Chapter 8

Pancreatic Hormones and Metabolic Regulations

Nam Deuk Kim, Ph.D.
1. The Endocrine Pancreas

The pancreas is *two glands* in one:

- Digestive gland
- Endocrine gland

**Digestive Gland**

- The *exocrine* tissue of the pancreas, which is concerned solely with *digestion*, secretes *alkaline pancreatic juice* rich in *digestive enzymes* into the *duodenum* through the pancreatic *duct* to aid digestion.
Endocrine Gland

The *endocrine* tissue of the pancreas consists of multiple *small clusters of cells* scattered throughout the gland called the *pancreatic islets* or *Islets of Langerhans* which discharge secretions *directly* into the bloodstream.

- Each islet is composed of several different types of cells, the *main* ones being
  - Islet *Alpha cells*
    - secrete *glucagon*
    - *raises* blood glucose
  - Islet *Beta cells*
    - secrete *insulin*
    - *lowers* blood glucose
  - Islet *Delta cells*
    - secrete *somatostatin*
    - *inhibits* secretion of glucagon and insulin
Fig. 11-2. (a) Schematic representation of the number and distribution of insulin-, glucagon-, and somatostatin-containing cells in the normal rat islet. Note the characteristic position of most glucagon- and somatostatin-containing cells at the periphery of the islet, surrounding the centrally located insulin-containing cells. (b) Schematic representation of the number and distribution of insulin-, glucagon-, and somatostatin-containing cells in the normal human islet. This pattern divides the total islet mass into smaller subunits, each of which contains a center formed mainly of insulin cells and surrounded by glucagon and somatostatin cells. Cell types for which a definite function and morphology have not been determined are intentionally omitted.
Factors affecting blood glucose concentration

2. Intermediary Metabolism

Factors that increase blood glucose

- Glucose absorption from digestive tract
- Hepatic glucose production:
  - Through glycogenolysis of stored glycogen
  - Through gluconeogenesis

Factors that decrease blood glucose

- Transport of glucose into cells:
  - For utilization for energy production
  - For storage
    - as glycogen through glycogenesis
    - as triglycerides
- Urinary excretion of glucose (occurs only abnormally, when blood glucose level becomes so high it exceeds the reabsorptive capacity of kidney tubules during urine formation)

Factors subject to hormonal control to maintain blood glucose level

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Fig. 11-3. General scheme of hormonal regulation of hepatic carbohydrate metabolism. The more prominent actions of insulin (solid arrows) and glucagon (open arrows) are indicated.
Fig. 11-4. General (top) and specific (bottom) scheme of amino acid–keto acid transamination.
3. Insulin

- Influences carbohydrate, protein, and fat metabolism
- Chief sites of influence are on liver cells, muscle, and adipose tissues (fat)
- Promotes entrance of glucose into cells
- Favors utilization of glucose as source of energy
- Promotes storage of glucose as glycogen
- In adipose tissue, it favors conversion of glucose into fat (triglycerides) and storage of newly formed triglyceride within fat cells
- Promotes entry of amino acids into cells and stimulates protein synthesis
- The main stimulus for insulin release is elevation of glucose in blood, as it occurs after a meal
Electron Microscopy Of The Beta Cell

Demonstration of Insulin in the Pancreatic Islets

- **Lumen of Capillary**
- **Nucleus of Capillary Endothelial Cell**
- **Insulin Granule Disintegrating in Space Between Cell and Capillary**
- **Basement Membrane of Beta Cell**
- **Insulin Granule Being Extruded**
- **Capsule of Insulin Granule Fusing With Cell Membrane**
- **Insulin Granules Enclosed in Capsular Sac**
- **Mitochondria**
- **Golgi Apparatus**
- **Cell Nucleus**

**Schematic Reconstruction of Portion of Beta Cell Based on Electron Microscopic Studies**

**Human**

**Dog**

**Cat**

**Electron Microscopic Appearance of Insulin Granules of Various Species**

**Insulin Demonstrated in Beta Cells of Rabbit Islet by Means of Insulin-Specific Antibodies Which Have Been Made Fluorescent by Addition of Fluorescin**

**Dextrose Injected (5 g/kg Body Weight), This Stimulates Output of Insulin**

**1/2 Hour After Intraperitoneal Dextrose Injection: Beta Cells Depleted of Insulin Granules**

**6 Hours After Injection: Insulin Granules Restored in Beta Cells; Islet Section Has Resting Stage Appearance**
Chemical Structure of Insulin and Glucagon

**Insulin (Beef)**

**Glucagon**
Fig. 11-5. Comparative primary structures of the vertebrate insulins.
Fig. 11-15. **Cellular events in glucose-induced insulin secretion in pancreatic β cells.** Glucose is transported into the cell by the glucose transporter GLUT2. It is then phosphorylated by glucokinase. Further glucose metabolism generates signals that inhibit the ATP-sensitive K⁺ channels, resulting in membrane depolarization. This activates the voltage-gated Ca²⁺ channels and increases intracellular Ca²⁺ levels. Ca²⁺ in turn triggers the fusion of pre-stored insulin vesicles with the plasma membrane.
Fig. 11-6. Primary structure of porcine proinsulin.
Metabolic actions of insulin in striated muscle, adipose tissue, and liver.
Uptake of Glucose by Different Cells
Insulin action on a target cell
Fig. 11-7. Diagrammatic structure of the insulin receptor, and schematic representation of insulin receptor stimulation, activation of insulin receptor substrate 1 (IRS-1), and binding and activation of PI-3 kinase by IRS-1. PIP3 is generated as a result of PI-3-kinase activity and mediates activation of several downstream effectors.19
Fig. 11-8. Insulin-activated intracellular signal transduction pathways.
Fig. 11-9. General scheme for the control of glycogen synthesis and degradation.
Glucose Transporter (GLUT)

- **Six** forms of GLUT
  - GLUT-1: across the blood-brain barrier
  - GLUT-2: transport glucose in the kidney as co-transport carriers
  - GLUT-3: main transporter in the neurons
  - GLUT-4: most cells of the body; *only at the binding of insulin and controlled; Insulin promotes glucose uptake by transporter recruitment.*
  - GLUT-5: small intestine
  - GLUT-6: most cells of the body
Fig. 11-10. Insulin activation of glucose transporters (GLUT-4).
4. Glucagon

![Primary structure of mammalian glucagon and related structures of avian glucagonos.](image)

Fig. 11-11. Primary structure of mammalian glucagon and related structures of avian glucagonos.
• **Glucagon** is structurally related to secretin, GIP, and VIP.
  - a hyperglycemic factor
  - a single-chain polypeptide of **29 aa**
  - **Glucagon** is essential for the complete metabolic syndrome of severe diabetes, previously attributed entirely to the direct consequences of insulin deficiency.

• **Glucagon** stimulates glycogenolysis, gluconeogenesis, and lipolysis.

• **Glucagon** activates receptors coupled to cAMP formation in hepatocytes and adipocytes.
Fig. 11-12. **Glucagon** activation of **hepatic adenylate cyclase** and the subsequent events in glucose formation.
5. Other Pancreatic Peptide Hormones

1) Somatostain (SST): also known as growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF)

- a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones.

- Secreted by:
  - Digestive system: stomach, intestine, D cells of the pancreas
  - Brain: produced by neuroendocrine neurons of the paraventricular nucleus of the hypothalamus.
• Somatostatin has **two active forms** produced by alternative cleavage of a single preproprotein: **one of 14 amino acids, the other of 28 amino acids**.

• In all vertebrates, there exists six different somatostatin genes which have been named SS1, SS2, SS3, SS4, SS5, and SS6.

• **Tetrapods** only possess SS1 and SS2, while **teleost fish** possess SS1 - SS6.

• The six different genes along with the five different somatostatin receptors allows somatostatin to possess a large range of functions.
Action mechanism of D cell and somatostatin: D cell is visible at upper-right, and somatostatin is represented by middle arrow pointing left.
2) **Pancreatic polypeptide (PP)** is secreted by pancreatic F cells
- A linear polypeptide
- Physiological functions: not clearly delineated

![Primary structure of human pancreatic polypeptide. Variations within ovine, porcine, and bovine PP sequences are shown.](image)

Fig. 11-13. Primary structure of human *pancreatic polypeptide*. Variations within ovine, porcine, and bovine PP sequences are shown.
6. Adipocytokines (Adipokines)

- Adipocyte-derived hormones, called adipokines or adipocytokines
- Critically important in regulating energy and glucose homeostasis.
- **Leptin**: the most intensely studied adipokine
  1) **Leptin** is an adiposity signal and suppresses food intake.
  2) **Adiponectin** is an endogenous insulin-sensitizing factor.
  3) **Resistin** can induce hepatic insulin resistance.
ENERGY BALANCE

• First law of thermodynamics
  – Energy cannot be created or destroyed
• Energy input-output balance
• Energy input
  – Energy in ingested food
• Energy output
  – External work
    • Energy expended when skeletal muscles are contracted to move external objects or to move body in relation to the environment
  – Internal work
    • All other forms of biological energy expenditure that do not accomplish mechanical work outside the body
      – Skeletal muscle activity used for purposes other than external work (postural maintenance contractions, shivering)
      – All the energy-expending activities that go on continuously just to sustain life
Energy Conversion

- Energy from nutrients that is not used energize work
  - Transformed into thermal energy or heat
    - Only about 25% of chemical energy in foods is harnessed to do biological work
    - Remainder is converted to heat
      - Much of this heat is used to maintain body temperatures
Metabolic Rate

Metabolic rate = energy expenditure/unit of time

- Basal metabolic rate (BMR)
  - Minimal waking rate of internal energy expenditure
  - Measured under following conditions
    - Person should be at physical rest
    - Person should be at mental rest
      - Minimizes skeletal muscle tone
      - Prevent rise in epinephrine
    - Measurement should be performed at a comfortable room temperature
      - Shivering can greatly increase heat production
    - Person should not have eaten any food within 12 hours before BMR determination
      - Avoid diet-induced thermogenesis
<table>
<thead>
<tr>
<th>FORM OF ACTIVITY</th>
<th>ENERGY EXPENDITURE (kcal/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping</td>
<td>65</td>
</tr>
<tr>
<td>Awake, lying still</td>
<td>77</td>
</tr>
<tr>
<td>Sitting at rest</td>
<td>100</td>
</tr>
<tr>
<td>Standing relaxed</td>
<td>105</td>
</tr>
<tr>
<td>Getting dressed</td>
<td>118</td>
</tr>
<tr>
<td>Typewriting</td>
<td>140</td>
</tr>
<tr>
<td>Walking slowly on level (2.6 mi/hr)</td>
<td>200</td>
</tr>
<tr>
<td>Carpentry, painting a house</td>
<td>240</td>
</tr>
<tr>
<td>Sexual intercourse</td>
<td>280</td>
</tr>
<tr>
<td>Bicycling on level (5.5 mi/hr)</td>
<td>304</td>
</tr>
<tr>
<td>Shoveling snow, sawing wood</td>
<td>480</td>
</tr>
<tr>
<td>Swimming</td>
<td>500</td>
</tr>
<tr>
<td>Jogging (5.3 mi/hr)</td>
<td>570</td>
</tr>
<tr>
<td>Rowing (20 strokes/min)</td>
<td>828</td>
</tr>
<tr>
<td>Walking up stairs</td>
<td>1100</td>
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</tbody>
</table>
Metabolic Rate

• **Measurement**
  – Direct calorimetry
    • Not practical
      – Calorimeter chamber is expensive and takes up a lot of space
  – **Indirect calorimetry**
    • Measures person’s O$_2$ uptake per unit of time

• **Factors influencing BMR**
  – Thyroid hormone
    • Primary determinant of BMR
  – Epinephrine
    • Increases BMR
Energy Balance

• Three possible states of energy balance
  – Neutral energy balance
    • Energy input = energy output
    • Body weight remains constant
  – Positive energy balance
    • Energy input is greater than energy output
    • Energy not used is stored primarily as adipose
    • Body weight increases
  – Negative energy balance
    • Energy input is less than energy output
    • Body must use stored energy to supply energy needs
    • Body weight decreases
Control of Food Intake and Energy Balance

• Food intake
  – Primarily controlled by hypothalamus
    • Appetite center
      – Signals give rise to hunger and promote eating
    • Satiety center
      – Signals lead to sensation of fullness and suppress eating

• Arcuate nucleus of hypothalamus
  – Contains two clusters of appetite regulating neurons
    • Neurons that secrete neuropeptide Y (NPY)
      – Increases appetite and food intake
    • Neurons that secrete melanocortins
      – Suppress appetite and food intake
Control of Food Intake and Energy Balance

- **Adipocytes**
  - Secrete hormone **leptin**
    - One of the most important **adipokines** (*Table 17-2*)
    - Reduces appetite and decreases food consumption
      - Inhibits NPY-secreting neurons
      - Stimulates melanocortins-secreting neurons

- **Insulin**
  - Hormone secreted by pancreas in response to rise in glucose concentration

- **Ghrelin**
  - Hunger hormone
  - Appetite stimulator produced by **stomach** and regulated by feeding status
  - Stimulates the hypothalamic NPY-secreting neurons
<table>
<thead>
<tr>
<th>ADIPOKINE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Released from stored fat; suppresses appetite; dominant long-term regulator of energy balance and body weight</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Secretion from adipocytes suppressed in obesity; promotes fatty acid oxidation by muscle; increases sensitivity to insulin; decreases body weight by increasing energy expenditure; has anti-inflammatory actions</td>
</tr>
<tr>
<td>Resistin</td>
<td>Released primarily in obesity; leads to insulin resistance</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Released primarily from visceral fat; stimulates glucose uptake; binds with insulin receptor at a site distinct from the insulin-binding site</td>
</tr>
<tr>
<td>Tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6)</td>
<td>Promote low-level inflammation in fat and throughout body</td>
</tr>
</tbody>
</table>

Table 17-2, p. 638
Control of Food Intake and Energy Balance

- **PYY$_{3-36}$**
  - Produced by small and large intestines
  - At lowest level before meal
  - Rises during meals and signals satiety
  - Believer to be an important mealtime terminator

- **Lateral hypothalamus area (LHA)**
  - Secretes orexins
    - Strong stimulators of food intake

- **Paraventricular nucleus (PVN)**
  - Releases neuropeptides that decrease food intake
Control of Food Intake and Energy Balance

• **Nucleus tractus solitarius (NTS)**
  – In brain stem
  – Serves as satiety center
  – Plays key role in short-term control of meals
  – Decrease food intake

• **Psychological and environmental factors** can also influence food intake above and beyond internal signals that control feeding behavior
Factors influence food intake

- Neurons that secrete neuropeptide Y (NPY): Increases appetite and food intake; other factors
  - Ghrelin
  - Orexins from LHA
  - Visfatin

- Neurons that secrete melanocortins: Suppress appetite and food intake; other factors
  - Leptin
  - Adiponectin
  - PYY\textsubscript{3-36}
  - Neuropeptides from PVN
  - NTS
  - Insulin
  - CRH
7. Control of Pancreatic Islet Function

- Insulin secretion: controlled by endocrine, neural, and metabolic factors.
- **Blood glucose** is the most important regulator.
- Amino acid arginine and leucine, as well as such keto acids as acetoacetic acid: also stimulatory to insulin secretion.
- Most amino acids stimulate (aminogenic action) the secretion of insulin and glucagon.

Fig. 11-14. (a) The effect of a large carbohydrate meal on the plasma concentration of pancreatic glucagon, insulin, and glucose in 11 normal humans. (b) The effect of an infusion of arginine on the peripheral venous plasma levels of pancreatic glucagon, insulin, and glucose in normal humans.
### TABLE 11.1 Pathology of the endocrine pancreas

**Type I (insulin-dependent diabetes mellitus, IDDM) [15]**
- Juvenile-onset diabetes. Viral-induced β-cell destruction
- Cytotoxic autoantibodies to β cells lead to β-cell destruction [24]

**Type II (non-insulin-dependent diabetes mellitus, NIDDM; previously called adult (maturity) onset diabetes)**
- Insulin resistance [1, 3, 14, 51]
  - Pre-receptor resistance
    - Antibodies against insulin
    - Mutant insulin structures
      - Defect in primary structure of insulin β chain at one or more positions
      - Familial hyperproinsulinemia
        - B-C proinsulin: mutation at the cleavage site between the B chain and the connecting (C) peptide
        - A-C proinsulin: mutation at the cleavage site between the A chain and the connecting (C) peptide
  - Receptor resistance
    - Type A. Decrease in insulin receptor number and/or affinity for the hormone
      - Point mutation in insulin receptor gene prevents processing of the receptor precursor
      - Impaired expression of receptor tyrosine kinase activity [47]
      - Point mutation blocks insertion of mature receptor into plasma membrane
    - Type B. Receptor blocked by circulatory antibodies to the receptor
      - Leprechaunism
        - An autosomal recessively inherited disorder of insulin function that leads to severe intrauterine growth retardation, characteristic dysmorphic features and a disturbed glucose homeostasis. The process underlying this disease is a structural defect in the insulin receptor
  - Post-receptor resistance
    - Decreased capacity of pancreatic β cells to compensate for the underlying insulin resistance by increased secretion of insulin [51]
      - Possible underexpression (down-regulation) of β-cell glucose transporters (therefore failure to recognize and respond to hyperglycemia)
      - Autoantibodies to the GLUT2 glucose transporter of β cells [24]
      - Mutation of the glucokinase gene may prevent uptake and metabolism of glucose necessary for the mechanism of insulin secretion. May be responsible for a young onset type II diabetes (MODY) [6, 25]

**Islet cell tumors**
- Insulinoma. Excess insulin secretion from a β-cell pancreatic tumor (severe hypoglycemia)
- Glucagonoma syndrome. Excess glucagon secretion from an α-cell pancreatic tumor
- Somatostatinoma. Excess somatostatin secretion from D-cell pancreatic tumor

**Hypoglycemic disorders**
- Hypoglucaagonemia (isolated glucagon deficiency). Possibly due to autosomal recessive inheritance
- Hyperinsulinemia (β-cell tumor)
- Antibodies (stimulatory) to the insulin receptor (increased glucose uptake by cells)
DIABETES MELLITUS: TWO TYPES

• Very common and important *metabolic* disease
• There are *two major groups*, depending on *cause*
  1. **Type 1 Diabetes;** cause is *insulin deficiency*
  2. **Type 2 Diabetes;** typically an *adult-onset diabetes; cause is inadequate response to insulin;* becoming more common in children.
• Manifestation is *elevated glucose levels* in blood called *hyperglycemia*
**TABLE 22.1**

**Comparison of two major types of diabetes mellitus**

<table>
<thead>
<tr>
<th></th>
<th><strong>TYPE 1</strong></th>
<th><strong>TYPE 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual age of onset</td>
<td>Childhood Young adulthood</td>
<td>Middle age or later</td>
</tr>
<tr>
<td>Body build</td>
<td>Normal</td>
<td>Overweight</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>Absent or low</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Complications</td>
<td>Ketoacidosis</td>
<td>Hyperosmolar coma</td>
</tr>
<tr>
<td>Response to insulin</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Response to oral antidiabetic drugs</td>
<td>Unresponsive</td>
<td>Responsive</td>
</tr>
</tbody>
</table>
Metabolic staging of type 1 diabetes mellitus

주요 원인:
1. 자가면역
   - 만성갑상선염
   - Graves 병
   - 근무력증
   - Addison 병
   - 악성빈혈

2. 환경 적요인
   - 바이러스
   - 화학물질(알록산, 스트렙토조토신, 쥐약 등)
   - 우유(분유), 단백질
Type 1 Diabetes Mellitus

• Occurs primarily in *children and young adults*
• As a result of damage to pancreatic islets, leading to *reduction or absence of insulin secretion*
• Often *follows a viral infection that destroys the pancreatic islets*
• *Abnormal immune* response may play part in causing disease as these patients have *autoantibodies* directed against their own cells
• May develop a *complication* called *diabetic ketosis*
• There is a *hereditary predisposition*
Metabolic Derangements

Type 1 Diabetes

Major metabolic derangements in type 1 diabetes mellitus.
Formation of Ketone Bodies

• In **Type 1**, fat deposition in adipose tissue is impaired and *body fat* is *metabolized* as a *source of energy*
• It *splits* first into a *fatty acid* and *glycerol*
• Further *chemical reactions* take place
• The *molecules* are *converted* by the *liver* into *compounds* called *ketone bodies*
• *Ketosis* results when there is an excess *accumulation of ketone bodies* in body
Fat Metabolism and Formation of Ketone Bodies

Structure of ketone bodies.

A  Condensation

B  Beta-hydroxybutyric acid

C  Acetone

An Introduction to Human Disease, 7th Edition
Leonard V. Crowley, M.D.
©2007 Jones and Bartlett Publishers
Fig. 11-16. Scheme of ketone biosynthesis: The hydroxymethylglutaryl-CoA cycle.
Type 2 Diabetes Mellitus

• It is by far the more common type
• More complex metabolic disease
• Occurs in older, overweight or obese adults; becoming more common in overweight/obese younger people
• Insulin secretion is normal or increased
• Tissues are insensitive or have impaired response to insulin
• Cause is not completely understood but weight reduction restores insulin responsiveness
• Islet function is not completely normal as pancreas is not able to increase insulin output to compensate for the insulin resistance
Metabolic staging of type 2 diabetes mellitus

1. Insulin Resistance
   a. Genetic defects of the insulin receptor and insulin signaling pathway
   b. Obesity and insulin resistance

2. β-Cell Dysfunction
1. Role of free fatty acids (FFAs)
2. Role of adipokines in insulin resistance
3. Role of the peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)) and thiazolidinediones (TZDs)
Type 2 Diabetes Mellitus

• May develop a *complication* called *hyperosmolar nonketotic coma* caused by marked *hyperglycemia*
• Is a *hereditary* disease where *genetic factors* play an even *greater* role
• *Children* of parents that have it are at significant *risk* of developing it
• *Incidence* in some populations as high as 40% (*example*: Pima Indians of Arizona)
Nonenzymatic Glycosylation

Advanced Glycosylation End Product (AGE)
Hyperosmolar Hyperglycemic Nonketotic Coma

Intracellular Hyperglycemia With Disturbances in Polyol Pathways

a. Increase of sorbitol and fructose
b. Increase of osmolarity
c. Increase of influx of water
d. Increase of osmotic cell injury
Sequence of metabolic derangements leading to diabetic coma in type 1 DM
Consequences of Insulin Deprivation

Glycosuria
Polyuria
Keto-aciduria
Mineral loss
Nitrogen loss

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Coma
Monitoring Control of Diabetes

Oral Glucose Tolerance Test

PATIENT FASTED OVERNIGHT; DRINKS 100 gm GLUCOSE IN 400 ml H2O
BLOOD SUGAR DETERMINED AT 0, ½, 1, 1½, 2 AND 2½ HOURS

β-CELL STIMULATION

BLOOD SUGAR mg/100 ml

DIABETES
DIABETES (?)
CRITICAL LEVELS
NORMAL

HOURS 1 2 3
당뇨, 미래의 재앙… 수백만 환자 합병증 덮치면 '건보론 감당 못해'
(조선일보 2013.3.24)

- 한국 성인 1,000만명이 당뇨증세
- 환자 320만명
- '단계 혈당장애 640만명 급증세'
- 고령화, 비만 영향
- 합병증: ‘국가 재앙’ 우려
- 환자 70% 혈당관리 소홀...
- 130만명, 치료도 안받아
- 30~44세 젊은 환자 절반은 자기가 걸린 줄도 몰라
- 유럽은 국가적 관리… 당뇨 교육받아야 건강보험 혜택

한국의 사망원인(2014)
1. Cancer (27.8%)
2. 심장질환
3. 뇌혈관질환
4. 자살
5. 당뇨병
6. 폐렴
7. 만성기관지질환
8. 간질환
9. 운수사고
10. 고혈압성 질환

혈당 상승시 혈액 속 당분이 과도하게 증가하여 혈청 당당간의 농도 차이가 발생, 뇌혈액순환 세동으로 미세혈관 전위, 혈관진화 설명 6선 7선 등이 발생하여 혈관 질환을 초래한다.

우리나라 당뇨병 환자 증가 현황

당뇨병과 공복 혈당 증가 기준
- 당뇨병: 8시간 급식 후 혈당이 126(mg/dL) 이상
- 공복 혈당 증가: 공복혈당이 100~125(mg/dL) 사이인 경우

※공복 혈당 증가: 급식 후 혈당이 정상치를 초과하지 않는 상태 당뇨병 혈당 단계
당뇨병 환자와 직접 단계 비율
자료: 대한당뇨병학회 '2012 한국인 당뇨병 연구 보고서'

당뇨병(%)  공복 혈당 정상(당뇨병 직전 단계, %)
18.4%  34.8
14.9  22.9
3.5  22.7
30~44세  45~64세  65세 이상

환자 70% 혈당관리 소홀…130만명, 치료도 안받아
30~44세 젊은 환자 절반은 자기가 절리 줄도 몰라
유럽은 국가적 관리… 당뇨 교육받아야 건강보험 혜택

◇ 당뇨병으로 인한 의료비 부담 급증
◇ 젊은 환자 절반이 모르고 지내
◇ 환자 70%, 제대로 혈당 관리 안 돼
◇ 국가적 당뇨병 관리 사업 필요

당뇨, 얼마나 무서운 병인가
심장병·뇌졸중·실명·신부전·치매…
합병증 증상 나타났을 때 이미 늦어

회복 경비로 발라야할 경우도 몸에 이상 없어도 검사 받아야

항병증 없이 이겨내는 법

환자 생활 습관만 바꿔도 약 없이 산다
매일 일정한 시간에 식사하고 걷기·자전거 등 가벼운 운동을
40대에서 50대가 되면 당뇨·고혈압 3배 급증(조선일보 2013.2.7)

연령별 고혈압·당뇨병 유병률
단위: %

- 고혈압
- 당뇨병

자료: 2010년 한국의료패널 기초분석 보고서(보건사회연구원)
Complications of Diabetes

1. Increased susceptibility to infection
2. Diabetic coma
3. Ketoacidosis
4. Hyperosmolar coma
5. Arteriosclerosis
6. Blindness
7. Renal failure
8. Peripheral neuritis
Long-term complication of Diabetes
Diabetic Nephropathy and Necrotizing Papillitis

Diabetic Neuropathy

Vascular Insufficiency In Diabetes
Other Causes of Hyperglycemia

Hyperglycemia: elevated blood glucose levels

- Other conditions may lead to impairment of glucose utilization and hyperglycemia, but they are less common than diabetes
- Chronic pancreatic disease: damage or destruction of pancreatic islets
- Endocrine diseases: overproduction of pituitary or adrenal hormones (they act to raise blood glucose)
- Ingestion of different drugs: as a side effect, glucose utilization is impaired
- Hereditary disease: carbohydrate metabolism is disturbed
Hypoglycemia in Diabetes

- The pancreas continually monitors the glucose and adjusts its output of insulin.
- In type 1 diabetes, the patient must adjust the dose of insulin to match the amount of carbohydrate to metabolize.
- If there is insufficient insulin, the glucose is high.
- If there is too much insulin, the glucose is low, a condition called hypoglycemia.

Two conditions predispose to hypoglycemia in a diabetic patient taking insulin.
Hypoglycemia in Diabetes

1. **Skipping a meal**: with reduced intake food, blood glucose falls; *carbohydrate intake is insufficient* in relation to amount *insulin*

2. **Vigorous exercise**: with increased activity, blood glucose falls, there is *increased glucose utilization*, and *relative excess of insulin*

- *Too much insulin* causes a *precipitous drop* in glucose, leading to *insulin shock*
Hypoglycemia in Diabetes

- Adrenal medulla responds by discharging epinephrine (adrenaline) which raises blood glucose.
- Neurologic manifestations appear if blood glucose continues to fall.

Other causes of hypoglycemia:
- Oral hypoglycemic drugs in type 2 diabetics.
- Self-administration of oral hypoglycemic drugs or insulin by emotionally disturbed person.
- Islet cell tumor.
**DIFFERENTIATION OF INSULIN SHOCK FROM KETOACIDOSIS AND HYPOSMOLAR COMA**

<table>
<thead>
<tr>
<th>DIAGNOSTIC FEATURE</th>
<th>INSULIN SHOCK</th>
<th>KETOACIDOSIS</th>
<th>HYPOSMOLAR COMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake</td>
<td>May be Insufficient</td>
<td>Normal or excessive</td>
<td>Normal or excessive</td>
</tr>
<tr>
<td>Insulin</td>
<td>Excessive</td>
<td>Insufficient</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Rapid</td>
<td>Gradual (several days)</td>
<td>Gradual (several days)</td>
</tr>
<tr>
<td>Skin</td>
<td>Cold sweat, pale</td>
<td>Dry and flushed</td>
<td>Dry and flushed</td>
</tr>
<tr>
<td>Respirations</td>
<td>Normal or shallow</td>
<td>Slow and deep</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Hyperactive</td>
<td>Depressed</td>
<td>Normal</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Rapid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal or slightly elevated</td>
<td>Low</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Glucose in urine</td>
<td>Absent</td>
<td>Large amount</td>
<td>Large amount</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Very low</td>
<td>High</td>
<td>Extremely high</td>
</tr>
<tr>
<td>Blood bicarbonate and pH</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Acetone in blood and urine</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Treatment of Diabetes

• Diet, where carbohydrate intake is controlled
• Type 1 diabetes also requires insulin, dosage being adjusted to control the level of blood glucose
• In type 2 diabetes, weight reduction and diet might be enough to manage condition
• If patient does not respond adequately to diet and exercise regimen, oral hypoglycemic drugs that promote release of insulin may be necessary
DRUG GROUPS

(Oral Hypoglycemic Agents)

- Insulin secretagogues
  - Sulfonylureas
  - Meglitinide analogue

- Insulin sensitizers
  - Biguanides

- α-glucosidase inhibitors

- Dipeptidyl Peptidase-IV inhibitors
  - Thiazolidinediones (TZD)