당뇨병의 진단 및 치료

2015년 3월 22일
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DIAGNOSIS AND CLASSIFICATION

Definition

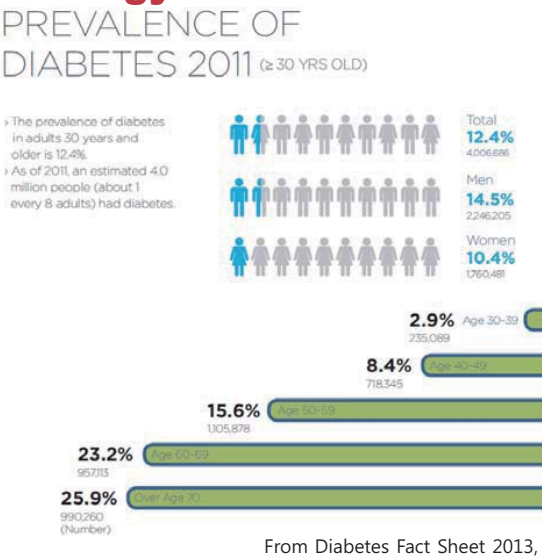
- **Diabetes Mellitus**
- 糖尿病

Definition (World Health Organization Report, 1999)

– Diabetes is characterized by **chronic hyperglycemia** together with disturbance in **carbohydrate, fat and protein metabolism** resulting from defects of **insulin secretion, insulin action or both**

DIAGNOSIS AND CLASSIFICATION

Epidemiology



From Diabetes Fact Sheet 2013, 대한당뇨병학회

MEMO

Diagnosis

1. ***A1c*** ≥ **6.5%**. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

OR

2. ***Fasting*** plasma glucose(FPG) ≥**126mg/dl**. Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h plasma glucose ≥**200mg/dl** during an ***OGTT***. The test should be performed as described by the World Health Organization, using a glucse load containing the equivalent of 75-g anhydrous glucose dissolved in water.

OR

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

※ In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day

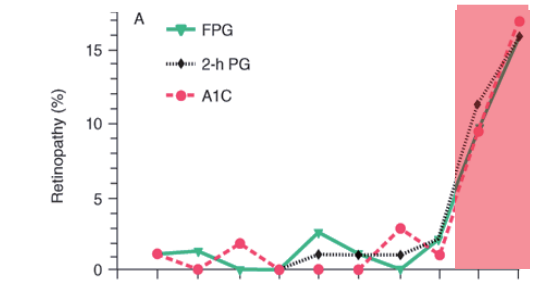
CASE VIGNETTE

1. 다음 중 당뇨병으로 진단이 가능한 경우가 **아닌** 것은?

1) 8시간 이상 공복을 유지하였으나 갈증이 심해서 생수를 마시고 1시간 뒤 측정한 혈당이 250 mg/dL 였다
2) 설명되지 않는 체중 감소로 시행한 당화 혈색소가 9.5% 였다
3) 1차로 검사한 공복혈당이 132 dg/dL 여서 다른 날 재검한 공복혈당이 140 mg/dL 였다
4) 특별한 증상이 없으나 점심 식사 후 우연히 측정한 모세혈관 혈당이 210 mg/dL 였다

DIAGNOSIS AND CLASSIFICATION

Why Fasting Plasma Glucose 126? Why Post Challenge 2-hour 200?



FPG (mg/dL)	70	89	93	97	100	105	109	116	136	226
2-h PG (mg/dL)	38	94	106	116	126	138	156	185	244	364
HbA1c (%)	3.4	4.8	5.0	5.2	5.3	5.5	5.7	6.0	6.7	9.5

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

MEMO

Hb A1c (당화혈색소)

Normal Hyperglycemia

Index of average glucose over the past 3 Months
(RBC life span = 120 Days)
More weighted on the past 1 Month

Classification

I. Type 1 Diabetes (β-cell destruction)
- Autoimmune
- Idiopathic

II. Type 2 Diabetes

III. Other Specific Types of Diabetes

IV. Gestational Diabetes

Other Specific Types of Diabetes

A. Genetic defects of β-cell function (Monogenic Diabetes of the Young, MODY)
1. Chr 12. HNF-1α
2. Chr 7. Glucokinase
3. Chr 20. HNF-4α
4. Chr 13. Insulin Promoter Factor-1
5. Chr 17. HNF-1β
6. Chr 2. NeuroD1
7. Mitochondrial DNA

B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes

C. Disease of exocrine pancreas
1. Pancreatitis
2. Trauma/Pancreatectomy
3. Neoplasia

D. Endocrinopathies
1. Cushing's syndrome
2. Glucagonoma
3. Hyperthyroidism

E. Drug or chemical
1. Vacor
2. Diazoxide
3. Glucocorticoid

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

G. Other genetic syndromes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Prader-Willi syndrome

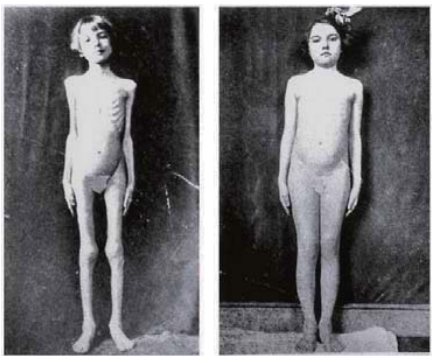
MEMO

Type 1 Diabetes

<Pathophysiology>
- Primarily β-cell destruction
- Absolutely no insulin secretion
- Insulin required for survival

<Etiology>
- Autoimmunity with anti-glutamic acid decarboxylase (anti-GAD)
- HLA DQ-B, DQ-A

<Presentation>
- **Diabetic Ketoacidosis**
- Non-obese
- Before age 30
- Less than 5% of diabetes patients in Korea



Journal of Metabolic Research, 1922

CASE VIGNETTE

2. 25세 남자. 직장 건강검진에서 발견된 고혈당으로 병원에 옴. 공복혈당이 284 mg/dL 였으며 당화 혈색소는 10.5% 였다. 최근 3개월간 다음, 다뇨, 다식, 체중 감소(67->62kg, 173cm)가 있었다고 한다. 상기 환자의 당뇨병 분류를 위한 설명으로 적절하지 **<u>않은</u>** 것은?

   1) 제1형 당뇨병 여부를 확인하기 위해 GAD Antibody, C-peptide level을 확인한다
   2) Other specific type of diabetes 여부를 확인하기 위해 약물, 수술력을 확인한다
   3) Monogenic form의 diabete를 확인하기 위해 가족력을 면밀히 조사한다
   4) 인슐린 분비능력이 현저히 감소한 경우 Acanthosis Nigricans가 목, 겨드랑이 처럼 접히는 부위에 발생한다

Acanthosis Nigricans

MEMO

TYPE 2 DIABETES

Type 2 Diabetes

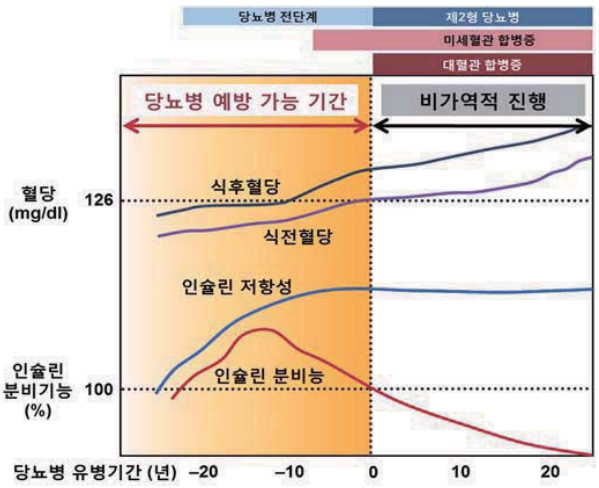
<Pathophysiology>
- Insulin resistance
- Relative insulin deficiency
- Do not require insulin injection for survival

<Etiology>
- Genetic predisposition
- Obesity and environmental

<Presentation>
- Obesity
- Onset at 50s to 60s
- Strong family history
- About 90% of diabetes
- High risk of cardiovascular disease, cerebrovascular disease, cancer …

TYPE 2 DIABETES

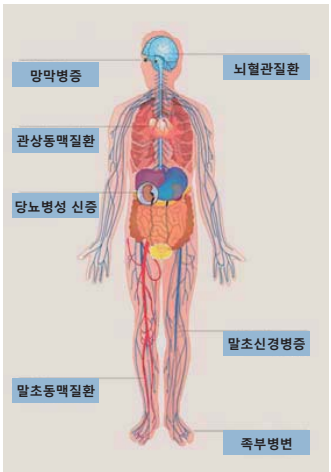
Type 2 Diabetes



COMPLICATIONS OF DIABETES

당뇨병의 만성 합병증

- **당뇨병에 의한 사망률**
  2010년 우리나라 **전체 사망의 11.3%** (2만9천명)
- **당뇨병성 망막병증**
  20-75세 사이 성인의 **가능 흔한 실명 원인**
- **당뇨병성 신증**
  2009년 우리나라 전체 **신부전 환자 중 45.5%가 당뇨병**에 의한 합병증
- **당뇨병성 신경병증**
  장기간 당뇨병 이환된 환자의 **약 50%에서 나타남**
- **당뇨병성 족부병변**
  교통 사고 제외하고 **하지 절단의 가장 흔한 원인**
- **관상동맥질환**
  Coronary Heart Disease risk equivalent
  -> 당뇨병 환자에서 관상동맥질환의 위험은 과거 관상동맥질환이 있었던 사람에서 관상동맥 질환이 재발할 확률과 유사함
- **뇌졸중**
  당뇨병 환자에서 **3배** 위험 증가



MEMO

CASE VIGNETTE

3. 55세 남자 환자가 타병원에서 당뇨병 진료를 받던 중 지난 1년 간 혈당 조절이 잘 안되어 병원을 바꿔 보고자 내원하였다. 상기 환자에서 확인해야 할 병력, 신체검진, 검사 사항으로 맞지 <u>않은</u> 것은?

   1) 최근 우울증 등 심리사회적 요인이 없는지 문지 한다
   2) 발에 대한 검진을 시행한다
   3) 소변 단백뇨를 측정한다
   4) 안과 검진은 당뇨병 진단 후 10년이 경과하면 시작한다

COMPREHENSIVE DIABETES EVALUATION

병력 청취

1. 발병 연령과 발병시 특이 사항 (DKA 여부, 검진에서 발견)
2. 식사습관, 운동습관, 영양상태, 체중변화
3. 심리사회적인 문제 (우울증), 치주질환 등 흔히 동반된 질환
4. 당뇨병 교육 이수 여부
5. 이전 치료력 (약물포함) 및 반응 (HbA1c)
6. 현재 치료 방법: 약물 및 순응도, 식사요법, 운동요법
7. 환자의 자가혈당 측정 기록
8. 저혈당의 빈도 및 무감지증
9. 미세혈관 합병증의 병력: 망막병증, 당뇨병성신증, 신경병증
10. 대혈관 합병증의 병력: 관상동맥질환, 뇌혈관질환, 말초혈관 질환

COMPREHENSIVE DIABETES EVALUATION

신체검진

1. 키, 몸무게, 체질량지수
2. 혈압 (필요시 기립시 혈압 변화)
3. 피부병변 (Acanthosis nigircans, 인슐린 주사 부위)
4. 발검진
   - 모양
   - Dorsalis Pedis Artery, Posterior Tibial Artery 촉지
   - Ankle reflex 여부
   - 10g 모노필라멘트 테스트
5. 갑상선 촉지, 안저 검사

MEMO

COMPREHENSIVE DIABETES EVALUATION

검사실 검사

1. HbA1c, 공복혈당
2. 공복 시 총콜레스테롤, LDL, HDL, 중성지방
3. Liver Function Test
4. 소변 Albumin to Creatinine Ratio
5. Serum Creatinine 과 eGFR
6. TSH (제1형 당뇨병, 고지혈증, 50세 이상 여성)

MANAGEMENT AND THERAPY

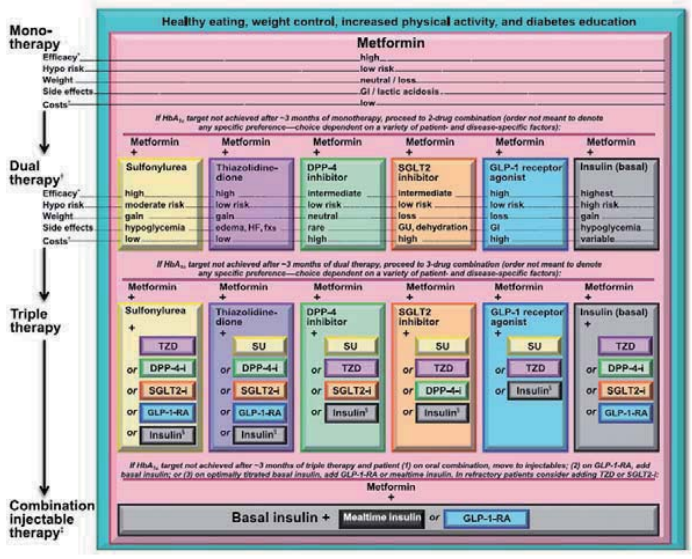
Goals of Therapy for Diabetes

I. Eliminate Symptoms Related to Hyperglycemia

II. Reduce or Eliminate the Long-term Vascular Complications

III. Allow the Patient to Achieve As Normal a Lifestyle as Possible

MANAGEMENT AND THERAPY



Inzucchi SE et al Diabetes Care 2015 Jan;38(1):140-149

MEMO

MANAGEMENT AND THERAPY

Summary of Glycemic Recommendations

● A1C	<7.0%*	
● Preprandial capillary plasma glucose	80-130 mg/dL	
● Peak postprandial capillary plasma glucose	< 180 mg/dL	
● Blood pressure	<140/90 mmHg†, should include ACEi or ARB	
● Lipids: LDL cholesterol	Overt CVD	High Dose Statin¶
	CVD Risk Factor‡	Moderate or High (40-75YA) Dose Statin¶
	None	Over 40 YA, Moderate Dose Statin
● Lipids: TG	< 150 mg/dL	
● Lipids: HDL cholesterol	> 40 mg/dL in men and > 50 mg/dL in women	

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on: **duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations**.

† Based on patient characteristics and response to therapy, higher or lower systolic blood pressure targets may be appropriate.

‡ CVD Risk Factor include **LDL ≥ 100mg/dl, High BP, Smoking, Overweight/Obesity**

¶ Moderate Dose: Atorvastatin 10mg / Pravastatin 40 mg / Simvastatin 20-40mg / Rosuvastatin 5-10mg
High Dose: Atorvastatin 40-80mg / Rosuvastatin 20-40mg

CASE VIGNETTE

4. 78세 여자 환자. 30년전 진단 된 당뇨병으로 Diamicron MR 60mg bid, Gemigliptin 50mg qd 투여 중이었다. 당뇨병성 신증이 진행하여 eGFR이 25 ml/min/1.73m^3 였고 1년 전에 관상동맥 우회수술을 받았다. 최근 당화혈색소는 7.8% 였다. 이환자에게 적당한 당화혈색소 목표는 얼마인가?

1) 6.0-6.5%
2) 6.5-7.0%
3) 7.0-7.5%
4) 7.5-8.0%

MANAGEMENT AND THERAPY

Individualized Glycemic Targets

- **HbA1c < 7.0%** (mean PG ~150-160 mg/dL)
- Pre-prandial PG <130 mg/dL)
- Post-prandial PG <180 mg/dL)
- **Individualization** is key:
  - **Tighter targets (6.0 - 6.5%)** - younger, healthier
  - **Looser targets (7.5 - 8.0%)** - older, comorbidities, hypoglycemia prone, etc.
- Avoidance of hypoglycemia

MEMO

MANAGEMENT AND THERAPY

Medical Nutritional Therapy

● **WEIGHT LOSS DIET (IN PREDIABETES AND TYPE 2 DM)**	
	Hypocaloric diet that is low-fat or low-carbohydrate
● **FAT IN DIET**	
	Minimal trans fat consumption
● **Carbohydrate in diet**	
	Monitor carbohydrate intake in regards to calories
	Sucrose-containing foods may be consumed with adjustments in insulin dose
	Amount of carbohydrate determined by estimating grams of carbohydrate in diet for (type 1 DM)
	Glycemic index reflects how consumption of a particular food affects the blood glucose
● **Protein in diet: as part of an optimal diet**	
● **Other components**	
	Nonnutrient sweeteners
	Routine supplements of vitamins, antioxidants, or trace elements not advised

MANAGEMENT AND THERAPY

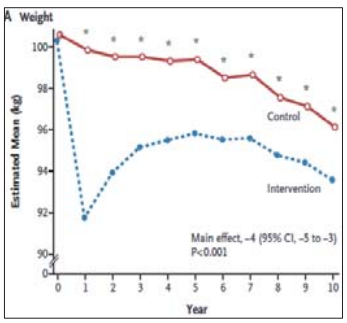
Life Style Intervention!!

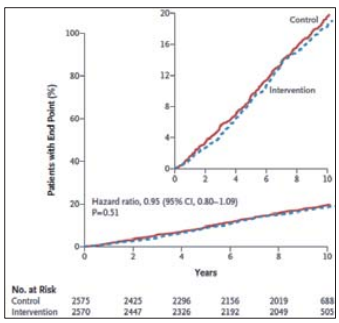
"But How?"

- **Weight Loss Goal**
  - ≥ 7% loss of initial weight during the 1st year
  - Request for ≥ 10%
- **Physical Activity Goal**
  - ≥ 175 min/wk
  - Moderate Intensity
  - Achieved by the 6th month
- **Physical Activity Intervention**
  - Four 10-minute bout = one 40-minute bout
  - Brisk walking
  - Using stairs, Walking, Pedometer 10,000 steps/day
- **Dietary Intervention: "Portion Control (식사량 조절)"**
  - 1200-1500 kcal/day
  - <30% of calories from fat, <10% from saturated fat
  - Replace 2 meals (breakfast and lunch) with Meal Replacements
  - Dinner (or Lunch) with Meal Plan

MANAGEMENT AND THERAPY

LOOK AHEAD TRIAL





- 5,145 overweight or obese type 2 diabetes patients
- Intensive lifestyle intervention: Promoting weight loss
- Median follow-up: 9.6 years
- **No difference in primary composite outcome of CV death, nonfatal MI/stroke, hospitalization for angina (HR 0.95, 95% CI 0.83-1.09, P=0.51)**
- Funded by NIH

MEMO

MANAGEMENT AND THERAPY

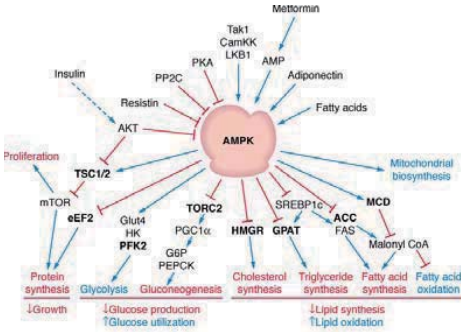
Treatment for Type 2 Diabetes

- 경구약
  - 메트포민 (metformin)
  - 설폰요소제 (sulfonylurea)
  - DPP-4 억제제 (dipeptidylpeptidase-4 inhibitor)
  - PPAR-γ 작용제 (peroxisome proliferator receptor -γ agonist)
  - 알파 글루코시다아제 억제제 (α-glucosidase inhibitor)
  - SGLT2 억제제 (SGLT2 inhibitor)
- 인슐린
- 인슐린 펌프
- GLP-1 유사체 (glucagon like peptide-1 analogue)
- 췌도이식 (실험적)

MANAGEMENT AND THERAPY

Metformin

- Decrease hepatic gluconeogensis and lipogenesis
- uncoupling mitochondrial oxidative phosphorylation
- Increase cellular AMP and activated AMP kinase
- Should be discontinued 2 days prior to Operation
- **Lactic Acidosis: rare**



French Lilac

MANAGEMENT AND THERAPY

How to titrate Metformin

- Begin with low dose 500mg bid or qd with meal, or 850mg qd
- After 5-7 days, increase to 1,000mg bid or 850mg bid
- If GI trouble, decrease to previous dose and retry later
- Maximal dose could be 1,000mg bid or 850mg tid
- XR formulation may have less GI trouble

MEMO

MANAGEMENT AND THERAPY

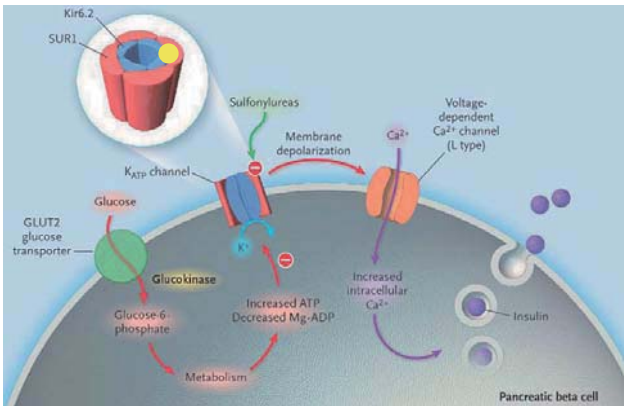
Contraindications of Metformin

- Pharmacokinetics
  - Time to maximal plasma concentration: 0.9 – 2.6 hr
  - Half life: 6 hr
  - Metabolism: Not metabolized
  - Elimination: 90% eliminated in urine
- Impaired Renal Function:
  - eGFR 60/ml/min/1.73m^2
  - 남자 1.5mg/dl, 여자 1.4mg/dl
- Hypoxic state: CHF, COPD, Sepsis
- Significant liver disease
- History of lactic acidosis, Alcohol abuse
- Pregnancy?

MANAGEMENT AND THERAPY

Sulfonylurea

- Sulfonylurea binds and closes the K^+ATP channel.
- Stimulates insulin secretion
- Amaryl (Glimepiride), Diamicron (Gliclazide), Euglucon (Glibenclamide)

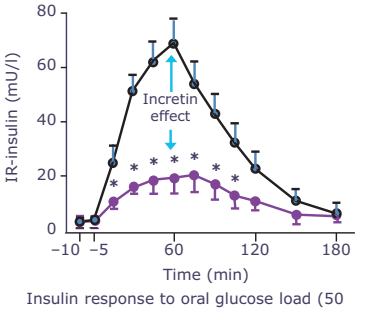


N ENGL J MED. 2004; 350;18:1839

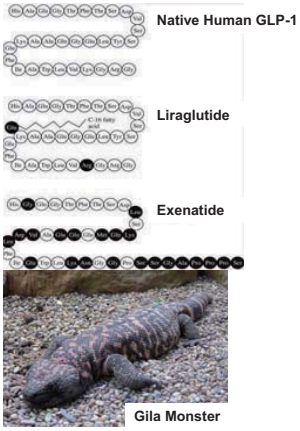
MANAGEMENT AND THERAPY

Incretin Therapy

- GLP-1 유사체 (glucagon like peptide-1 analogue)
- DPP-4 억제제 (dipeptidylpeptidase-4 inhibitor):
  Januvia(sitagliptin), Galvus(Vildagliptin), Trajenta (Linagliptin)



Insulin response to oral glucose load (50 g/400 ml, ●) and during isoglycaemic i.v. glucose infusion (◉)



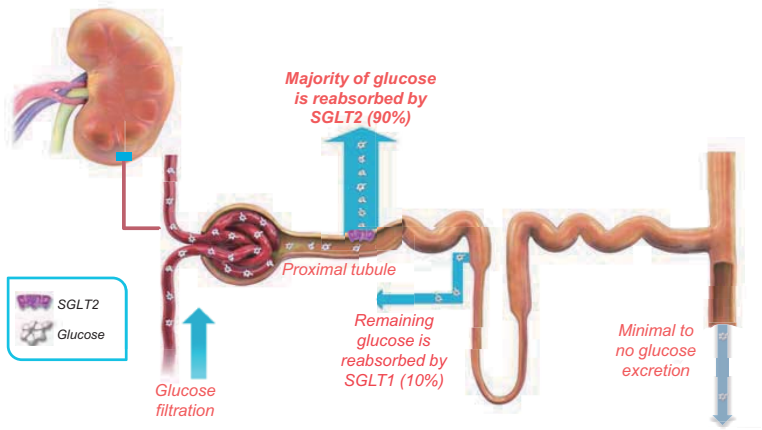
MEMO

Dipeptidyl Peptidase 4 Inhibitors

일반명	상품명	제조사	일반용량	인슐린 병용	Creatinine Clearance		Hepatic Impairment		1일 약값	복합제 (Metformin)
					<30 ml/min	30-50 ml/min	Mild/Moderate	Severe		
Sitagliptin	Januvia	Merck	100mg qd	가능[D]	25mg qd	50mg qd	No change	Do not use	924원	50/500, 50/850, 50/1000
Vildagliptin	Galvus	Novartis	50mg bid	불가	50mg qd	50mg qd	Do not use	Do not use	906원	50/500, 50/850, 50/1000
Saxagliptin	Onglyza	AstraZeneca/BMS	5mg qd	가능[D]	2.5mg qd	2.5mg qd	Caution	Do not use	850원	5/500, 5/1000
Linagliptin	Trajenta	Boehringer Ingelheim	5mg qd	가능[D]	No change	No change	No change	No change	831원	2.5/500, 5/1000
Gemigliptin	Zemiglo	LG Life Science	50mg qd	불가	No change	No change	No change	No change	815원	25/500
Alogliptin	Nisina	Takeda	25mg qd	가능[D]	6.25mg qd	12.5mg qd	No change	No change	777원	

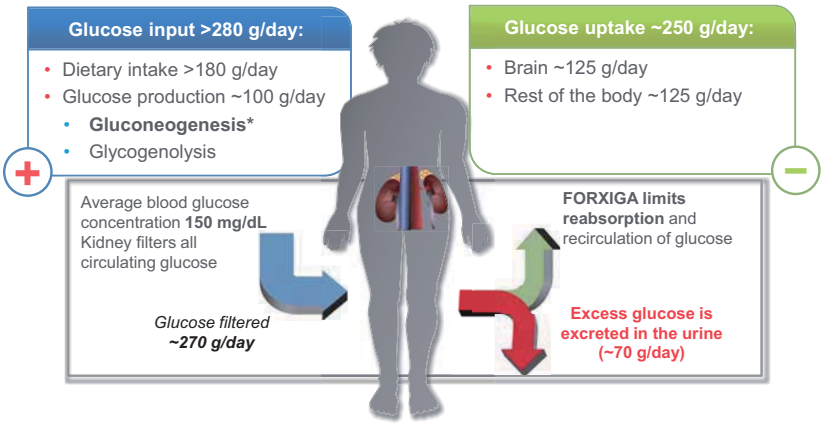
- Possible Side Effects
  - Upper Respiratory Infection, Urinary Tract Infection
  - Angioedema, Anaphylaxis
  - Hemorrhagic necrotizing pancreatitis

SGLT2 Inhibitors



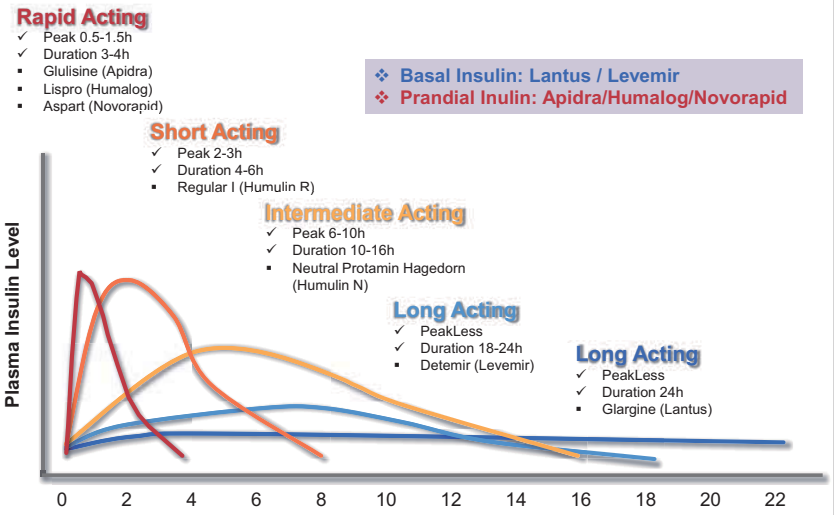
SGLT, sodium-glucose co-transporter.

SGLT2 Inhibitors



MEMO

MANAGEMENT AND THERAPY



CASE VIGNETTE

5. 39세 여자. 3년전 제2형 당뇨병을 진단 받았다. 컴퓨터 프로그래머로 밤을 세워 일하는 경우가 많으며 잦은 야식과 조절되지 않는 폭식이 동반됨. 정신과적 문제는 없었음. 체중이 98kg, 키 165cm로 체질량지수가 36kg/m^2 이었다. 경구 당뇨약으로 Glimepiride 4mg bid, Metformin 1,000mg bi 투여 중임에도 HbA1c가 8.9%였다. 이 환자에서 체중 감소를 동반할 수 있는 당뇨병 약제는?

   1) Thiazolidinedione
   2) Dipeptidyl Peptidase 4 Inhibitor
   3) Glucagon Like Peptide -1 Agonist
   4) Sodium Glucose Cotransporter 2 Inhibitors

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