Endocrine disorders

Dental Course
Thyroid hormone synthesis and physiology

• ANATOMY:
  weighs 10-20 gm in nl adults in the USA
  slightly greater in M > F
  Size increases with age and body weight,
  Size decreases with increasing iodine intake.
THYROID HORMONE BIOSYNTHESIS

• Thyroxine (T4) and 3,5,3'-triiodothyronine (T3):
  Composed of a phenyl ring attached to a tyrosine
• Both have 2 iodine atoms on tyrosine (inner) ring
• T4 has 2 iodine atoms on its phenyl (outer) ring, T3 has only one

• If an iodine is removed from the inner ring of T4:
  
  3,3',5'-triiodothyronine is formed (reverse T3): has no biological activity
Iodine economy

• Foods rich in iodine:
  - seafood, seaweed, kelp, dairy products.
  - Iodized salt is available (iodized salt in the US contains 45 to 80 mcg/g)
The recommended daily iodine intake:
infants 0 - 6 months: 110 mcg;
infants 7 - 12 months: 130 mcg;
children 1 - 8 years: 90 mcg;
children 9-13 years: 120 mcg;
adolescents and adults: 150 mcg;
pregnant women: 220 mcg;
lactating women: 290 mcg.
Iodine deficiency

• Iodine deficiency is defined by urinary iodine excretion, as follows:
  -mild  50- 99 mcg/L
  -moderate 20-49 mcg/L
  -severe <20 mcg/L
Severe iodine deficiency in fetuses and infants:
- severe mental and growth retardation,
Mild iodine deficiency:
- thyroid enlargement and learning disabilities in children
Thyroid hormones synthesis

1. iodide transport: Iodide transport is linked to sodium

   Sodium iodine transporter is a protein on the basolateral membrane of follicular cells

   perchlorate and pertechnetate are competitive inhibitors of iodide transport.
2. Tyrosyl iodination:

In follicular cells, iodide is transported by pendrin, a membrane iodide-chloride transporter, to exocytotic vesicles at apical cell membrane.
The oxidation of iodide is catalyzed by thyroid peroxidase (requires hydrogen peroxide). TPO catalyzes iodination of about 10% of the tyrosine residues of thyroglobulin.
Hormone synthesis-3

3. Coupling of iodotyrosyl residues of thyroglobulin:

T4 is formed by coupling of two diiodothyrosine residues and T3 by coupling of one monoiodothyrosine and one diiodothyrosine within a thyroglobulin molecule.

Catalyzed by thyroid peroxidase.
Triiodothyronine (T3)

- 80% is produced by extrathyroidal deiodination of T4
- 20% by the thyroid
- Reverse T3 : Nearly all by extrathyroidal deiodination of T4
REGULATION OF THYROID HORMONE PRODUCTION

• Regulation by thyrotropin (TSH), and thyrotropin-releasing hormone (TRH).
• Regulation of extrathyroidal conversion of T4 to T3 by nutritional, hormonal, and illness-related factors.
Thyroid hormone deiodinases

- **Type I 5'-deiodinase (D1):** liver, kidneys, and muscle, activity is reduced in hypothyroidism
- **Type II 5'-deiodinase (D2):** thyroid, heart, and skeletal muscle. *Produces the majority of circulating T3 in humans.* activity is increased in hypothyroidism
- **Type III 5-deiodinase (D3):** inactivates T4. In placenta, developing brain, and skin
The role of thyroxine (T₄) and triiodothyronine (T₃) in the regulation of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). Thyroidal T₄ must be converted to T₃ to produce its effects. This conversion may take place in the thyroid (T), liver (L), and kidney (K) and is catalyzed either by the propylthiouracil-sensitive iodothyronine 5'-deiodinase (D₁) or the propylthiouracil-insensitive iodothyronine 5'-deiodinase (D₂). D₂ is present in the human pituitary, central nervous system, thyroid (T), and skeletal muscle (SM) and may be present in cardiac muscle (CM). Somatotropin release–inhibiting hormone (SRIH) also is called somatostatin. (Modified from Larson PR, Davis TF, Hay ID: The thyroid gland. In Wilson JD, Foster DW, Kronenberg HM, Larson PR (eds): Williams Textbook of Endocrinology, 9th ed. Philadelphia, WB Saunders, 1998.)
• HYPOTHYROIDISM
CLINICAL MANIFESTATIONS

1. generalized slowing of metabolic processes:
   - fatigue
   - slow movement and slow speech
   - cold intolerance
   - constipation
   - weight gain (but not morbid obesity)
   - delayed relaxation of deep tendon reflexes
   - bradycardia
Accumulation of matrix glycosaminoglycans in the interstitial spaces:

- coarse hair and skin
- puffy face
- enlargement of the tongue
- hoarseness
Skin signs

Cool and pale.
dryness
Sweating is decreased
Hair loss, with brittle nails
Nonpitting edema (myxedema)
Eyes

Periorbital edema

Graves' ophthalmopathy may persist after treatment of Graves' hyperthyroidism.
- Pericardial effusion
- BP increases are small (< 150/100 mmHg)
- Hypercholesterolemia: decreased cholesterol metabolism
Gastrointestinal disorders

- Decreased gut motility: constipation.
- Decreased taste sensation
- Gastric atrophy due to the presence of antiparietal cell antibodies.
- Celiac disease is 4 x more common in hypothyroidism
- Modest weight gain due to decreased metabolic rate and accumulation of fluid (nonpitting edema).
- Marked obesity is not characteristic
- Ascites is rare
Reproductive abnormalities

• hypothyroid women: 77% had normal cycles, 16% had oligo- or amenorrhea, and 7% had hypermenorrhea-menorrhagia
  in normal women: 92%, 7%, and 1%.
• Decreased fertility: and increased likelihood for early abortion
• Hyperprolactinemia
Metabolic abnormalities

- Hyponatremia: reduction in free water clearance
- Reversible increases in s Cr in 20 - 90 %
- High Cholesterol: 56 %,
- High Cholesterol and TG: 34 %,
- High TG: 1.5 %
- 8.5 %: normal lipids
PRIMARY HYPOTHYROIDISM

• Subclinical hypothyroidism: high TSH with normal free T4 and T3

• Overt hypothyroidism: high TSH with low free T4
1. Chronic autoimmune (Hashimoto's) thyroiditis

The most common cause in iodine-sufficient areas of the world.

goitrous or atrophic,

Similar pathophysiology:

- Cytotoxic T cells may directly destroy thyroid cells.
• > 90% of pts have high serum ab’s to TG, TPO, or Na/I transporter.

• Ab’s block the action of TSH on the TSH receptor or are cytotoxic to thyroid cells.
Prevalence

- high serum TPO ab: 5% of adults and 15% of older women
- Subclinical hypothyroidism: 5%-15% (adults)
- Overt hypothyroidism: 0.1-2%
- Hypothyroidism: (5-8x) F > M
Susceptibility and risk factors

• more common in older women
• most common cause of hypothyroidism in children
• genetic susceptibility
• Turner's syndrome and Down syndrome associated with a higher rates
2. iatrogenic disease

1. Thyroidectomy: 2-4 wks after total thyroidectomy.

2. RAI Rx: mostly in first yr, the rest become hypothyroid at a rate of 0.5 - 2 % / yr.

3. External neck irradiation: subclinical hypothyroidism **several years** before developing overt disease.
3. Iodine

Iodine deficiency is the most common cause of hypothyroidism (and goiter) worldwide.
- defined as an iodine intake < 100 mcg/day
• The excess iodine sources:
  - cough medicines
  - kelp tablets
  - iodine-containing substances (Betadine)
  - amiodarone
  - radiographic contrast agents
4. Drugs

• Methimazole and PTU
• Ethionamide: an antimycobacterial drug. structurally similar to methimazole
• Lithium carbonate
• amiodarone
• interferon alfa
• interleukin-2
5. Rare Causes

- Infiltrative disease: fibrous thyroiditis (Reidel's thyroiditis), hemochromatosis, scleroderma, leukemia.
- Infections: TB and Pneumocystis carinii
- Sarcoidosis
DIAGNOSIS

• Primary hypothyroidism: high serum TSH and a low serum free T4
  - high TSH and a nl FT4 = subclinical hypothyroidism

• Central hypothyroidism: low T4 and a TSH that is not appropriately elevated
Rx of hypothyroidism

- T4 usual replacement dose 1.6 mcg/kg
- Dose adjustment: 6-8 weeks later.
- Once euthyroid: f/u every 6-12 months
Myxedema coma

- decreased mental status, hypothermia, and bradycardia
- Rx on clinical suspicion without waiting for laboratory results
TREATMENT of Myxedema

• Mortality rate is high 30 -40 % :
  - Elderly patients
  - cardiac complications
  - reduced consciousness
  - persistent hypothermia
  - sepsis
Treatment

- Thyroid hormone (T4 200-400 mcg loading followed by 1.6 mcg/kg daily),
- supportive measures
- glucocorticoids in stress doses
Hyperthyroidism
SKIN

- warm and smooth

• Sweating

• Onycholysis, and softening of the nails.

• Hyperpigmentation in severe cases: increased cortisol metabolism, leading to increased ACTH secretion

• Pruritus

• Vitiligo and alopecia areata

• Thinning of the hair
• **Infiltrative dermopathy** in pts with Graves'
• The most common site is on the shins: **raised**, hyperpigmented, violaceous, orange-peel textured papules
EYES

- Lid lag and retraction
- Proptosis (exophthalmos)
- Ophthalmopathy: more common in smokers
- Optic neuropathy and even blindness
CARDIOVASCULAR

• sysHTN is common
• High output CHF
• AF: 10 - 20 % of pts, more common in elderly
• Subclinical hyperthyroidism: 3-fold increased risk of AF
GASTROINTESTINAL

• Weight loss: increased metabolic rate (hypermetabolism), and increased gut motility.
• Celiac disease is more prevalent in Graves'
• Anorexia may be prominent in elderly
• Vomiting and abdominal pain
• Dysphagia due to goiter
• Abnormal LFT (high alk phosphatase, and rarely cholestasis)
BONE

• T4/T3 **stimulate bone resorption**
• Alk phosphatase and osteocalcin are high
• may lead to hypercalcemia
• The net effect is osteoporosis
NEUROPSYCHIATRIC

- psychosis, agitation, and depression
- Anxiety, restlessness, irritability, and emotional lability
- Insomnia
Physical examination

- Stare (lid retraction) and lid lag
- The skin is warm and moist
- Hair: thin and fine
- Tachycardia
- Sys HTN
• Tremor, proximal muscle weakness, and hyperreflexia
• Exophthalmos
• infiltrative dermopathy (pretibial myxedema) occur only in patients with Graves' disease
THYROID FUNCTION TESTS

The best screening test: serum TSH
If TSH is normal: hyperthyroidism is very unlikely
Overt hyperthyroidism

• low TSH and high free T4 and T3

• T3-toxicosis:
  - disproportionate increase in thyroidal T3 secretion
  - increased conversion of T4 to T3
RADIOIODINE UPTAKE

1 • high radioiodine uptake: intathyroidal synthesis of hormone

2 • low (nearly absent) radioiodine uptake:
   a - inflammation and destruction of thyroid tissue
   b - extrathyroidal source of thyroid hormone.
• Treatment of Graves Hyperthyroidism
Thionamides

Methimazole is preferred:
- longer duration of action
- more rapid efficacy,
- lower incidence of s/e

PTU is preferred during pregnancy

• The goal of Rx: euthyroid state within 3 - 8 wks
Radioiodine ablation

- First line Rx in USA
- Associated with increased risk of worsening Graves' ophthalmopathy

• Primary Rx: mild, well-tolerated hyperthyroidism.
• Pts are pretreated with a thionamide if:
  - Not tolerating hyperthyroidism well
  - Elderly
  - Underlying heart disease
Surgery/indications

- obstructive goiter / very large goiter
- pregnant women who are allergic to ATD
- pts who have allergies or poor compliance on antithyroid drugs but refuse RAI
- coexisting suspicious or malignant thyroid nodule
- Pts who want rapid euthyroidism
• Steroid use and S/E
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<th>Equiv. dose</th>
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<th>Duration</th>
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<tr>
<td>Cortisol 20</td>
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<tr>
<td>HC 20</td>
<td>1</td>
<td>1</td>
<td>8 to 12</td>
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<tr>
<td>Prednisone 5</td>
<td>4</td>
<td>0.8</td>
<td>12 to 36</td>
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<tr>
<td>Prednisolone 5</td>
<td>4</td>
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<td>Methylpredn 4</td>
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<td>0.5</td>
<td>12 to 36</td>
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<tr>
<td>Triamcinolone 4</td>
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<td>0</td>
<td>12 to 36</td>
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<td>Fludrocortisone Δ</td>
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<td>125</td>
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<tr>
<td>Dexa 0.75</td>
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<td>36 to 72</td>
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</table>
S/E steroids

- Dermatologic and soft tissue
- Skin thinning and purpura
- Cushingoid appearance
- Alopecia
- Acne
- Hirsutism
- Striae
- Hypertrichosis
• Eye
• Posterior subcapsular cataract
• Elevated intraocular pressure/glaucoma
• Exophthalmos
- Cardiovascular
- Arrhythmias (with intravenous pulse therapy)
- Hypertension
- Perturbations of serum lipoproteins
- Premature atherosclerotic disease
• Gastrointestinal
• Gastritis
• Peptic ulcer disease
• Pancreatitis
• Steatohepatitis
• Visceral perforation
• Renal
• Hypokalemia
• Fluid volume shifts

• Genitourinary and reproductive
• Amenorrhea/infertility
• Intrauterine growth retardation
• Bone
• Osteoporosis
• Avascular necrosis
• Muscle
• Myopathy
• Neuropsychiatric
• Euphoria
• Dysphoria/depression
• Insomnia/akathisia
• Mania/Psychosis
• Pseudotumor cerebri
• Endocrine
• Diabetes mellitus
• Hypothalamic-pituitary-adrenal insufficiency
• Infectious disease
• Heightened risk of typical infections
• Opportunistic infections
• Herpes zoster
Diabetes Mellitus
Estimated prevalence of diabetes worldwide in 2025

A projected 300 million people with diabetes worldwide by 2025

Symptoms

- Polyuria, increased frequency of urination, nocturia.
- Increased thirst, and dry mouth
- Weight loss
- Blurred vision
- Numbness in fingers and toes
- Fatigue
- Impotence (in some men)
Signs

• Weight loss: muscle weakness
• Decreases sensation
• Loss of tendon reflexes
• Foot Inter-digital fungal infections
• Retinal changes by fundoscopy
Criteria for the diagnosis of diabetes

1. A1C ≥6.5 percent. *

2. FPG ≥126 mg/dL. Fasting is defined as no caloric intake for at least 8 h.*

3. Two-hour plasma glucose ≥200 mg/dL during an OGTT. 75 g anhydrous glucose dissolved in water.*

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL.

* In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.
Type 1 diabetes
A. Immune-mediated
B. Idiopathic

Type 2 diabetes

Other specific types
A. Genetic defects of beta cell function
   1. Chromosome 12, hepatocyte nuclear factor (HNF)-1-alpha (MODY3)
   2. Chromosome 7, glucokinase (MODY2)
   3. Chromosome 20, HNF-4-alpha (MODY1)
   4. Chromosome 13, insulin promoter factor-1 (IPF-1MODY4)
   5. Chromosome 17, HNF-1-beta (MODY5)
   6. Chromosome 2, NeuroD1 (MODY6)
   7. Mitochondrial DNA
   8. Others
B. Genetic defects in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
   4. Lipoatrophic diabetes
   5. Others
C. Diseases of the exocrine pancreas
   1. Pancreatitis
   2. Trauma/pancreatectomy
   3. Neoplasia
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculous pancreatopathy
   7. Others
D. Endocrinopathies
   1. Acromegaly
   2. Cushing's syndrome
   3. Glucagonoma
   4. Pheochromocytoma
   5. Hyperthyroidism
   6. Somatostatinoma
   7. Aldosteronoma
   8. Others

Classification of Diabetes Mellitus Based Upon the 2004 Expert Committee-II

E. Drug- or chemical-induced
   1. Vacor
   2. Pentamidine
   3. Nicotinic acid
   4. Glucocorticoids
   5. Thyroid hormone
   6. Diazoxide
   7. Beta-adrenergic agonists
   8. Thiazides (minimal effect with low dose therapy)
   9. Phenytoin
   10. Interferon alfa
   11. Others

F. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others

G. Uncommon forms of immune-mediated diabetes
   1. "Stiff man" syndrome
   2. Anti-insulin receptor antibodies
   3. Others

H. Other genetic syndromes sometimes associated with diabetes
   1. Down syndrome
   2. Klinefelter syndrome
   3. Turner syndrome
   4. Wolfram syndrome — diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD)
   5. Freidrich ataxia
   6. Huntington chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Porphyria
   10. Prader-Willi syndrome
   11. Others

Gestational diabetes mellitus

MAJOR RISK FACTORS (Type 2 DM)

- Family history of diabetes
- Overweight (BMI > 25 kg/m²)
- Physical inactivity
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans)
- Previously identified IFG or IGT
- History of GDM or delivery of a baby weighing >9 lbs
- Signs of insulin resistance or conditions associated with insulin resistance:
  * Hypertension (140/90 mmHg in adults)
  * HDL cholesterol 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l)
  * Polycystic ovary syndrome
  * Acanthosis nigricans
In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.
Development of Type 2 Diabetes: A Long-term Process

Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.
ROLE OF DIET, OBESITY, AND INFLAMMATION

• Increasing weight and less exercise

• Obesity epidemic

• Increasing T2DM in children and adolescents
Importance of body weight and exercise on development of type 2 diabetes
Adjusted incidence of type 2 diabetes mellitus in 5990 men in relation to body mass index (BMI, in kg/m²) and the level of physical activity (in kcal/wk). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for men with a BMI below 24. Data from Helmerich, SP, Ragland, DR, Leung, RW, Paffenbarger, PS, N Engl J Med 1991; 325:147.
3234 obese (average BMI 34 kg/m²) subjects aged 25-85 yrs at high risk for DM (Obese+ IFG/IGT) were randomized to:

• 1. **Intensive lifestyle changes** with the aim of reducing weight by 7% through a low-fat diet and exercise for 150 minutes per week.

• 2. Treatment with **metformin** (850 mg BID) **plus information on diet and exercise**

• 3. **Placebo plus information on diet** and exercise
The diet and exercise group lost an average of 6.8 kg (7%) of weight in the first year.

At three years, fewer patients in this group developed diabetes (14 versus 22 and 29 percent in the metformin and placebo groups, respectively).

Lifestyle intervention was effective in men and women in all age groups and in all ethnic groups.
Management of Type2DM

• 1. Lifestyle modifications:
  • - Medical nutrition therapy
  • - increased physical activity
  • - weight reduction

• 2. Oral Drug Therapy/Noninsulin sc therapy

• 3. Insulin therapy
complications

• **Acute:**
  
  • 1. Diabetic Ketoacidosis
  
  • 2. Hyperglycemic Hyperosmolar state
  
  • 3. Hypoglycemia: (patients under treatment)
EPIDEMIOLOGY

- DKA: usu. with type1DM.
- Also in T2DM under extreme stress: serious infection, trauma, cardiovascular events.
- DKA is more common in younger (<65 years) diabetic patients and F>M.
- Mortality in DKA: due to the underlying precipitating illness.
• The prognosis of DKA is worse at the extremes of age and in the presence of coma and hypotension.

• **HHS**:
  - older than 65 yrs with type 2 DM.
  - Mortality is higher :range 5 -20 % (mostly due to the underlying illness or comorbidity)
PATHOGENESIS

- Two hormonal abnormalities:
  - **Insulin** deficiency and/or resistance.
  - **Glucagon** excess (from removal of the normal suppressive effect of insulin)

- Increased secretion of **catecholamines and cortisol** can contribute
CLINICAL PRESENTATION

• DKA usually evolves rapidly / 24 hr
• HHS presents with polyuria, polydipsia, and weight loss for several days
• Later : lethargy, focal signs, and obtundation, and coma
• Neurological symptoms are most common in HHS
• Hyperventilation and abdominal pain are limited to DKA.
# Diagnostic criteria for (DKA) and (HHS)

<table>
<thead>
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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>HHS</th>
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<td><strong>Plasma glucose (mg/dL)</strong></td>
<td>&gt;250</td>
<td>&gt;250</td>
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<td><strong>Arterial pH</strong></td>
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<td>7.00-7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
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<tr>
<td><strong>Serum bicarbonate (mEq/L)</strong></td>
<td>15-18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;18</td>
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<td><strong>Urine ketones</strong></td>
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<td>Positive</td>
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<tr>
<td><strong>Small</strong></td>
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<tr>
<td><strong>Small</strong></td>
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<td><strong>Effective s. osm. (mOsm/kg)</strong></td>
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<td><strong>Mental status</strong></td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td></td>
</tr>
</tbody>
</table>

- Calculation: $2[\text{measured Na (mEq/L)}] + \text{glucose (mg/dL)}/18$.
- $\Delta$ Calculation: $(\text{Na}^+) - (\text{Cl}^- + \text{HCO}_3^-)$ (mEq/L).
Management - DKA

• 1. Underlying cause
• 2. IV Fluids
• 3. Insulin Therapy
• 4. Electrolyte management
• 5. Bicarbonate Therapy
Hypoglycemia

• With insulin or insulin secretagogues Rx.
• Higher risk in type I compared to type II.
• Higher risk with tight/near normal glycemic control
• Hypoglycemia unawareness with repeated hypoglycemia.
• Severe prolonged hypoglycemia can lead to permanent neurological deficit
Symptoms/signs

- Feeling of hunger
- Palpitations
- Sweating
- Tremors
- Reduced concentration
- Blurred vision
- Dizziness
- Seizures
- Coma
hypoglycemia

- Management
- Mild-moderate: self, oral glucose (15-20 gm)
- Severe (loss of consciousness): needs help by others, IV glucose, glucagon injection
• Thank you