# Endocrine Considerations in XP

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## Disclosures:

- Nothing to disclose
- Will discuss non FDA approved therapies

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# Sunlight, Vitamin D, and XP

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## Vitamin D involved in:

- Calcium/phosphate homeostasis = skeletal health.
- Muscle and nervous functions
- Cardiovascular homeostasis
- Immune response

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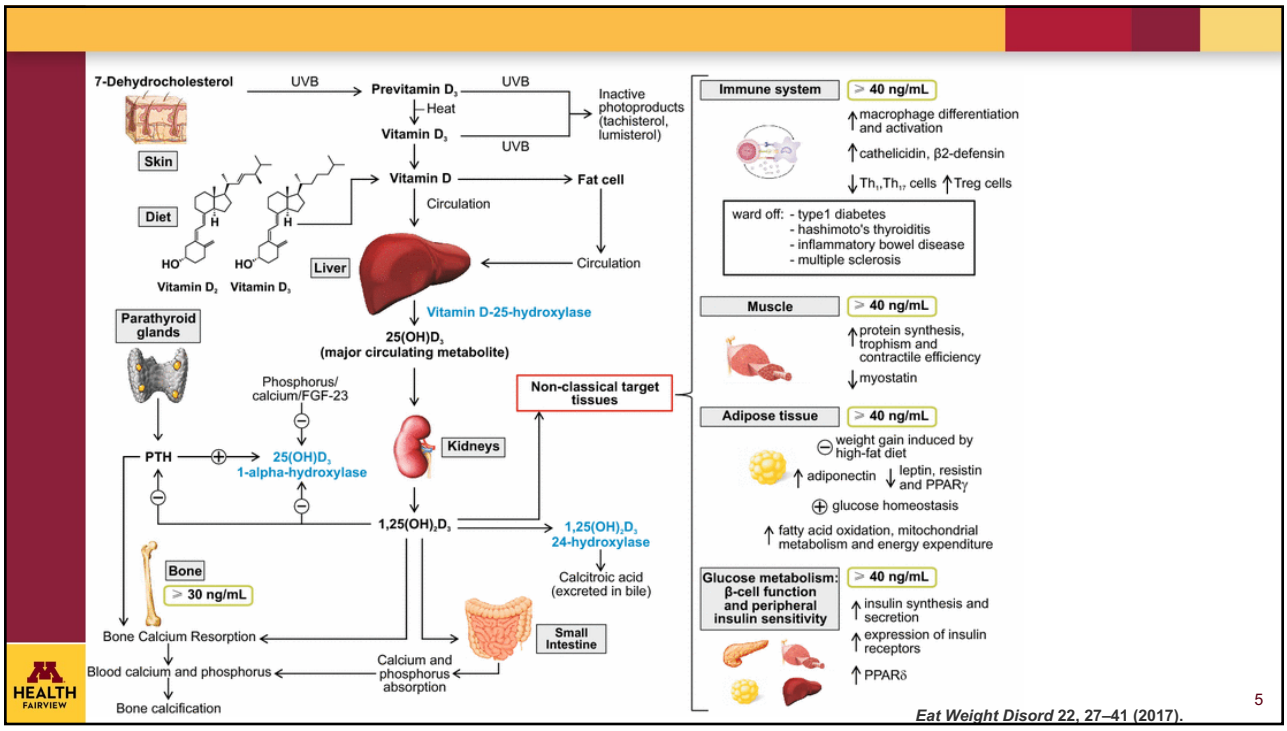


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# Sunlight, Vitamin D, and XP

- Sunlight (UV-B radiation) is an important factor for endogenous vitamin D production
  - 10–20% of human's requirement can be achieved through dietary intake
  - 80-90% of the required vitamin D needs to be photosynthesized in the skin
- UV-A and UV-B radiation form reactive oxygen species (ROS) that alter DNA, proteins, and cell membranes through oxidation which can cause single-strand DNA breaks (1)

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https://doi.org/10.1016/j.mce.2017.05.001

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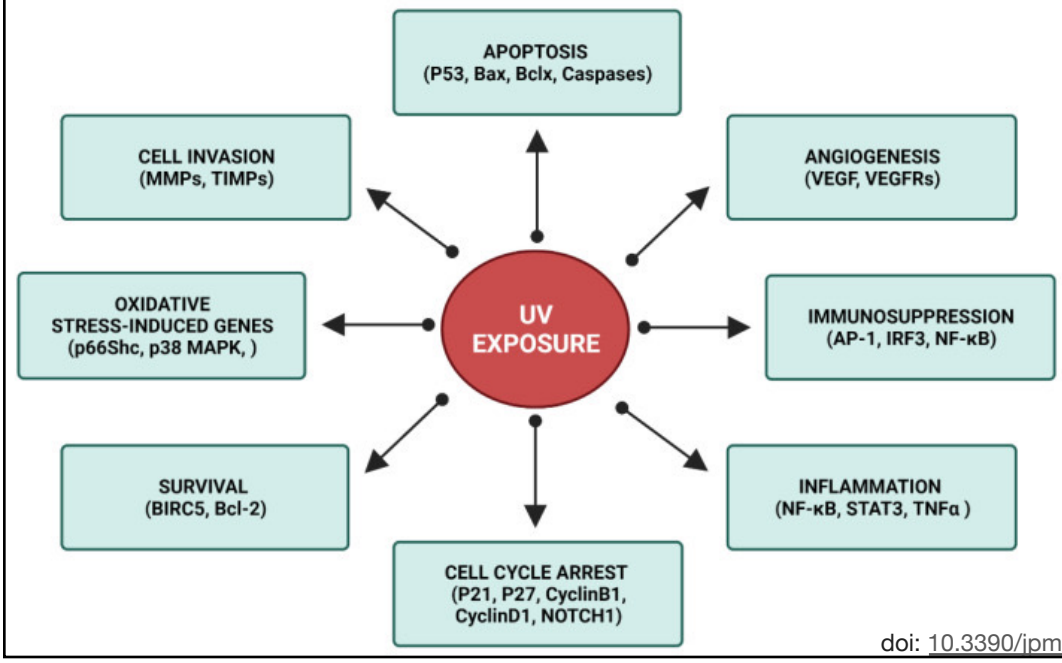


doi: 10.3390/jpm11111146

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# Physical / Chemical Photo protectors

- XP patients:
  - Inability to repair UV-induced lesions
  - Exhibit an increased risk for UV-induced nonmelanoma skin cancer (NMSC):
    - Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) as well as melanoma.
- Numerous sunscreens have been produced and commercialized to enhance the ultraviolet protection of XP patients
  - UVA/UVB coverage
  - Sun protection factor (SPF)
  - Water resistance
  - Effective duration of shielding

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- VDR has been suggested to be a tumor suppressor in the skin
- It has been suggested that calcitriol and analogs can be used to prevent as well as treat NMSC (2)
  - Calcitriol and analogs have been shown to have antiproliferative effects in mouse and human BCC and SCC cell lines in vitro.



(2) doi.org/10.1016/j.mce.2017.05.001



# Vitamin D deficiency in patients with XP

- Few studies to analyze the consequences of stringent sun protection in XP patients in association with vitamin D levels.
  - The ones available have shown contradictory results.
  - Vitamin D levels may be normal, increased, or decreased, but are not causally linked to sun-protective measures (3).
  - Other studies reported vitamin D deficiency and a shorter stature in XP patients (4) and vitamin D deficiency in XP-A patients
  - Rickets is a rather rare complication of XP management

(3) https://doi.org/10.1038/ejcn.2015.1
(4) https://doi: 10.4103/ijo.IJO_1319_18.

# Thyroid issues in XP

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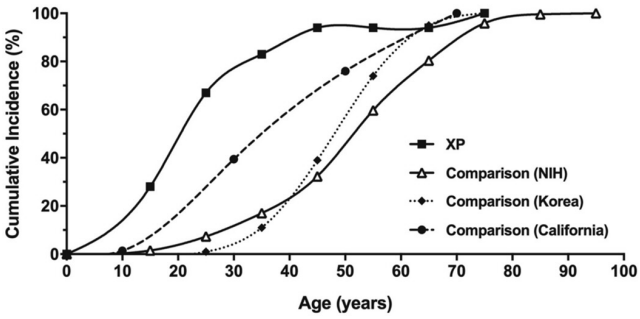
## Thyroid nodules in patients with XP

- Previous reports of patients from North Africa had been reported
  - Mutations in the *XPC* gene
  - NIH cohort:
    - 18/29 had thyroid nodules
    - Half of XP patients with thyroid nodules had detectable nodules by 20 years of age
  - Early onset of thyroid nodules in XP patients is a feature of premature aging
    - Suggests a role of DNA repair in the prevention of thyroid nodules

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doi: 10.1007/s40618-020-01451-x

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# Reproductive Health in XP

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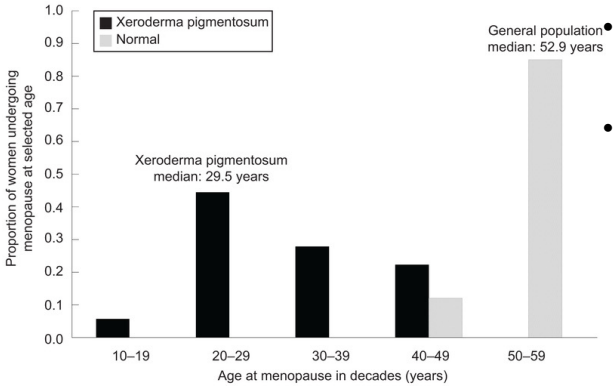


- Normal menarche: median age of 12.0 years (9–17 years)
- Premature menopause
  - 31% of women with XP
  - Median age 29.5 years (20 years younger than general population)
  - Most with XPC gene mutations

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doi:10.1097/AOG.0000000000003490.

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# Therapies in XP

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# Immune Checkpoint Inhibitors (ICIs)

- Anticancer drugs targeting T-cell proteins involved in the activation of immune response toward malignancies
  - Pembrolizumab and nivolumab first approved for advanced melanoma (2014).
  - Recent studies showed treatment with pembrolizumab reduced the size of metastases and led to regression of cutaneous carcinomas in patients with XP
- ICI-induced immune system activation:
  - Could lead to the loss of self-tolerance, presenting as autoimmune inflammation and dysfunction of various tissues and organs
  - Typical side effects of ICIs include immune-related adverse events (irAEs)
    - Affecting numerous endocrine glands: thyroid, hypophisitis

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https://doi.org/10.1111/bjd.16270

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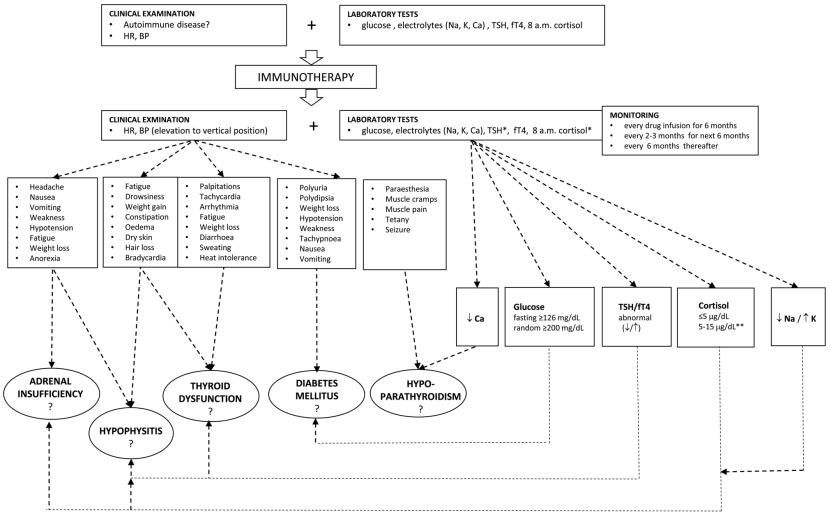
# Immune Checkpoint Inhibitors (ICIs)




* when not on high-dose GCSs, GCSs inhibit ACTH and cortisol, and decrease TSH levels; after discontinuation of GCS, adrenal insufficiency may persist, which would require further diagnostics and possibly hydrocortisone replacement
** if symptomatic consider SST (peak cortisol ≤18 µg/dL indicates AI)

**Endocrine Connections 9, 10; 10.1530/EC-20-0342**

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# Retinoids (isotretinoin)

- Used as chemo preventive of skin cancer.
  - Being vitamin A derivatives, facilitate and promote cellular differentiation, and apoptosis
- Oral isotretinoin was shown to prevent new skin cancer formation in XP patients.
- Important toxicity and side effects:
  - Lipids: Hyperlipidemia, hypertriglyceridemia
  - Stiffness
  - Retinoid dermatitis
  - Teratogenicity

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# Acetohexamide / Glimeperide

- First-generation sulfonylurea (antidiabetic drug)
- UV sensitivity-alleviating compound in nucleotide excision repair-deficient cells
- Side effects:
  - Hypoglycemia
  - Increase in cardiovascular mortality?



# mTOR inhibitors

- Involved in many cellular processes, such as cell growth, survival, transcription, translation, apoptosis, metabolism, motility and autophagy.
- Common side effects
  - Metabolic syndrome (insulin resistance, hyperglycemia with new onset diabetes mellitus)
  - Dyslipidemia.

# 5-Fluorouracil

- Thought to promote apoptosis in skin cancer cells
- Increasing serum thyroid hormone-binding proteins
  - Increased total $T_4$ and $T_3$ levels
  - Patient are clinically euthyroid
- Other side effects:
  - Oligo o azoospermia (transient)
  - Cardiac

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# Thank You

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