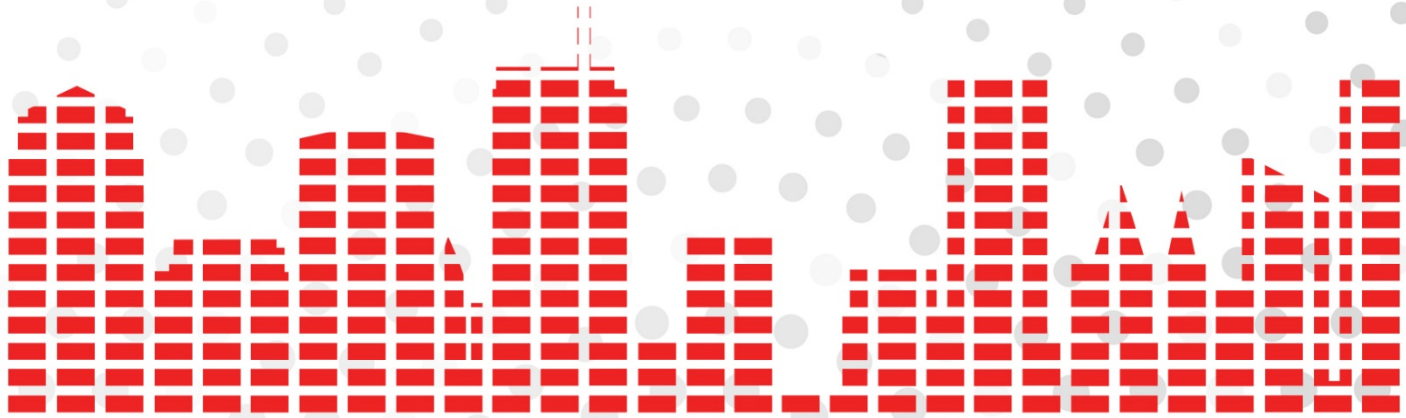

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Hearing Loss and the Pancreas: Screening, Diagnosis and Treatment/Monitoring

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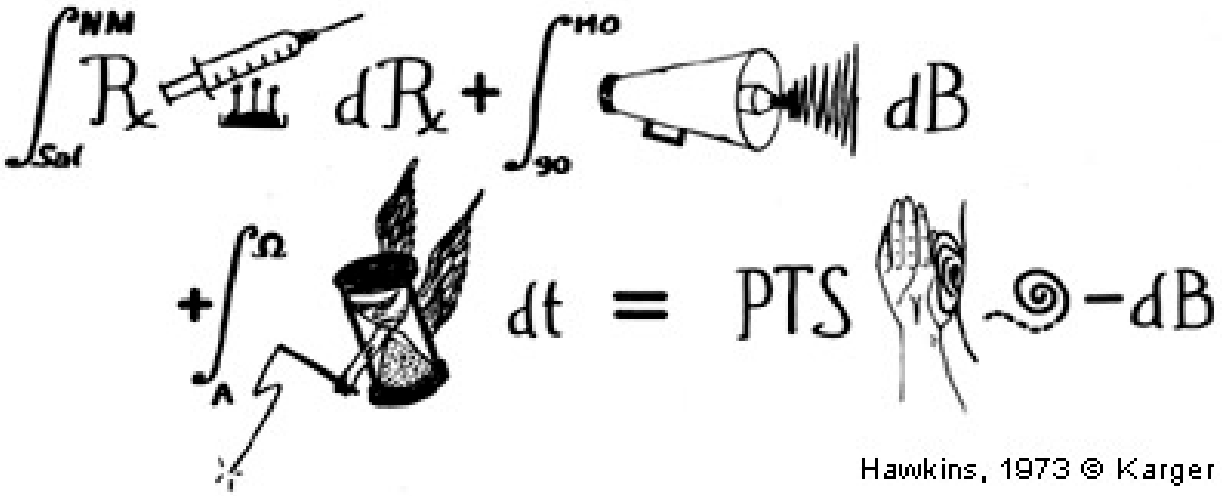
Conflict of Interest

- Employee of UMMC
- Associate editor for Audiology Today
- No other COI to report

Learning Objectives

1. Participants will be able to describe direct and indirect effects of pancreatic function on auditory physiology and pathophysiology
2. Participants will be able to compare and contrast screening and diagnostic approaches to hearing loss in persons with diabetes
3. Participants will be able to describe preventative strategies for hearing conservation for persons with diabetes



Hawkins, 1973 © Karger

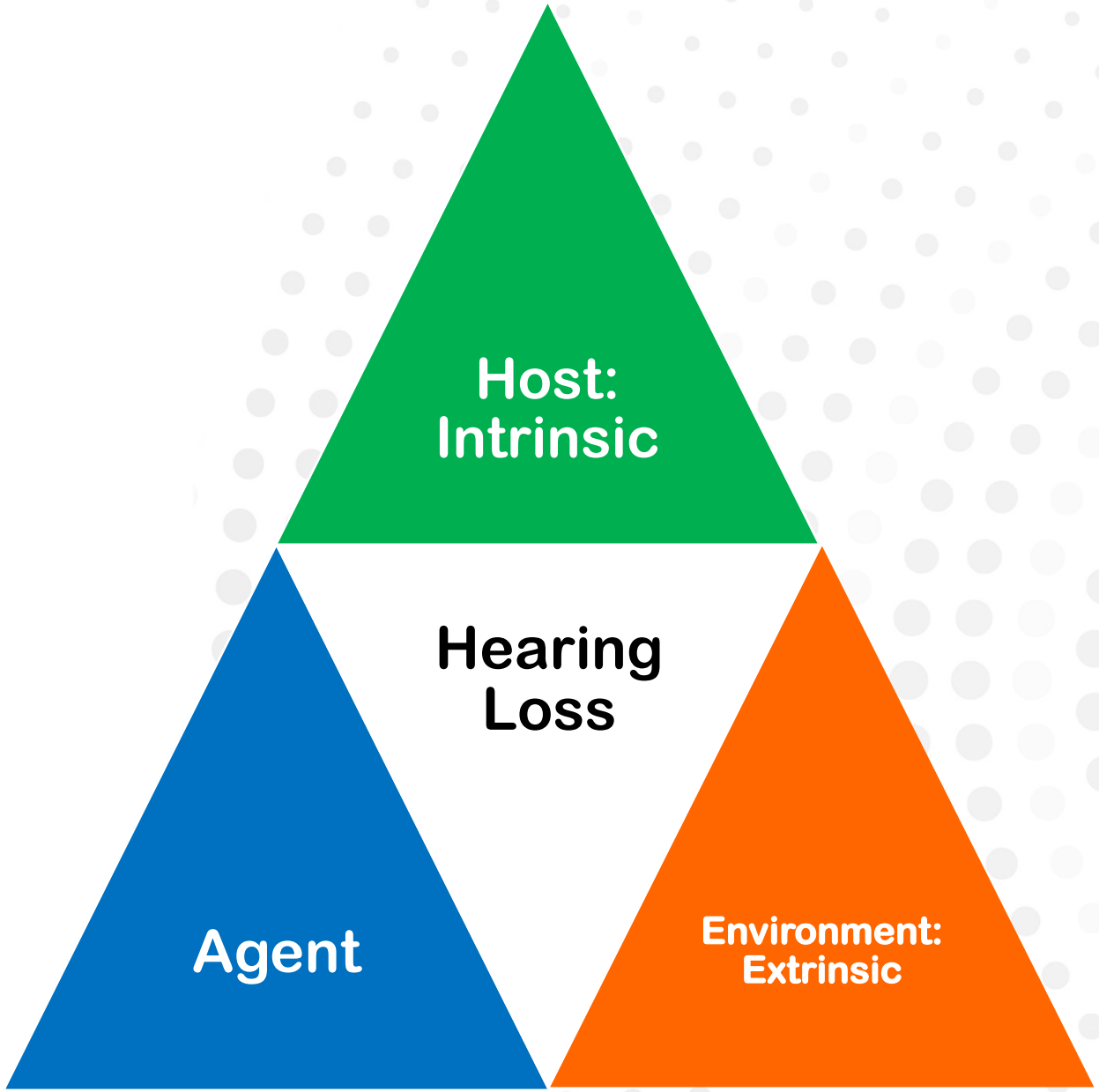
SNHL is a neurosensory medical pathology, not an inevitable benign component of aging, and cumulative exposure to extrinsic factors modified by susceptibility related to intrinsic factors determine our hearing status over our lifespan.

Non-Modifiable

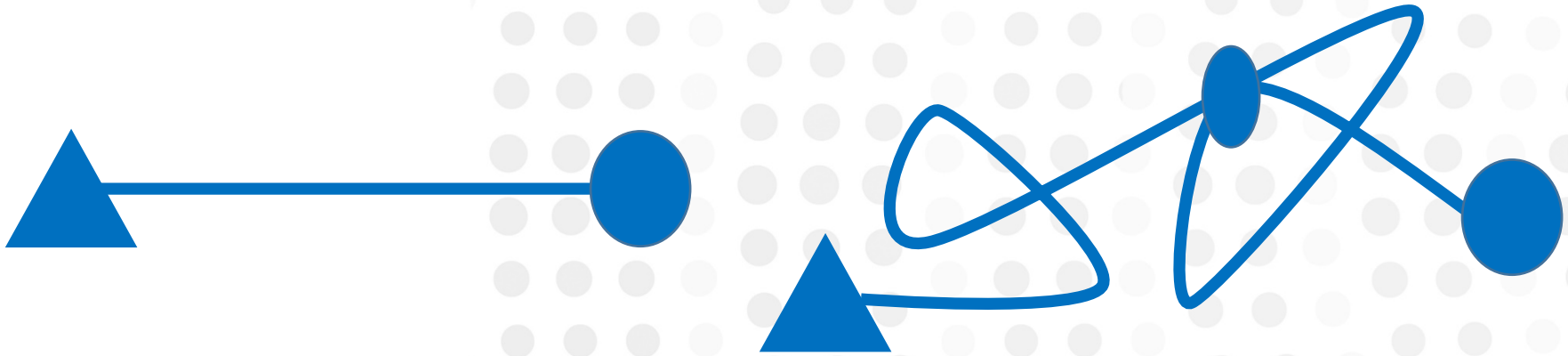
- Genetics
- Race/Ethnicity
- Age
- Sex

Modifiable

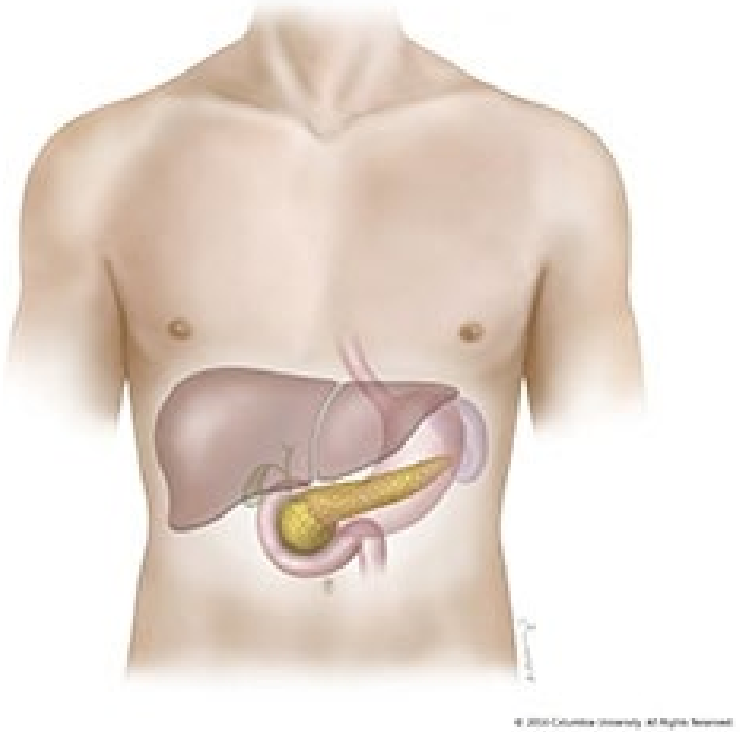
- SES/PIR/Education
- Health/Disease
- Environment
  - Noise, solvents, temperature
- Lifestyle & Diet

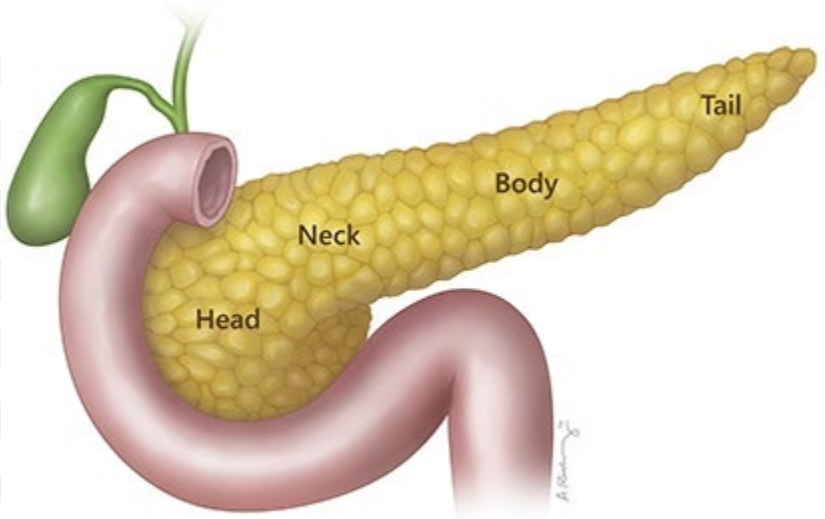

Host:
Intrinsic
Hearing
Loss
Agent
Environment:
Extrinsic

Direct Effect Vs. Indirect Effect



Physiology: The Pancreas





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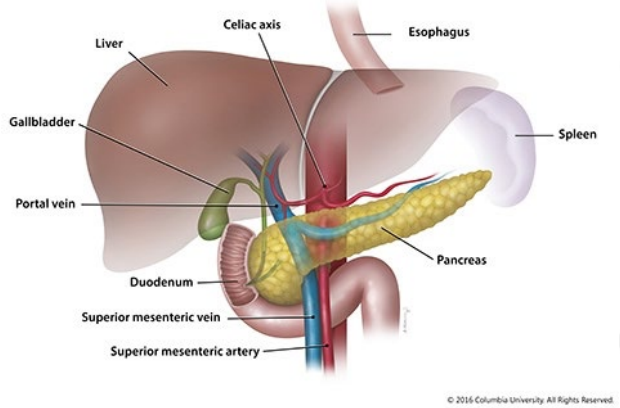
Physiology



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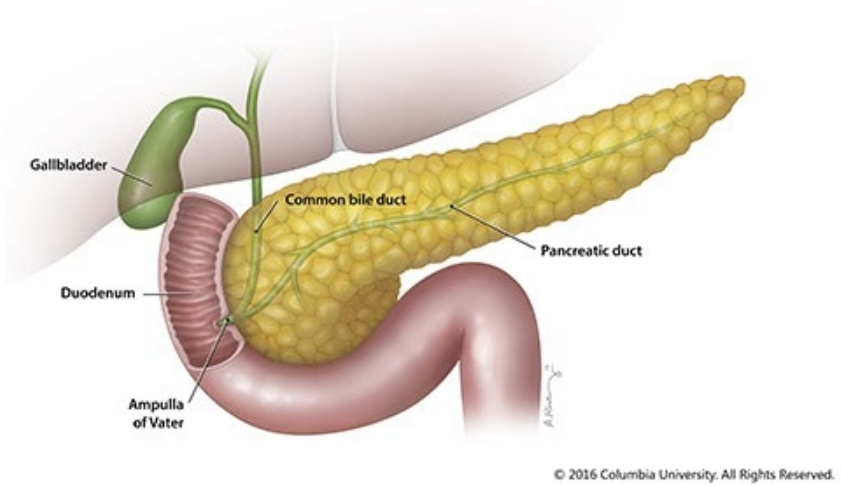
- The pancreas is a glandular organ located in the abdomen with two functions; exocrine and endocrine:
  - Exocrine- produces enzymes for digestion; trypsin and chymotrypsin to digest proteins; amylase to digest carbohydrates; and lipase to break down fats
    - 95% of pancreas is exocrine tissue
    - Pancreatic enzymes (secreted by **acinar cells**) travel down the **pancreatic duct** which joins with the **common bile duct** from the **gallbladder** to form the **ampulla of Vater** located at the duodenum, the first portion of the small



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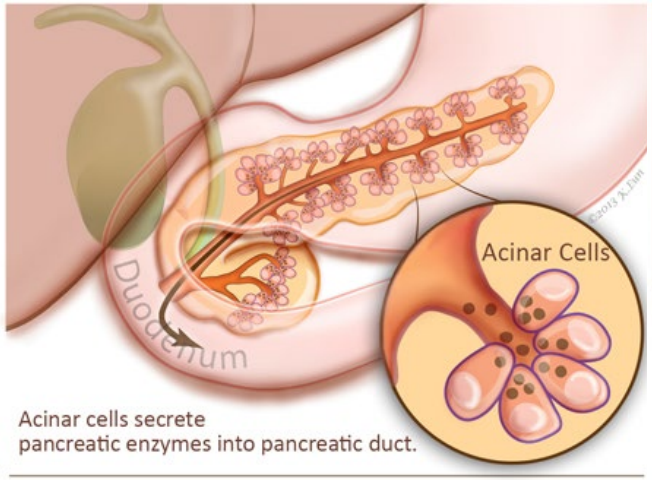
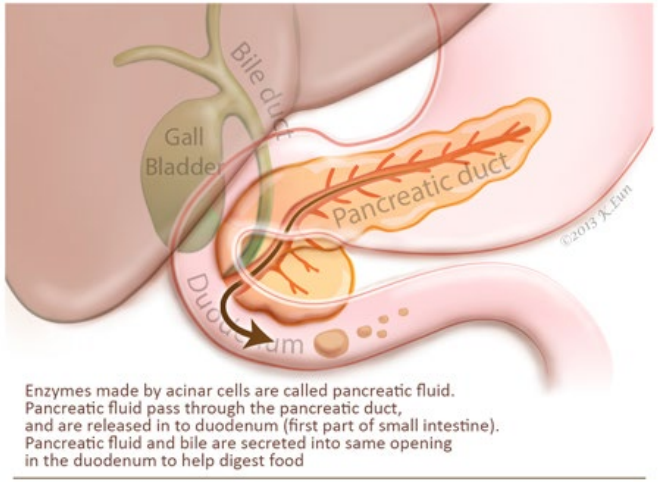
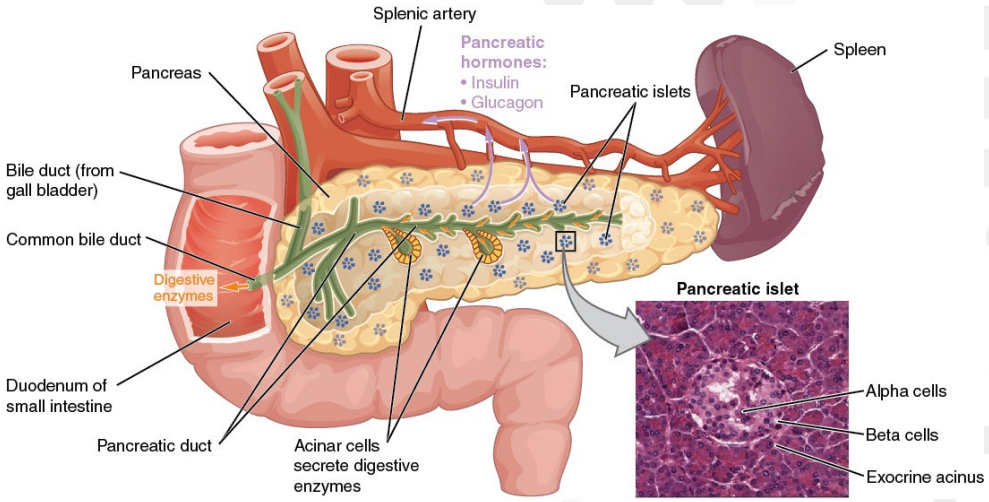
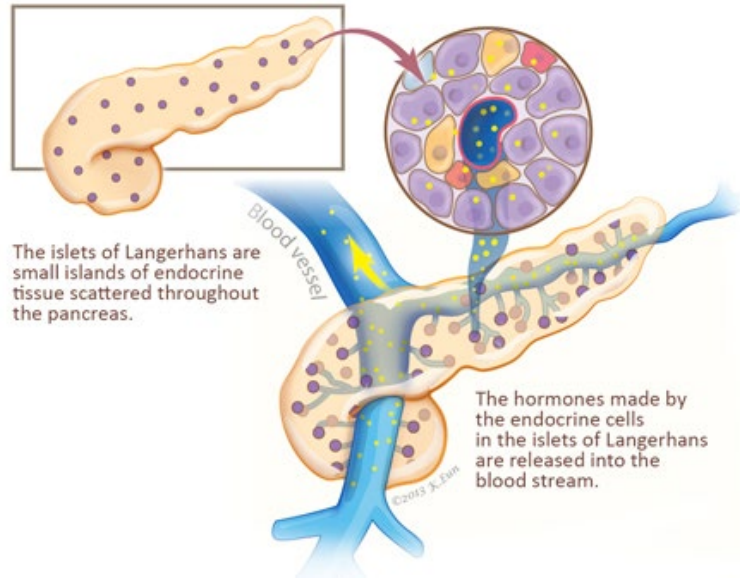




Physiology

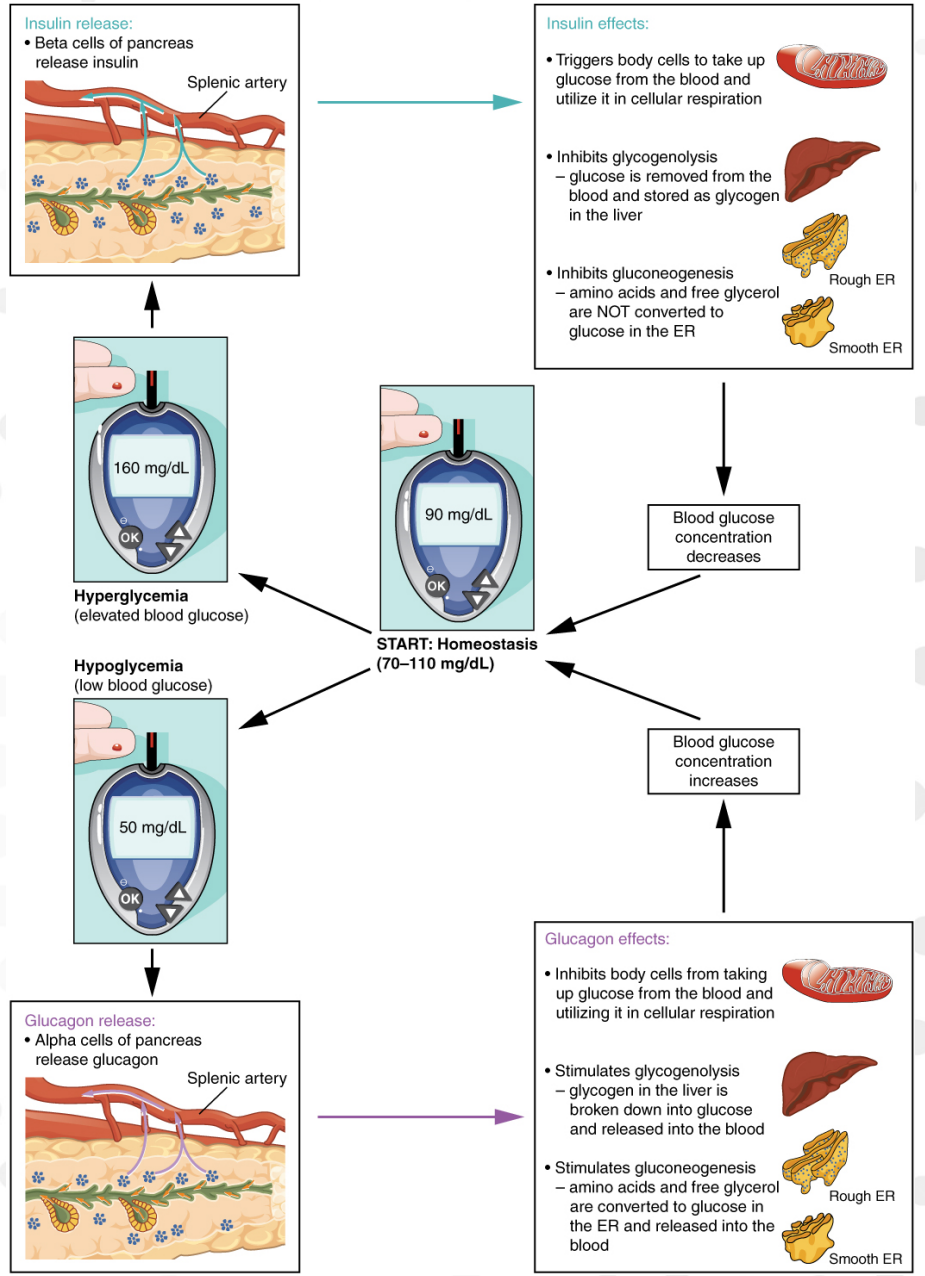
- The pancreas is an organ located in the abdomen with two functions; exocrine and endocrine:
  - Endocrine-The endocrine component of the pancreas consists of islet cells (islets of Langerhans) that produce hormones to regulate blood sugar
    - Two main hormones are **insulin** and **glucagon**, they do not use the pancreatic duct, but rather are released into the blood stream
    - Pancreatic islet cells include alpha cells, beta cells, delta cells, and PP cells



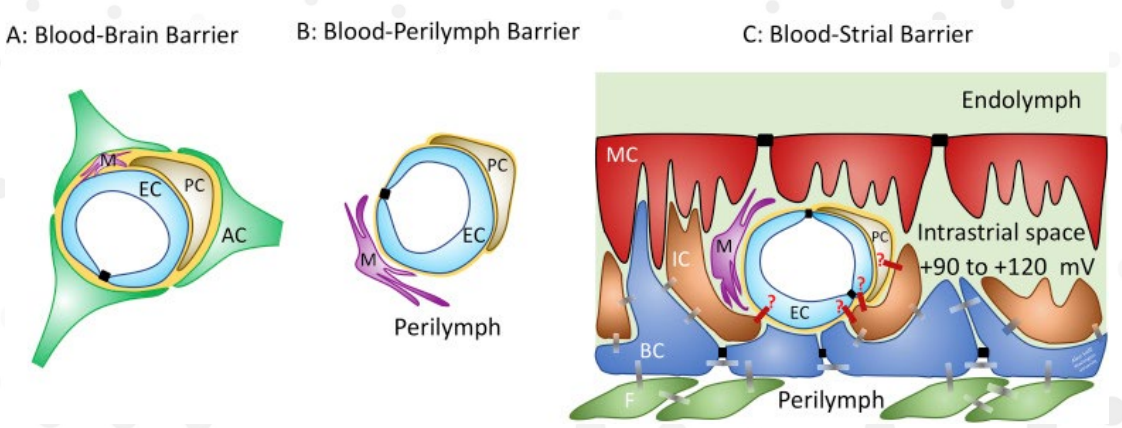


Physiology

- The pancreas is an organ located in the abdomen with two functions; exocrine and endocrine:
  - Glucagon-receptors in pancreas can sense decline in blood glucose and **alpha cells** release glucagon
    - Glucagon stimulates the liver to convert stores of glycogen back into glucose and release into circulation, called **glycogenolysis**
    - Stimulates liver to take up amino acids to convert into glucose, called **glyconeogenesis**
    - And stimulates lipolysis, the breakdown of triglycerides into free fatty acids and glycerol, some of that glycerol can be converted to glucose by the liver
  - Insulin-facilitates the uptake of glucose into body cells
    - Skeletal muscle and adipose cells are the primary targets of insulin
      - Red blood cells, cells of the brain do not have insulin receptors
    - Presence of food in intestine triggers the release of GI hormones (e.g. glucose dependent insulinotropic peptide), which pulls the trigger for insulin production and release by the **beta cells** of the pancreas
    - The insulin surge allows for rapid movement of glucose into cells for **glycolysis**, the metabolism of glucose for generation of **ATP**
    - Insulin stimulates the liver to convert excess glucose into glycogen and promotes triglyceride and protein synthesis
    - Delta cells (somatostatin) inhibit insulin and glucagon release
    - Pancreatic polypeptide (PP cells) are involved in appetite



Physiology

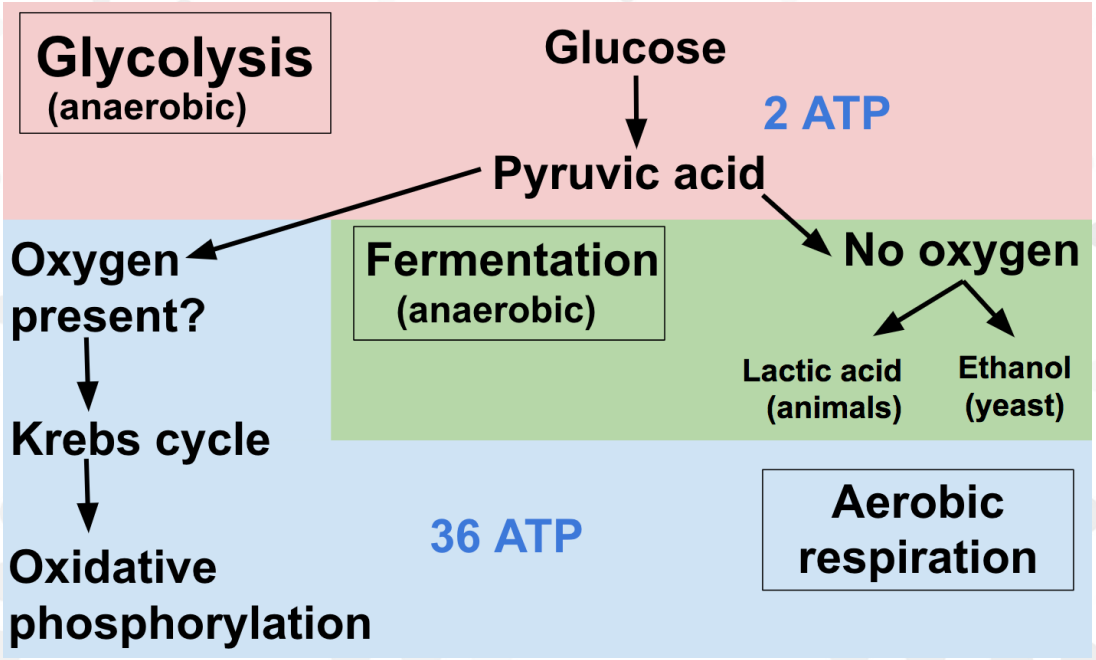


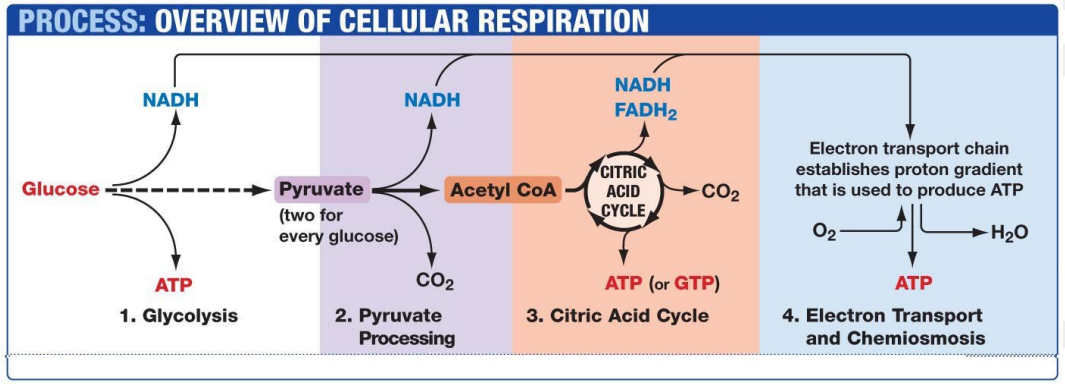
Salt & Hirose (2018)

- Energy metabolism is central to the physiology of a cell including cells of the inner ear
  - Glucose is the **primary energy source** (fatty acids and amino acids also contribute) of the **inner ear** (Kambayahsi et al. 1982)
  - Glucose is supplied to the cochlea via the vascular system and crosses the blood-labyrinth barrier by transporters (GLUT)
  - No exocrine role, no digestion in the inner ear

Physiology

- Glucose is converted to ATP via glycolysis and the Krebs cycle
  - Lack of lactate in the cochlea has implicated the aerobic pathway as the dominating source of energy (ATP)
  - Byproduct is free radicals





Physiology

- Glucose levels in the cochlear fluids are in general parallel to those in the blood, yet there is a delay of an hour between changes observed in the blood and in the cochlea.
  - This has been observed in numerous experiments manipulating blood glucose levels
    - Little more on this later

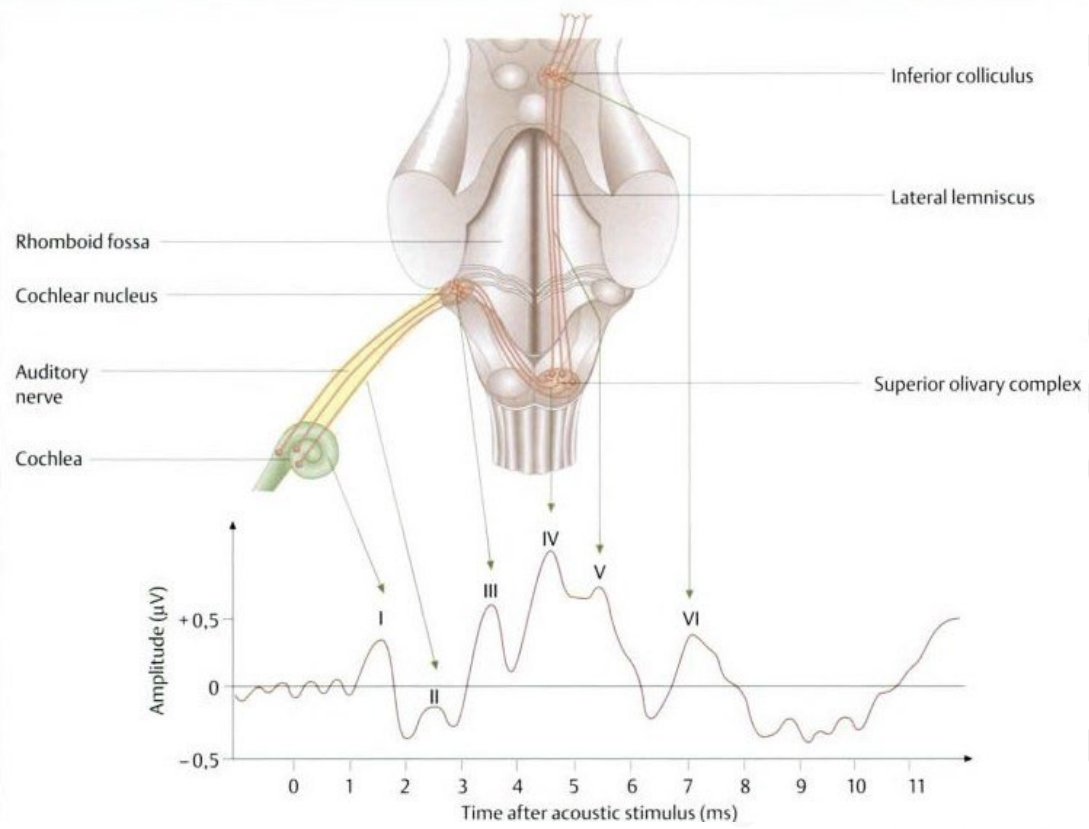
Physiology

- Insulin is an anabolic polypeptide hormone with numerous roles , with the regulation of glucose and metabolism as a major function.
- Insulin receptors exist in the cochlea, but is not believed to regulate glucose uptake, it is rather involved in protein synthesis and phospholipid signaling (Wang & Schacht 1990).

Physiology

- Moderate noise exposure significantly increases glucose uptake in the cochlea, however intense acoustic trauma creates ischemia and reduced utilization of glucose (Canlon & Schacht, 1983)
- Hypoglycemia will reduce this driving force and reduce active mechanism (Angelie et al. 2009)
  - Otoacoustic emissions: an objective measure of reflections and distortions from the cochlea are sensitive to changes in glucose
    - OAEs have been explored as an indirect measure of glucose status (Jacobs et al. 2012)
    - Sheep given a bolus injection of insulin demonstrated a transient reduction in DPOAEs (Zuma e Maia et al. 2006, 2008)

Physiology



- Glucose can also affect peripheral nerve conduction including auditory evoked potentials
  - Hypoglycemia can cause delay in latency of later ABR waves (Kern et al. 1994)
  - Effects can also be seen on efferent pathway

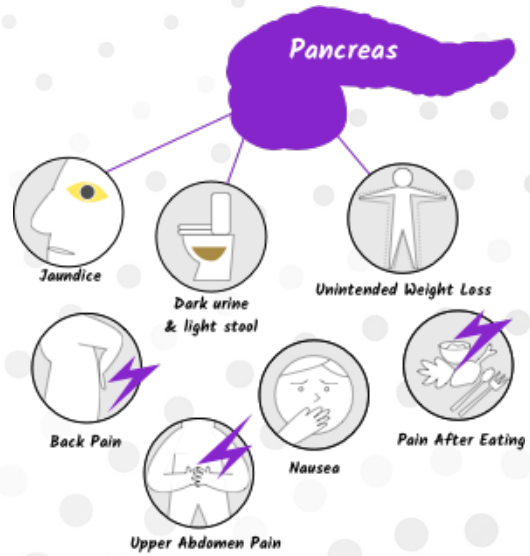
Physiology

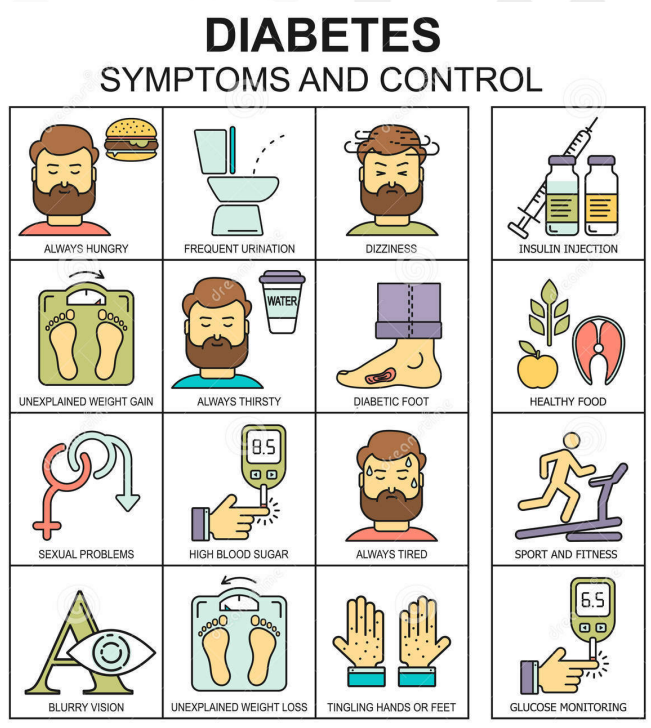
- The effects of acute hyperglycemia on inner ear function is less clear
  - Some studies suggest minimal effect on OAEs (Sasso et al. 1999)
  - Others suggest increased OAE amplitude (Jacobs et al. 2012)
  - And others decreased OAE amplitude (Suckfull et al. 1999)
  - MOC function is altered with hyperglycemia, with increased inhibition of OAEs (Jacobs et al. 2012)

  Possibly more than one mechanism at play. Elevated glucose in the cochlea increases ATP which can change the polarization of the hair cell to be less sensitive to sound, this may offset the increase in EP and cancel each other out!

Pathophysiology of Pancreas

- Exocrine dysfunction
  - Pancreatitis-inflammation of pancreas causing build up of enzymes and damage to organ; commonly related to alcohol abuse, some studies suggest 80g alcohol/day for many years = 8 drinks a day
  - Pancreatic cancer-tumors of the pancreas, most common **adenocarcinoma** impacting the cells lining the pancreatic duct, less than 5% of tumors are endocrine
  - Really no data supporting relationship between hearing loss and pancreatitis; couple of SSNHL case reports
  - Some application of cisplatin for pancreatic cancer
    - Average lifespan is 6 mo to 1 year; 20% 1 year survival and 7% 5 year
- Endocrine dysfunction
  - Dysfunction of insulin production can lead to diabetes mellitus (siphon and honey)
    - Type 1-autoimmune disease affecting beta cells with a genetic component, do not produce insulin
    - Type 2-95% of diabetes, this is acquired and related to poor lifestyle (diet and activity); cells become resistant to insulin, beta cells increase release but then become exhausted
    - Over time high levels of glucose causes inflammation and damage to blood vessels leading to impaired kidney function (which helps to filter glucose), neuropathy, vision difficulties, and **hearing loss**.
    - When deprived of glucose cells will also turn to fat stores for fuel, the liver then uses a process called **ketogenesis** to produce ketones to be used for energy production; this is a normal process, but when impaired can result in **ketoacidosis**.

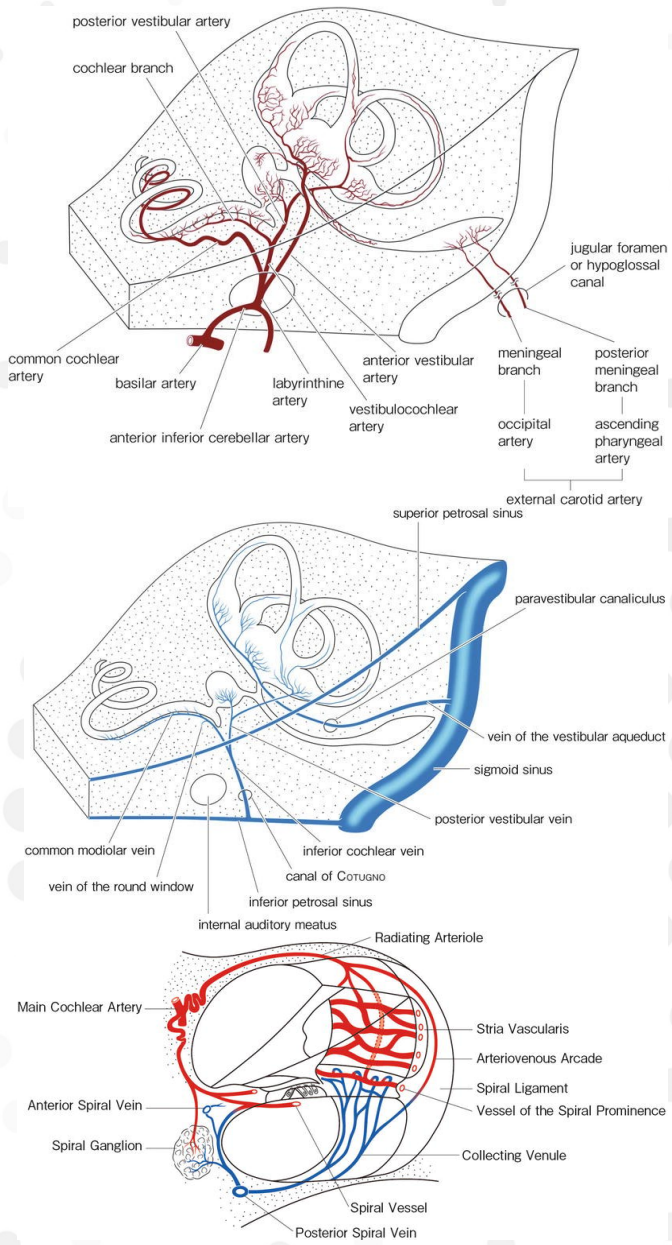


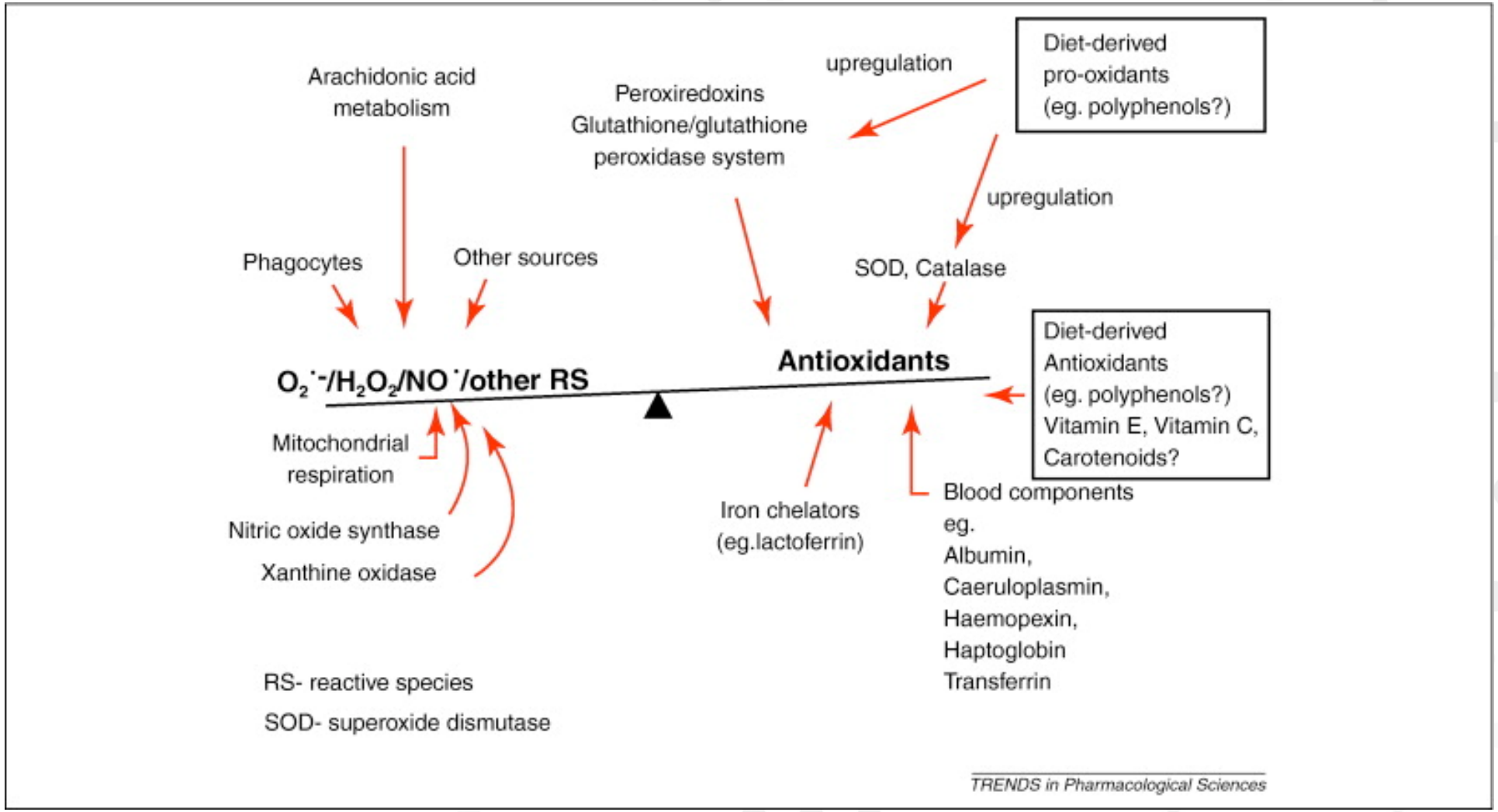


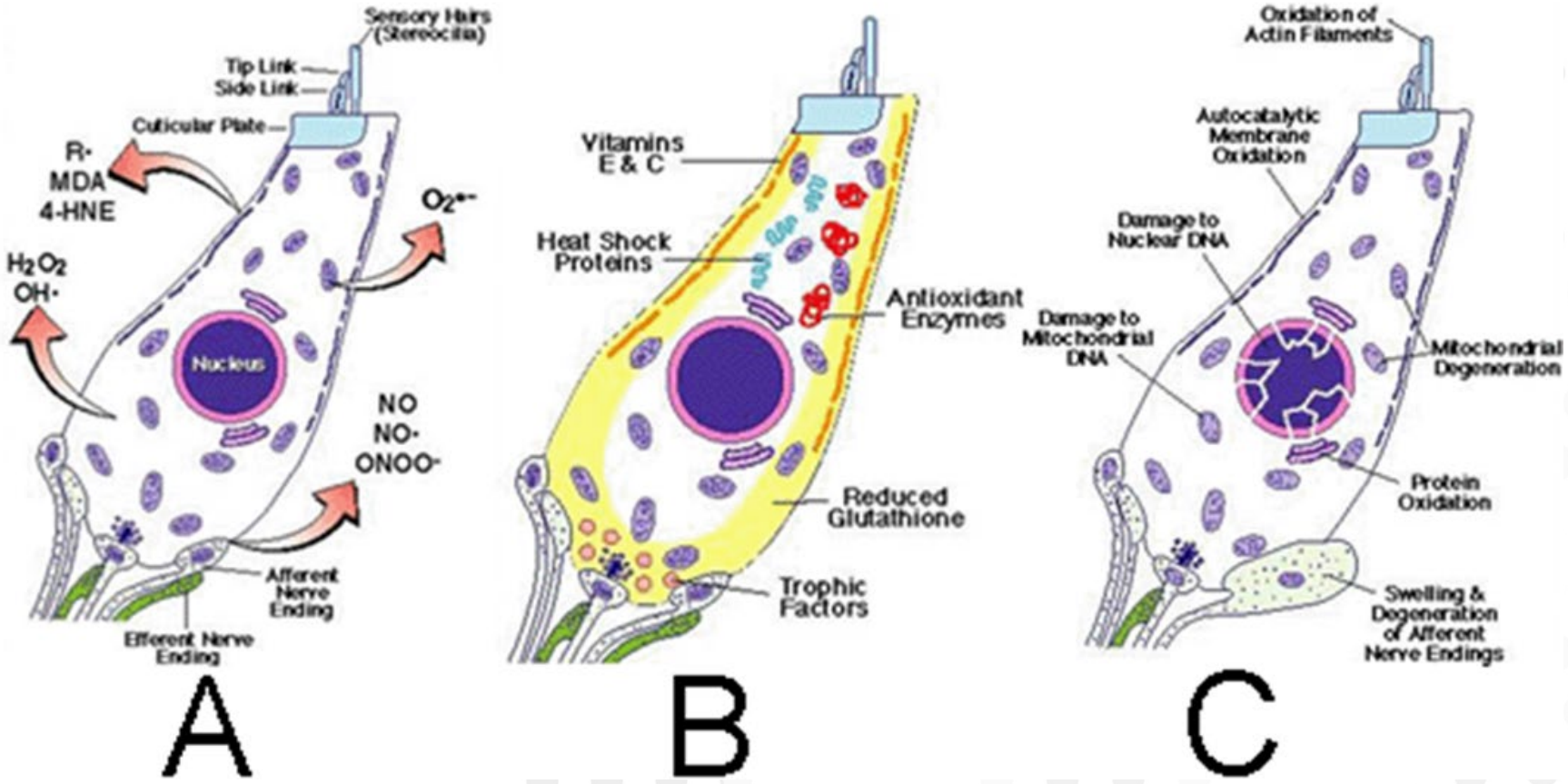
Download from Dreamstime.com

Pathophysiology and Diabetes

- Microangiopathy
- Mitochondrial dysfunction
- Advanced glycation end products
- Inflammation
- Glutathione dysregulation
- Protein synthesis dysfunction
- Glutamate excitotoxicity



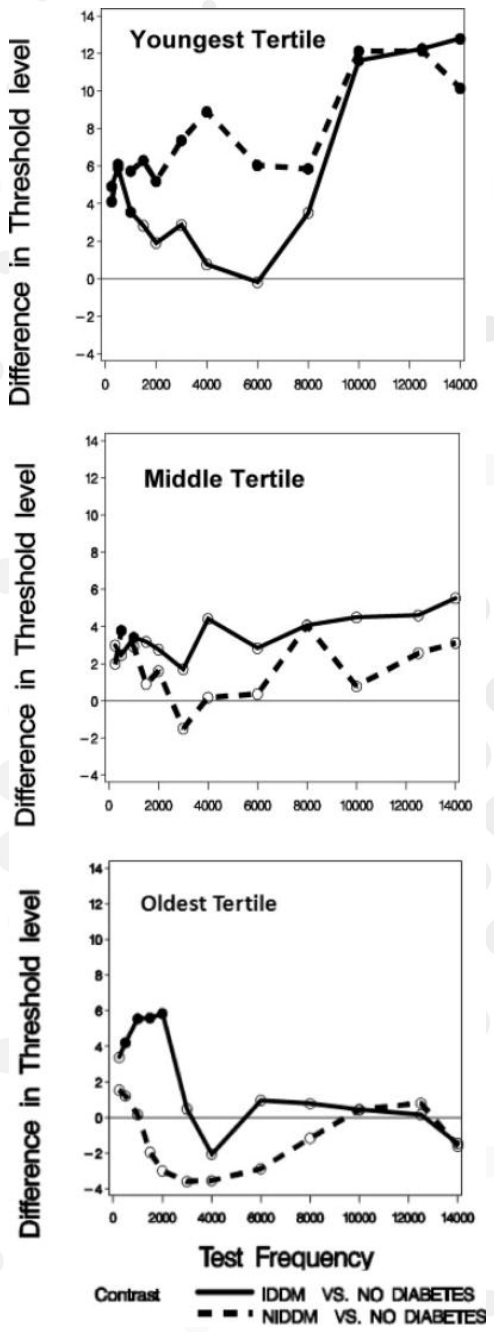

Arachidonic acid metabolism
Peroxiredoxins
Glutathione/glutathione peroxidase system
upregulation
Diet-derived pro-oxidants (eg. polyphenols?)
upregulation
Phagocytes
Other sources
SOD, Catalase
$O_2^{\cdot-}/H_2O_2/NO^{\cdot}$/other RS
Antioxidants
Diet-derived Antioxidants (eg. polyphenols?) Vitamin E, Vitamin C, Carotenoids?
Mitochondrial respiration
Nitric oxide synthase
Xanthine oxidase
Iron chelators (eg.lactoferrin)
Blood components eg. Albumin, Caeruloplasmin, Haemopexin, Haptoglobin Transferrin
RS- reactive species
SOD- superoxide dismutase
TRENDS in Pharmacological Sciences


Sensory Hairs (Stereocilia)
Tip Link
Side Link
Cuticular Plate
R·
MDA
4-HNE
$O_2^{\bullet-}$
H_2O_2
OH·
Nucleus
NO
NO·
ONOO⁻
Afferent Nerve Ending
Efferent Nerve Ending
A
Vitamins E & C
Heat Shock Proteins
Antioxidant Enzymes
Reduced Glutathione
Trophic Factors
B
Oxidation of Actin Filaments
Autocatalytic Membrane Oxidation
Damage to Nuclear DNA
Damage to Mitochondrial DNA
Mitochondrial Degeneration
Protein Oxidation
Swelling & Degeneration of Afferent Nerve Endings
C

Kopke, 2002

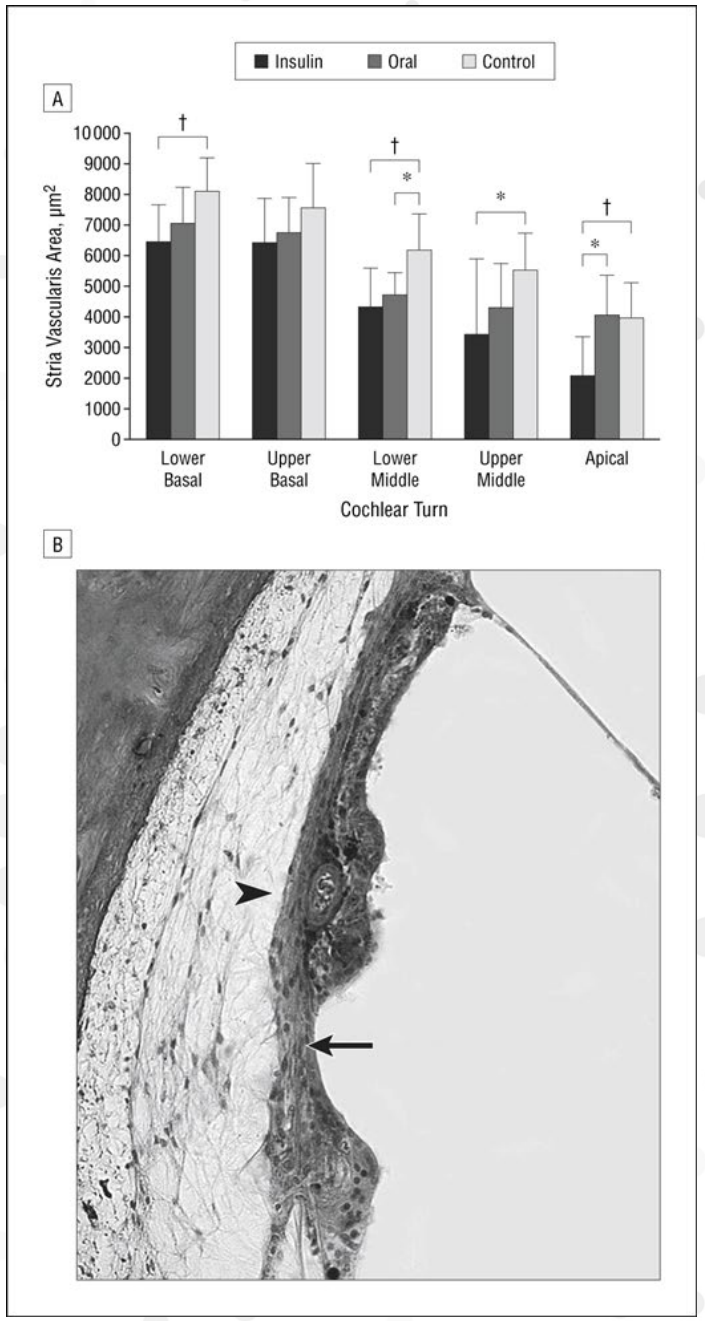
Human and Animal Evidence

- Human Clinical Studies:
  - All over the place
    - Why? **Inadequate controls for confounds**
    - Literature overall supports diabetes as a significant factor contributing to hearing loss and tinnitus (Austin et al. 2009; Bainbridge et al. 2008, 2010).
      - Younger patients with greater differences in extended high frequencies > 8000 Hz
      - Older patients with greater differences below 500 Hz
      - Risk factors for diabetes related hearing loss: low HDL, coronary heart disease, neuropathy, poor health (Bainbridge et al. 2010)
      - Diabetes doubles odds of hearing loss (Bainbridge et al. 2008)
      - Diabetes creates earlier onset of hearing loss (Brainbridge et al. 2008 and Austin et al. 2009)



Human and Animal Evidence

- Human Temporal Bone Studies (Fukushima et al. 2006 and 2005)
  - Thickening of BM
  - Thickening of vessels of the SV
  - Atrophy of SV
  - Greater loss of OHC



Human and Animal Evidence

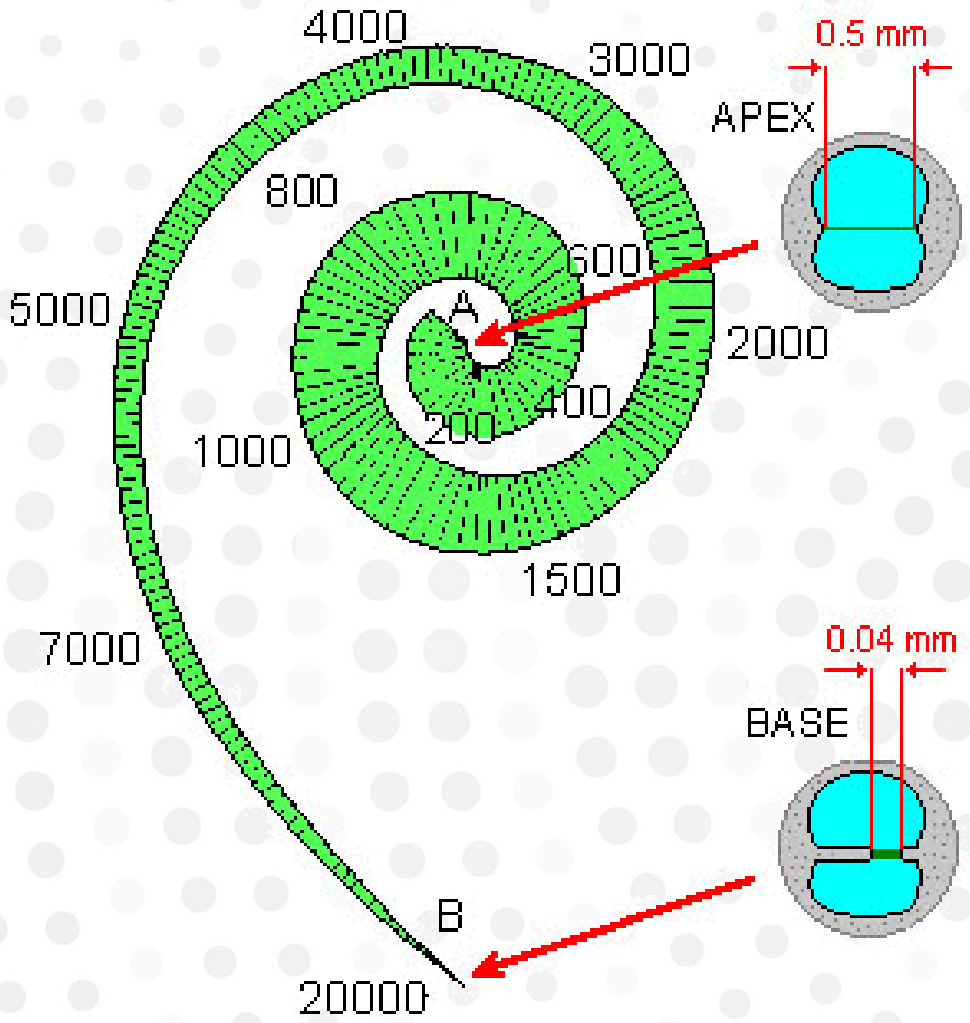
- Animal Studies
  - In general show diabetes increases damage
  - Exacerbates risk for NIHL and changes with age
  - Animal Model Considerations:
    - Streptozocin-treated rat (STZ)
      - Agent to induce ‘diabetes’ is ototoxic; drug destroys pancreatic islet β-cells
    - SHR/N-cp rat
      - Develop ‘diabetes’ at 12mo, hearing loss starts at 5 months
    - WBN/Kob rat
      - Develop pre-diabetes and diabetes, reduced ABR, SV atrophy
    - T2DN rat
      - Decline with age, larger ABR at younger ages
    - NOD (non-obese diabetic) mice
      - Autoimmune effects, significant hearing loss by 3 mo
    - Ob/ob mouse
      - Obesity and diabetes, early onset of hearing loss

Human and Animal Evidence

- Summary of Literature
  - Overall the evidence indicates that diabetes is a significant determinant of hearing dysfunction
  - Human and Animal studies suggest both cochlear and neural deficits
  - Diabetes can create earlier onset of hearing loss and increase risk for other hearing loss related factors (e.g. noise)

Site of Lesion

- Low Frequency
  - Apical portion of cochlea
    - Microangiopathy?
    - Fluid composition & dynamics?
- Mid Frequency
  - 3000-6000 Hz
    - Resonance area for broadband sound
    - High susceptibility to Noise
- Higher Frequency
  - Basal portion of the cochlea
    - High metabolic requirement
    - Lower levels of glutathione
    - High susceptibility to noise and ototoxic drugs



Diagnostic Considerations :

The Audiology Project

https://www.theaudiologyproject.com

Site of Lesion

- Testing low frequencies
  - Low frequency hearing loss associated with Diabetes and risk for cardio-metabolic risk (Friedland et al. 2009)
- Testing mid frequencies
  - 3000-6000 Hz region particularly susceptible to effects of noise
  - Diabetes can increase risk for noise pathology (Wu et al. 2009; Win et al. 2015, Ishii et al. 1992)
- Testing higher frequencies
  - Testing > 8000 Hz may be a useful marker for early effects of DM (Austin et al. 2009)
  - High metabolic demand and sensitive to both noise and ototoxic drugs

Diagnosis & Triage

- Sensorineural Hearing Loss
  - Damage to sensory and neural receptors of the inner ear
  - More common type of hearing loss expected
- Conductive Hearing Loss
  - Limited data on CHL and Diabetes
  - General increase for infections warrants exclusion
- Tinnitus and Sound sensitivity
  - Commonly related to hearing loss and associated with diabetes even without hearing loss

Table 4. Multivariate[a] adjusted odds ratios for persistent tinnitus by definition of normal audiometric threshold.

Normal Audiometric Threshold (Pure Tone Average (PTA) 0.5, 1.0, 2.0, 4.0 kHz ≤ 25 dBHL)	
Variables Related to Persistent Tinnitus	**Odds Ratio (95% Confidence Interval)**
Hearing Difficulty	**3.96 (1.54–6.18)**
Diabetes	**3.23 (1.64–6.36)**
Cancer	1.43 (0.71–2.87)
Arthritis	**2.62 (1.81–3.79)**
Vision Difficulties	**2.23 (1.54–3.21)**
Confusion/Memory	**4.63 (2.85–7.52)**
Analgesics Use	**1.90 (1.30–2.77)**
Healthy Eating Index	**0.98 (0.97–0.99)**
Hearing Tested	**2.26 (1.21–4.21)**
Balance	**3.08 (1.96–4.83)**
Loud Noise non-Work	**1.97 (1.27–3.05)**
Pain/Tingling in hands/feet	**3.44 (2.19–5.40)**
Numbness in hands/feet	**2.49 (1.57–3.93)**
Alcohol Use, 5 + per day	**2.05 (1.21–3.47)**
Prescription Past Month	1.31 (0.91–1.88)

Spankovich et al. 2018

Bold = significant p ≤ 0.05.
a. Adjusted for age, sex, and high and low frequency pure tone averages.

Screening Recommendations

- When to Screen?
  - Upon diagnosis a baseline hearing evaluation is recommended
  - Hearing loss can manifest early
- High risk considerations:
  - Reduced hearing (particularly in noise)
  - Tinnitus perception
  - History of high noise exposure
  - History of ototoxic drug use
  - Sensitivity to sound
  - Ear pain or drainage
  - Dizziness complaints

Screening Recommendations

- Key Questions to ask diabetes patients
  - Have you had your hearing tested in the past two years?
  - Do you know how diabetes can affect your hearing and balance?
  - Do you know what to do if you perceive a change in hearing or balance function?
  - Do you know how to reduce your risk for hearing loss or falls?

If respond **no** to any question, patient should be referred to audiologist

Diagnostic Recommendations

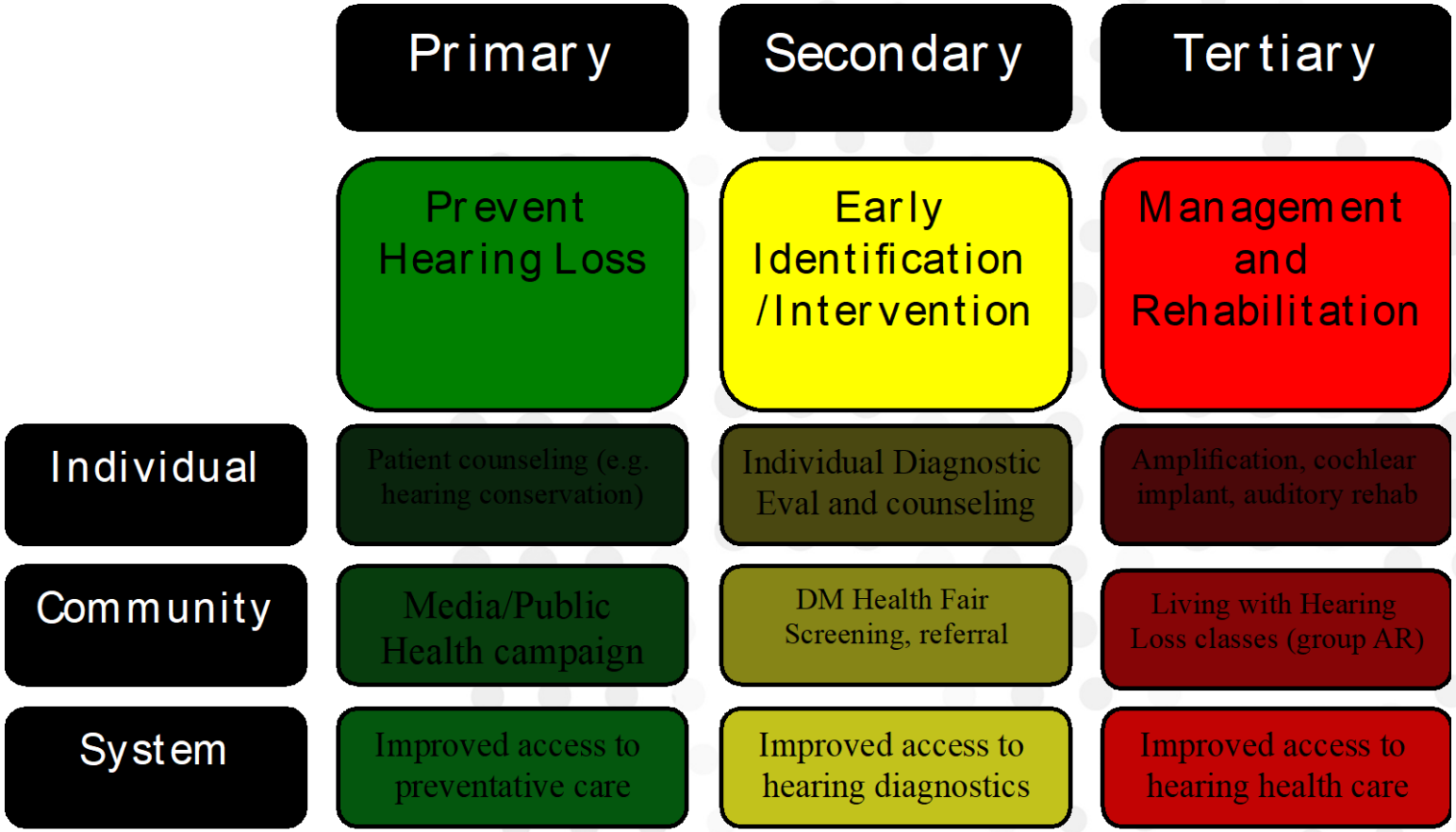
- At minimal:
  - Comprehensive audiological evaluation
    - Air Conduction
    - Bone Conduction
    - Speech Audiometry
- At least every 2 years, annual or greater if high risk factors indicated or patient reports change in hearing status

Diagnostic Considerations

- Extended High Frequencies
  - >8000 Hz may show early changes, consider testing based on patient subjective complaints if hearing below 8000 Hz within normal range
- Otoacoustic Emissions
  - Can show subtle changes due alterations in cochlear active process prior to changes in thresholds
- Auditory Evoked Potentials
  - Can show effects sensitivity to neuropathology and glutamate excitotoxicity
- Tinnitus Evaluation
- Central Auditory Processing

Prevention and Treatment

Prevention 3 x 3



Prevention: Direct

- Patient Counseling
  - Persons with DM have greater susceptibility to acquired hearing loss
    - Noise: Use hearing protection
    - Ototoxic medication: Careful monitoring
    - Earlier onset related to age: difficulty understanding speech in background noise, tinnitus
  - Evaluation is important
    - Baseline
      - Threshold assessment, speech in noise, otoacoustic emissions
      - Follow-up at least every 2 years, earlier if **at risk**
    - Further counseling

Prevention: Indirect

- Patient Counseling
  - Diabetes control and presence of co-morbidities is associated with greater incidence of cochlear and auditory neural pathology
    - Insulin Control
  - Physical activity and Diet are associated with diabetes susceptibility and control
    - and hearing loss

Physical Activity

- Fitness and NIHL (Kolkhorst et al., 1998): Better markers of physical fitness reduced level of TTS to 108 dB SPL for 10 min.
- 2 month of aerobic training reduced TTS (Cristell et al., 1988)
- Sedentary behavior increases odds of hearing loss (Loprinzi et al., 2013).
- Association between odd of of hearing loss and lower physical activity (Gispen et al., 2014).
- Association with physical activity and hearing loss in persons with diabetes (Loprinzi et al., 2014)

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

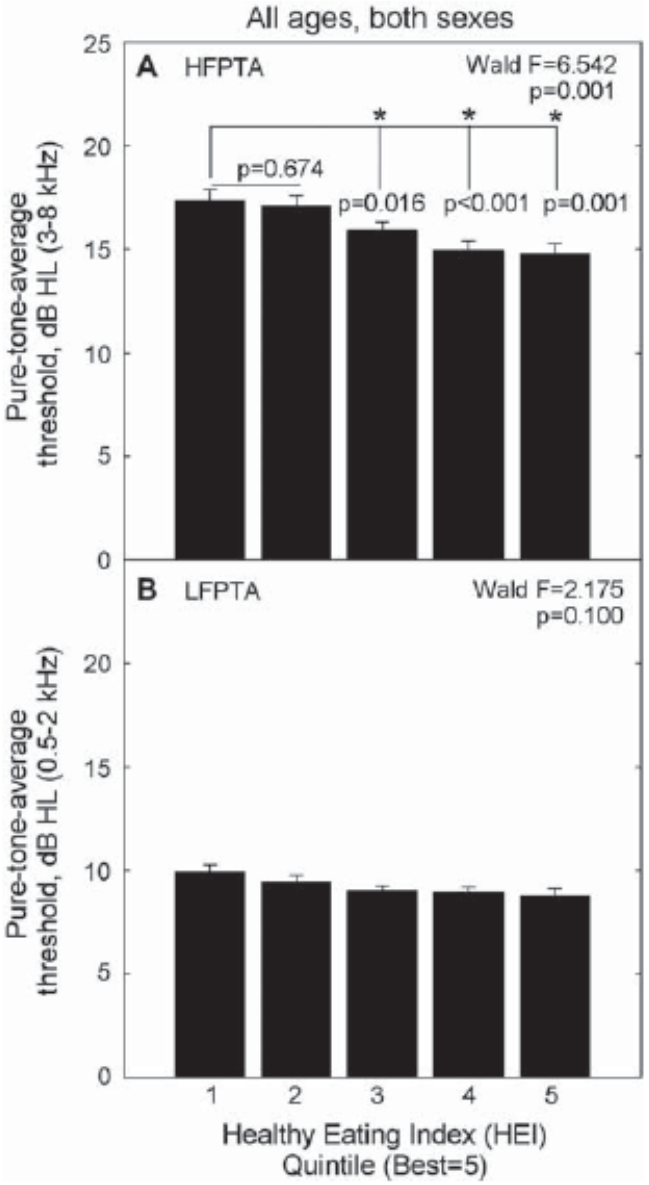
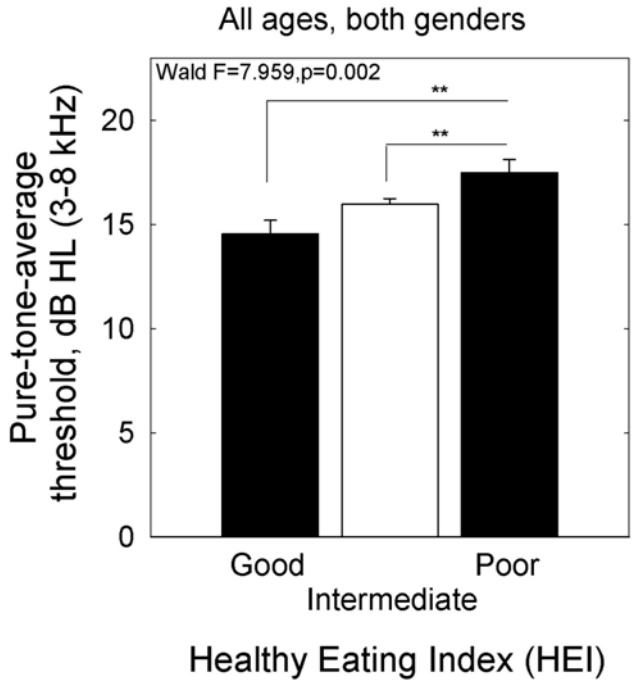


Figure 1. A. High frequency (HFPTA) and B. low frequency pure-tone average (LFPTA) and healthy eating index quintiles.



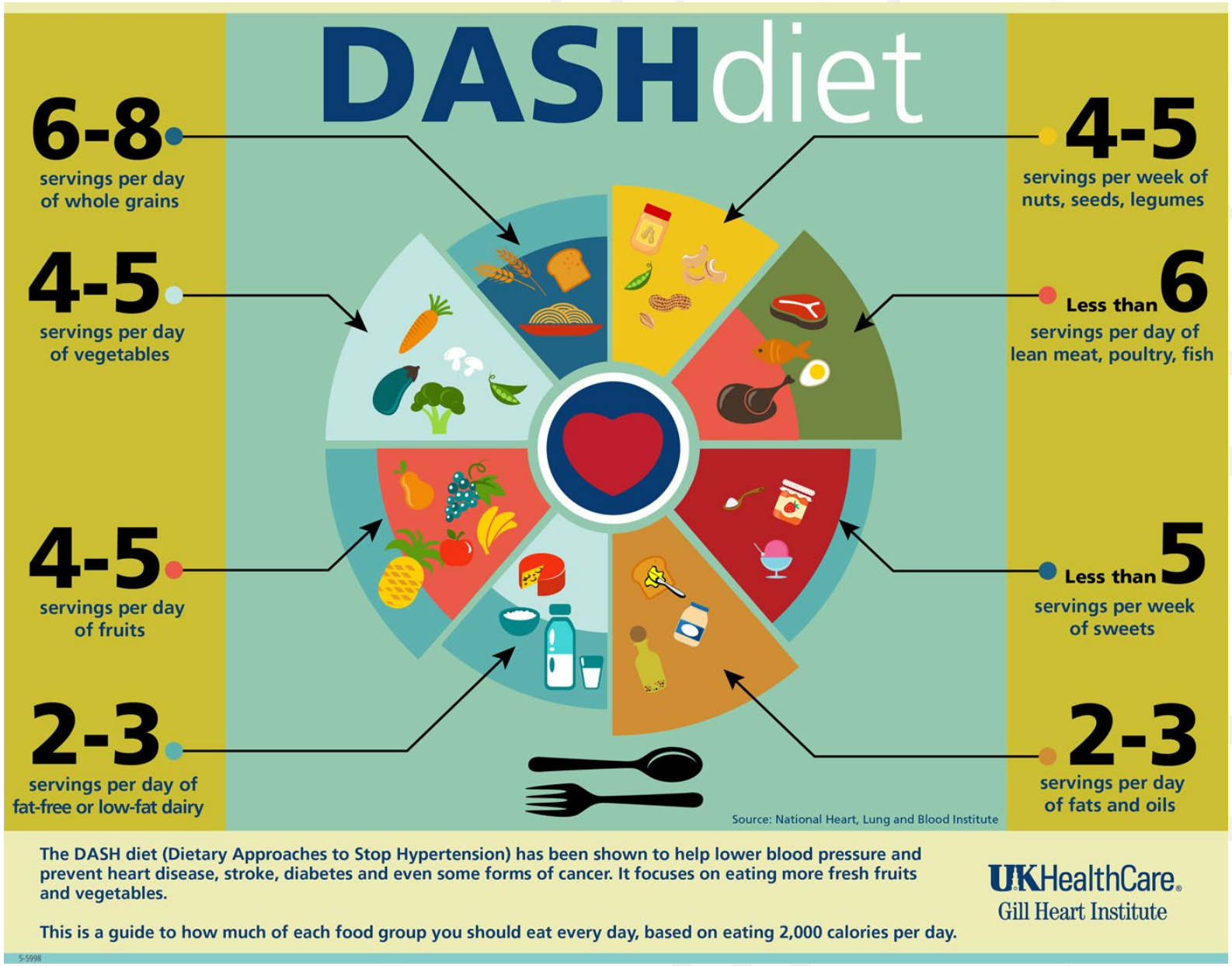
Spankovich & Le Prell (2013)

Table 2. HFPTA comparison for HEI subscales of NHANES 1999–2002 with sample weights applied.

Subscales of HEI	*HFPTA threshold: Bottom 40% (SEM, CI)*	*HFPTA threshold: Top 60% (SEM, CI)*
Fruit intake*	16.51 (.33, 15.84–17.18)	15.53 (.38, 14.7–16.32)
Vegetable intake*	16.44 (.35, 15.75–17.16)	15.72 (.32, 15.07–16.37)
Dairy intake*	16.76 (.37, 15.98–17.52)	15.38 (.32, 14.72–16.04)
Variety*	16.94 (.35, 16.23–17.66)	15.32 (.31, 14.70– 5.95)
Fat intake	16.52 (.42, 15.65–17.38)	15.81 (.33, 15.12–16.49)
Saturated fat intake	16.41 (.41, 15.56–17.25)	15.81 (.35, 15.09–16.53)
Cholesterol intake	16.22 (.53, 15.14–17.32)	16.01 (.31, 15. 37–16.64)
Sodium intake	15.64 (.33, 14.95–16.32)	16.43 (.33, 15.76–17.11)
Grain intake	16.35 (.36. 15.61–17.08)	15.75 (.30, 15.14–16.36)
Meat and meat alternative intake	16.08 (.36, 15.35–16.81)	16.06 (.34, 15.37–6.76)

*indicates significant difference.

Spankovich & Le Prell (2013)


DASHdiet
6-8
servings per day
of whole grains
4-5
servings per day
of vegetables
4-5
servings per day
of fruits
2-3
servings per day of
fat-free or low-fat dairy
4-5
servings per week of
nuts, seeds, legumes
Less than 6
servings per day of
lean meat, poultry, fish
Less than 5
servings per week
of sweets
2-3
servings per day
of fats and oils
Source: National Heart, Lung and Blood Institute
The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to help lower blood pressure and prevent heart disease, stroke, diabetes and even some forms of cancer. It focuses on eating more fresh fruits and vegetables.
This is a guide to how much of each food group you should eat every day, based on eating 2,000 calories per day.
UKHealthCare
Gill Heart Institute
5-5998

Know Your ABCs to Prevent Diabetes Complications

A 1c LESS THAN **7%**

B lood Pressure LESS THAN **140/90** MMHG

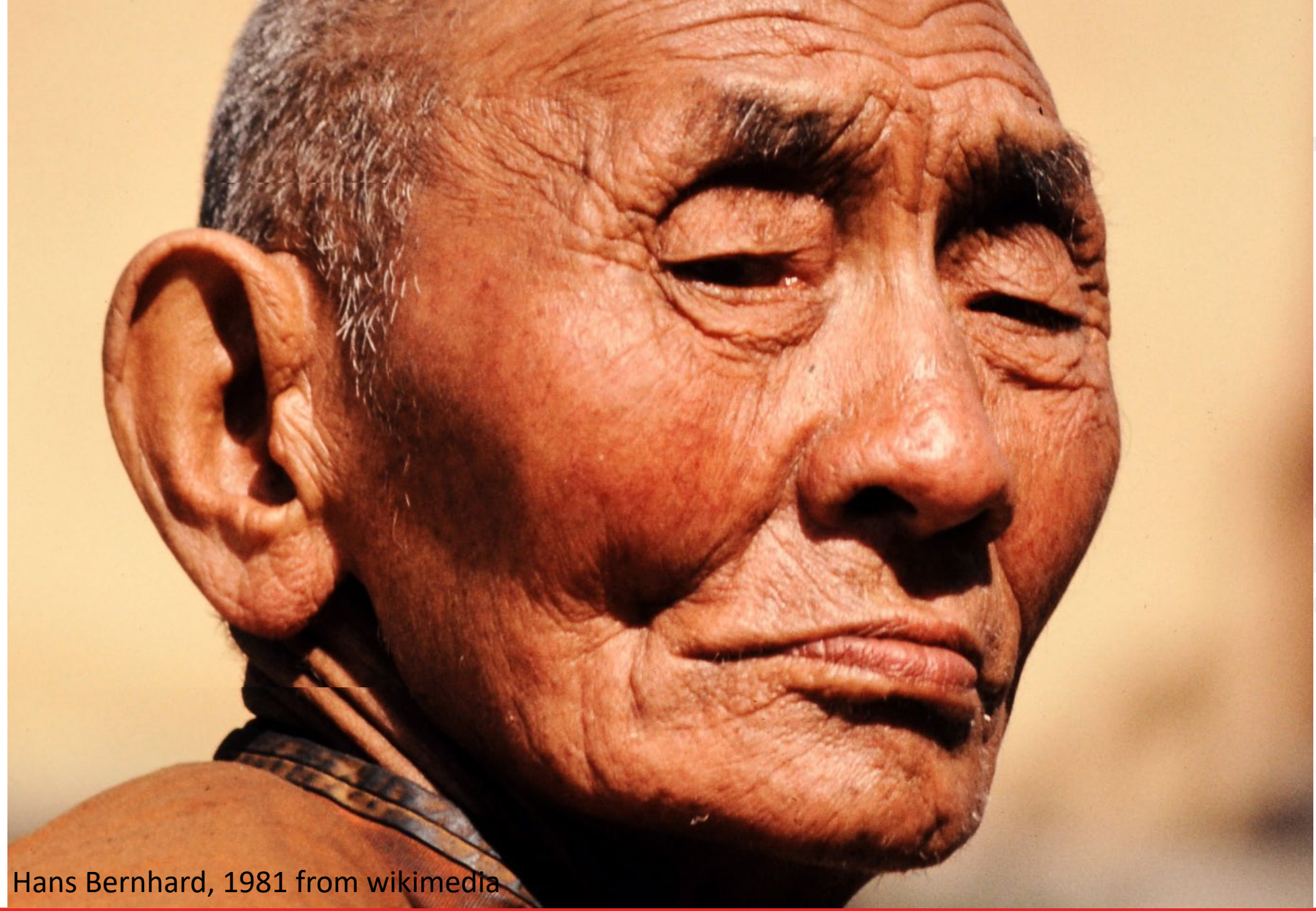
C holesterol Levels for LDL LESS THAN **100** MG/DL

Goals may be different for each person.
Ask your doctor what your goal should be.

Diabetes and Hearing

- Direct and Indirect Effects
- Prevention 1,2,3 is
  - Auditory and DM Control
  - Hearing conservation, Lifestyle (diet + physical activity)
  - Improved Access
  - ABCs
- Early Identification
  - Thresholds including extended high frequencies
  - Otoacoustic emissions
  - Auditory Brainstem Response
  - Improved Access
- Management
  - Auditory rehabilitation
  - Amplification/CI
  - Improved Access

	Primary	Secondary	Tertiary
	Prevent Hearing Loss	Early Identification /Intervention	Management and Rehabilitation
Individual	Patient counseling (e.g. hearing conservation)	Individual Diagnostic Eval and counseling	Amplification, cochlear implant, auditory rehab
Community	Media/Public Health campaign	DM Health Fair Screening, referral	Living with Hearing Loss classes (group AR)
System	Improved access to preventative care	Improved access to hearing diagnostics	Improved access to hearing health care



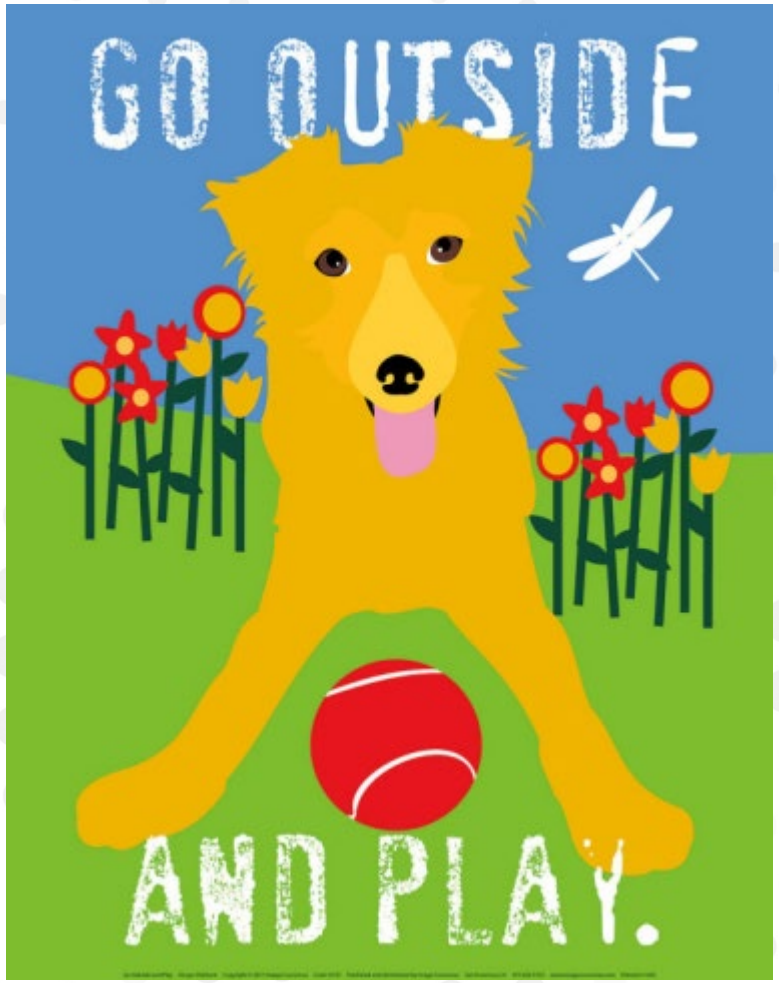
Hans Bernhard, 1981 from wikimedia

DIABETES AND YOU:

Healthy Ears Matter!

THE AUDIOLOGY PROJECT
Kathy Dowd, AuD

http://www.theaudiologyproject.com



Any Questions?
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