

The Aging Metabolism Endocrinology for Older Adults

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LECOM HEALTH

Outline

- Metabolism?
- Obesity
- Pharmokinetics
- BMI and Atherosclerotic Cardiovascular Disease



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Metabolism...

- You've noticed that as you age, you can't eat like your younger self.
- That's because your "*metabolism tends to slow with age*", making it easier to add a few extra pounds and harder to lose them.
- A few reasons for this include muscle loss, being less active and the "*natural aging of your metabolic processes*".



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Metabolism??

- The **whole range of biochemical processes** that occur within a living organism.
- Consists of **anabolism** (the buildup of substances) and **catabolism** (the breakdown of substances).
- The term *metabolism* is commonly used to refer specifically to the breakdown of food and its transformation into energy.



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Speed of your metabolism: 4 factors



1. Resting metabolic rate (RMR):

How many calories you burn while you are resting or asleep.

2. Thermic effect of food (TEF):

How many calories you burn through digesting and absorbing food.

- TEF is usually 10% of your daily calories burned.



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Speed of your metabolism: 4 factors



3. Exercise:

How many calories you burn through exercise.

- Over a quarter of Americans aged 50–65 don't exercise outside of work.
- For people over 75, this increases to over a third.

4. Non-exercise activity thermogenesis (NEAT)

Calories burned through non-exercise activities, such as standing, fidgeting, washing the dishes and other chores.

- Older adults burn roughly 29% fewer calories through NEAT



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Muscle loss with age - Sarcopenia

- The average adult loses 3–8% of muscle during each decade after 30.
- By the age of 80, there is a loss of roughly 30% of muscle compared to age 20.
- Muscle loss results in less resting metabolic rate as well
- Other reasons include consuming fewer calories and protein.
- As well as a decrease in the production of hormones, such as estrogen, testosterone and growth hormone.



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What's really “slowing down” ?

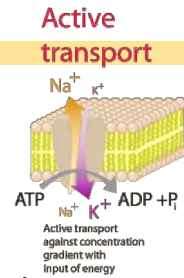
- Two cellular components that drive these reactions are your **sodium-potassium pumps** and **mitochondria**
- The sodium-potassium pumps help generate nerve impulses and muscle contractions
- While the mitochondria create energy for your cells



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What's really “slowing down”?

Sodium-potassium pumps:



- A study compared the rate of the sodium-potassium pumps between 27 younger men and 25 older men.
- The pumps were 18% slower in older adults, resulting in burning 101 fewer calories per day.
 - J Clin Endo Metab 1993 Sodium-potassium pump activity contributes to the age-related decline in resting metabolic rate



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What's really “slowing down”?

Mitochondria:

- A study compared changes in the mitochondria between younger adults (average age of 39) and older adults (average age 69).
- It was found that older adults had 20% fewer mitochondria.
- Additionally, their mitochondria were nearly 50% less efficient at using oxygen to create energy.



Frisard MI, Broussard A, Davies SS, et al. Aging, resting metabolic rate, and oxidative damage: results from the Louisiana Healthy Aging Study.

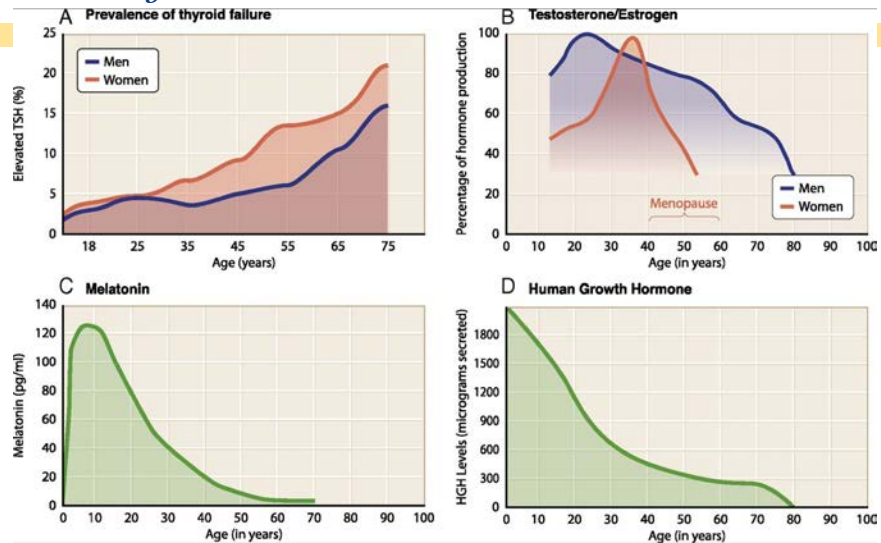
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What's really “slowing down”?

As one ages, maintaining muscle mass is incredibly important in order to maintain metabolic rate.



“As well as a decrease in the production of hormones, such as estrogen, testosterone and growth hormone”



Human aging and disease: Lessons from age-related macular degeneration
 Jennings Luu, Krzysztof Palczewski Proceedings of the National Academy of Sciences Mar 2018, 115 (12) 2866-2872;



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Obesity

- Men often gain weight until about age 55, and then begin to lose weight later in life.
 - This may be related to a drop in testosterone.
- Women usually gain weight until age 65, and then begin to lose weight.
- Weight loss later in life occurs partly because fat replaces lean muscle tissue, and fat weighs less than muscle.



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- Metabolism?
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Pharmacokinetics in older Adults

- Absorption
- Distribution across body compartments
- Metabolism
- Excretion

- With aging, there are changes in all these areas
- Some are more clinically relevant



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Pharmacokinetics in older Adults

- The metabolism and excretion of many drugs decrease, requiring that doses of some drugs be decreased.
- Toxicity may develop slowly because concentrations of chronically used drugs increase for 5 to 6 half-lives, until a steady state is achieved.



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Pharmacokinetics - Absorption

- Despite an age-related:
 - decrease in small-bowel surface area
 - slowed gastric emptying
 - and an increase in gastric pH (less acidic)

- ...changes in drug absorption tend to be clinically inconsequential for most drugs.

- One clinically relevant exception is **calcium carbonate**, which requires an acidic environment for optimal absorption.



Pharmacokinetics - Absorption

- Thus, increases in gastric pH—which may be age-related (such as with atrophic gastritis) or drug-related (such as with proton pump inhibitors)—can decrease calcium absorption and increase the risk of constipation.

- Thus, older adults should use a calcium salt (eg, calcium citrate) that dissolves more easily in a less acidic environment.



Pharmacokinetics - Absorption

- Another example of altered absorption with increased gastric pH is early release of **enteric-coated dosage forms**
- eg, enteric-coated aspirin, enteric-coated erythromycin
 - increasing the risk of GI adverse effects



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Pharmacokinetics - Distribution

- With age, body fat generally increases and total body water decreases.
- Increased fat increases the volume of distribution for highly lipophilic drugs and may increase their elimination half-lives.



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Pharmacokinetics - Distribution

- Serum **albumin** decreases and **alpha 1-acid glycoprotein** (AGP) increases with age, but the clinical effect of these changes on serum drug binding varies with different drugs.
- **Alpha-1-acid glycoprotein** (AGP, also known as AAG) is an important plasma protein involved in the binding and transport of many drugs, especially basic compounds.



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Pharmacokinetics - Distribution

- In patients with an **acute disorder or malnutrition**, rapid reductions in serum albumin may enhance drug effects because serum concentrations of unbound (free) drug may increase.
- **Phenytoin** and **warfarin** are examples of drugs with a higher risk of toxic effects when the serum albumin level decreases.



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Pharmacokinetics – Metabolism

- Overall hepatic metabolism of many drugs through the **cytochrome P-450 enzyme system** decreases with age.
- For drugs with decreased **hepatic metabolism clearance** typically decreases 30 to 40%.
- Theoretically, maintenance drug doses should be decreased by this percentage; however, rate of drug metabolism varies greatly from person to person, and dose adjustments should be individualized.



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Pharmacokinetics – Metabolism

- Hepatic clearance of drugs metabolized by phase I reactions (oxidation, reduction, hydrolysis) is more likely to be prolonged in older adults.
- Usually, age does not greatly affect clearance of drugs that are metabolized by conjugation and glucuronidation (phase II reactions).



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Pharmacokinetics – Metabolism

- First-pass metabolism (metabolism, typically hepatic, that occurs before a drug reaches systemic circulation) is also affected by aging, **decreasing by about 1%/yr after age 40.**
- Thus, for a given oral dose, older adults may have higher circulating drug concentrations.
- Important examples of drugs with a high risk of toxic effects include:
 - nitrates
 - propranolol
 - Phenobarbital
 - nifedipine



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Pharmacokinetics – Metabolism

- Other factors can also influence hepatic metabolism of drugs being taken, including:
 - smoking
 - decreased hepatic blood flow in patient with heart failure
 - taking drugs that induce or inhibit cytochrome P-450 metabolic enzymes



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Pharmacokinetics - Elimination

- One of the most important pharmacokinetic changes associated with aging is **decreased renal elimination** of drugs.
- After age 40, **creatinine clearance** decreases an average of 8 mL/min/1.73 m²/decade
- **GFR** generally declines at a rate of 1 mL/min/year
- however, the age-related decrease varies substantially from person to person.



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Pharmacokinetics - Elimination

- Serum creatinine levels often remain within normal limits despite a decrease in GFR because older adults generally have less muscle mass and are generally less physically active than younger adults and thus produce less creatinine.
- Maintenance of normal serum creatinine levels can mislead clinicians who assume those levels reflect normal kidney function.

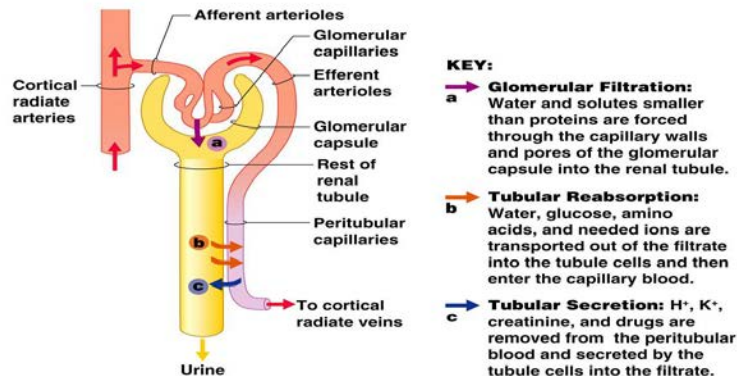


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Pharmacokinetics - Elimination

- Decreases in tubular function with age parallel those in glomerular function.

Urine Formation



Pharmacokinetics - Elimination

- These changes decrease renal elimination of many drugs
- Clinical implications depend on the extent that renal elimination contributes to **total systemic elimination** and on the drug's **therapeutic index** (ratio of maximum tolerated dose to minimum effective dose)

□

Metformin - FDA changes April 2016

- Before the initiation of metformin, obtain the patient's estimated GFR (eGFR).
- For all patients on current metformin therapy, obtain an annual eGFR.
- Estimated GFR can be assessed more frequently among patients with risk factors for declining renal function (i.e. elderly patients).
- Do not use metformin among patients with an eGFR less than 30.
- Do not start metformin among patients with an eGFR between 30 to 45.
- Complete a risk-benefit analysis of metformin if a patient's eGFR drops to less than 45.
- Stop metformin prior to iodinated contrast imaging procedure, especially among those patients with eGFR between 30 to 60. Re-evaluate renal function after 48 hours; if normal, metformin can be re-initiated.



Pharmacokinetics - Elimination

- Creatinine clearance (measured or estimated using computer programs or a formula), such as Cockcroft-Gault is used to guide dosing for most drugs eliminated by the kidneys.

Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$



Pharmacokinetics - Elimination

- The daily dose of drugs that rely **heavily on renal elimination** should be lower and/or the frequency of dosing should be decreased.
- Because renal function is dynamic, maintenance doses of drugs may need adjustment when patients become ill or dehydrated or have recently recovered from dehydration.
-



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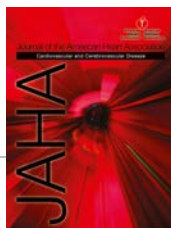


Weight and Heart Failure Risk

JAHA

Journal of American Heart Association

Body Mass Index From Early-, Mid, and Older- Adulthood and Risk of Heart and Atherosclerotic Cardiovascular Disease: MESA (Multi-Ethnic Study of Atherosclerosis)



Originally published Nov 14th, 2018



Weight and Heart Failure Risk

- Obesity contributes significantly to risk of atherosclerotic cardiovascular disease (ASCVD) and especially for heart failure (HF).
- An elevated body mass index (BMI)* in older adults might not carry the same risk as in younger adults,
- but measured weights at other lifetime points are often not available.
- *(BMI less than 25 kg/m² was normal, BMI 25 and 30 was considered overweight, and 30 and above was considered obese.)



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Weight and Heart Failure Risk

- The study determined whether asking individuals about a self-reported weight history from early (age 20 years) or mid adulthood (age 40 years) added any incremental prognostic information to current assessment of heart failure risk.



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Weight and Heart Failure Risk

- Obesity is a major public health problem that contributes significantly to morbidity, mortality, and healthcare costs in the United States.
- The prevalence of obesity in the United States is strikingly high, seen in **36% of adults**.



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Weight and Heart Failure Risk

- Prior work has found obesity to be even more strongly associated with heart failure (HF) risk than with other forms of cardiovascular diseases (CVD)*.
- However, exactly **when** during an individual's lifetime that weight exerts the greatest influence on CVD risk is not entirely understood.

- * Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, Folsom AR, Coresh J. Obesity and subtypes of incident cardiovascular disease. **J Am Heart Assoc.** 2016



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Weight and Heart Failure Risk

- The “**obesity paradox**” suggests that being overweight later in life, especially in the setting of chronic diseases, may actually be “*protective*” against mortality, although this idea has been contested.
- Indeed, a recent study found that while a single baseline measurement of body mass index (BMI) had an inverse association with mortality, this obesity paradox was **reversed** when considering a maximum BMI over long-term follow-up.



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Weight and Heart Failure Risk

- Thus, considering a patient's **lifetime weight history** might be **more prognostic** of HF or atherosclerotic CVD (ASCVD) risk than a current office visit BMI, especially for older adults.



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Weight and Heart Failure Risk

- Despite this, in clinical practice healthcare providers typically counsel patients on their ASCVD/HF risk based only on a single office BMI or from a few office-obtained BMI measures obtained within a relatively short time interval.
- Measured weights from earlier life-points, such as early- and mid-adulthood, are often not available.

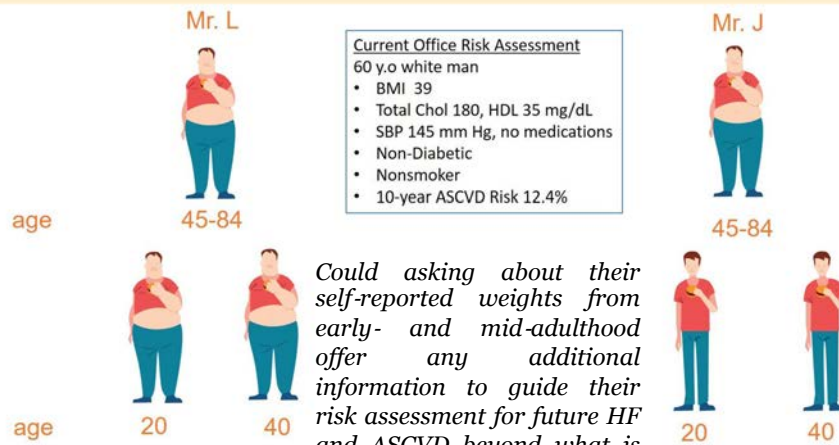


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Consider 2 hypothetical patients, Mr. L and Mr. J, with similar current weights and ASCVD risk profiles

Central Illustration: Tale of 2 Patients



Could asking about their self-reported weights from early- and mid-adulthood offer any additional information to guide their risk assessment for future HF and ASCVD beyond what is known from their current profile?

Body Mass Index From Early-, Mid-, and Older-Adulthood and Risk of Heart Failure and Atherosclerotic Cardiovascular Disease: MESA, Volume: 7, Issue: 22, DOI: (10.1161/JAHA.118.009599)

MESA

- 6437 MESA (Multi-Ethnic Study of Atherosclerosis) participants (aged 45–84, free of baseline HF/ASCVD) with self-reported weights at ages 20 and 40 years (by questionnaire).
- measured weights at up to 5 in-person examinations (2000–2012), and follow-up for adjudicated HF/ASCVD events.
- Participant mean±SD age at the baseline examination was 62.2±10.2 years.



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Weight and Heart Failure Risk

- Participants of 4 race/ethnicities were recruited from 6 US communities:
 - Baltimore, MD
 - Chicago, IL
 - Forsyth County, NC
 - New York City, NY
 - Los Angeles County, CA
 - St. Paul, MN



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Weight and Heart Failure Risk

- Participants were excluded if they were missing self-reported weight at age 20 or 40 years (N=31)
 - had no follow-up information for ASCVD or HF (N=27)
 - or were missing key covariates (N=319)
- The final sample size was 6437 participants



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Weight and Heart Failure Risk

- Over median follow-up of 13 years:
 - 290 HF events and
 - 828 ASCVD events occurred.



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MESA

- After adjustment for cardiovascular risk factors and baseline BMI,
- higher self-reported weights at ages 20 and 40 years were independently associated with increased risk of incident HF with hazard ratios (95% confidence interval) of 1.27 (1.07–1.50) and 1.36 (1.18–1.57), respectively, per 5-kg/m² higher BMI.



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MESA

- Even after accounting for current measured body mass index and cardiovascular risk factors,
- it was found that self-reported elevated body mass index is associated with **future heart failure risk:**
 - **3-fold risk** for obesity at age 20 years
 - **2-fold risk** for obesity at age 40 years



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Clinical Perspective

- The study determined whether asking individuals about a self-reported weight history from early (age 20 years) or mid adulthood (age 40 years) added any incremental prognostic information to current assessment of heart failure risk.

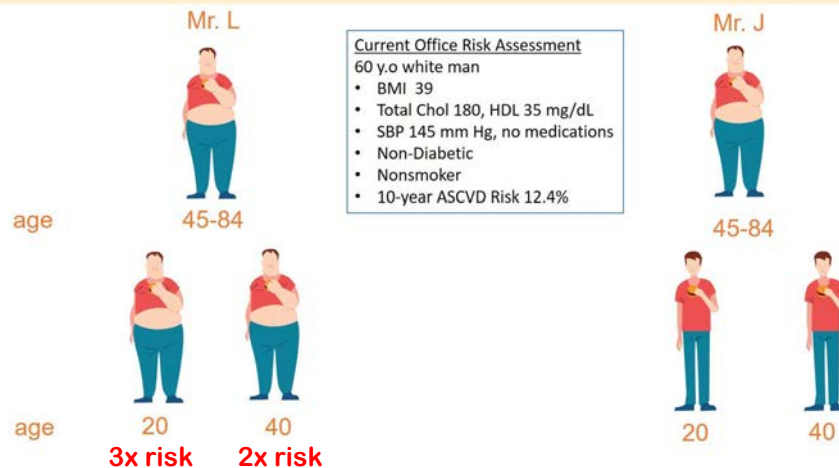


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Increase your Metabolism, No Matter Your Age

- If a decline in muscle mass is the number one reason metabolic rate drops
- and we gain weight as we age,
- building muscle is the primary way to help prevent, or even reverse, the process



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Increase your Metabolism, No Matter Your Age

- **It's possible to build muscle during every stage of life.**
- Harvard researchers followed **10,500** healthy middle-aged and elderly men over the course of 12 years,
- those who participated in 20 minutes per day of **strength training**, enjoyed smaller increases in age-related abdominal fat compared to those who spent the same amount of time involved in cardiovascular exercise.



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Increase your Metabolism, No Matter Your Age

- To obtain optimum muscle - and metabolism-boosting results from your strength routine...
- ones need to supply your muscles with the building blocks necessary for them to recover after each workout and grow back bigger and stronger: **protein**



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Increase your Metabolism, No Matter Your Age

- And while the current recommended daily allowance for protein is set at 0.8 grams of protein per kilogram of body weight (about 65 grams of protein per day for an 180-pound person),
- 2014 research published in the American Journal of Physiology – Endocrinology and Metabolism shows that,
- consuming double that amount is ideal for older adults trying to prevent muscle wasting and promote muscle building.



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Thank you!



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Title



- This
- Is
 - How it
 - Would work
 - With the levels



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Title



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Introduction

- Elderly patients have a disproportionately higher prevalence of endocrine and metabolic dysfunction
- Thus, it makes sense for endocrine academia to acknowledge and highlight these aspects
- Elderly citizens have a physiology which is different from that of younger adults, and leads to unique patterns of morbidity in them.



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More frequent with age:

- adult hypopituitarism
- hypothyroidism
- osteoporosis
- diabetes mellitus
- adrenal insufficiency
- various forms of hypogonadism
- endocrine malignancies



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