-one disease" concept
- Vitamin D has pleomorphic effects far beyond it was originally assumed to help prevent & cure
- Any level beyond that required to prevent rickets & osteomalacia as "sufficient" needs to be reexamined
- The latitude between optimal & toxic levels offers plenty of wiggling room
- How much is enough will eventually be defined
- Its role in non-skeletal health benefits remains to be established

Prospective Vitamin D Trials

- Bischoff Meta-analysis; Arch Intern Med, 03/09
- Chapuy French hip Fx trial
- Trivedi UK Fx trial
- Dawson-Hughes US BMD/?Fx Trial
- Jackson WHI US trial
- VITAL Trial due in 2017

Suggested Reading

1. **Rao DS.** Perspective on assessment of vitamin D nutrition. J Clin Densitometry. 1999;2:457-64.
2. **Rao DS**, Honasoge M, Divine GW, Phillips ER, Lee MW, Ansari MR, et al. Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. Journal of Clinical Endocrinology and Metabolism. 2000;85:1054-8.
3. Guardia G, Parikh N, Eskridge T, Phillips E, Divine G, **Rao DS.** Prevalence of vitamin D depletion among subjects seeking advice on osteoporosis: a five-year cross-sectional study with public health implications. Osteoporosis International. 2008;19(1):13-9.
4. Carlin AM, **Rao DS**, Yager KM, Parikh NJ, Kapke A**.** Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial. Surgery for Obesity & Related Diseases. 2009;5(4):444-9.
5. Hobbs RD, Habib Z, Alromaihi D, Idi L, Parikh N, Blocki F, **Rao DS.** Severe vitamin D deficiency in Arab-American women living in Dearborn, Michigan. Endocrine Practice. 2009;15(1):35-40.
6. Tolouian R, **Rao DS,** Goggins M, Bhat S, Gupta A**.** Seasonal variation of vitamin D in patients on hemodialysis. Clinical Nephrology. 2010;74(1):19-24.
7. Eide MJ, Johnson DA, Jacobsen GR, Krajenta RJ, **Rao DS,** Lim HW, et al. Vitamin D and Nonmelanoma Skin Cancer in a Health Maintenance Organization Cohort. Arch Dermatol. 2011:archdermatol.2011.231.
8. Sage RJ, **Rao DS**, Burke RR, Lim HW**.** Preventing vitamin D toxicity in patients with sarcoidosis. Journal of the American Academy of Dermatology. 2011;64(4):795-6.
9. Cassidy-Bushrow AE, Peters RM, Johnson DA, Li J, **Rao DS.** Vitamin D Nutritional Status and Antenatal Depressive Symptoms in African American Women. J Womens Health (Larchmt). 2012.
10. Valcour A, Blocki F, Hawkins DM, **Rao SD.** Effects of Age and Serum 25-OH-Vitamin D on Serum Parathyroid Hormone Levels. Journal of Clinical Endocrinology & Metabolism. 2012.
11. Shah VN, Shah CS, Bhadada SK, **Rao DS.** Effect of 25 (OH) D replacements in patients with primary hyperparathyroidism (PHPT) and coexistent vitamin D deficiency on serum 25(OH) D, calcium and PTH levels: a meta-analysis and review of literature. Clinical Endocrinology. 2014;80(6):797-803.

Thank you very much
for your attention