Type 1 and Type 2 Diabetes

Disease Overview

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β- and α-Cells in the Pancreas of Normal Individuals

β-Cells	α-Cells
Comprise about 70%–80% of the endocrine mass of the pancreas[1,2]	Comprise about 15% of the endocrine mass of the pancreas[1]
Located in the central portion of the islet[1,2]	Located in the periphery of the islet[1]
Produce insulin and amylin[3]	Produce glucagon[1]
Insulin released in response to elevated blood glucose levels[1]	Glucagon released in response to low blood glucose levels[1]

1. Cleaver O et al. In: *Joslin's Diabetes Mellitus*. Lippincott Williams & Wilkins; 2005:21–39.
2. Rhodes CJ. *Science*. 2005;307:380–384.
3. Kahn SE et al. *Diabetes*. 1998;47:640–645.

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Pathophysiology of Type 1 Diabetes

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Type 1 Diabetes Mellitus

- Characterized by absolute insulin deficiency
- Pathophysiology and etiology
  - Result of pancreatic beta cell destruction
    - Prone to ketosis
  - Total deficit of circulating insulin
  - Autoimmune
  - Idiopathic

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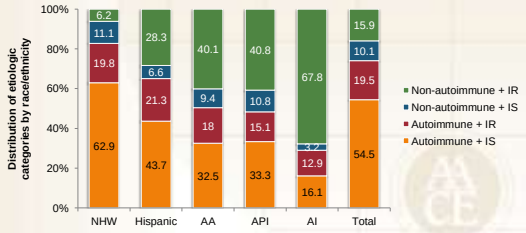
Type of Diabetes in Youth by Race/Ethnicity and Etiology

SEARCH for Diabetes in Youth Study (N=2291)



AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.
Dabelea D, et al. *Diabetes Care*. 2011;34:1628-1633.

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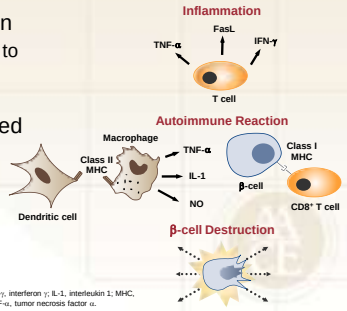
Type 1 Diabetes Pathophysiology

- β-cell destruction
  - Usually leading to absolute insulin deficiency
- Immune mediated
- Idiopathic



CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon γ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

Pathophysiologic Features of Type 1 Diabetes

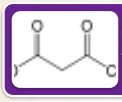
- Chronic autoimmune disorder
  - Occurs in genetically susceptible individuals
  - May be precipitated by environmental factors
- Autoimmune response against
  - Altered pancreatic β-cell antigens
  - Molecules in β-cells that resemble a viral protein
- Antibodies
  - Approximately 85% of patients: circulating islet cell antibodies
  - Majority: detectable anti-insulin antibodies
  - Most islet cell antibodies directed against GAD within pancreatic β-cells

GAD, glutamic acid decarboxylase.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

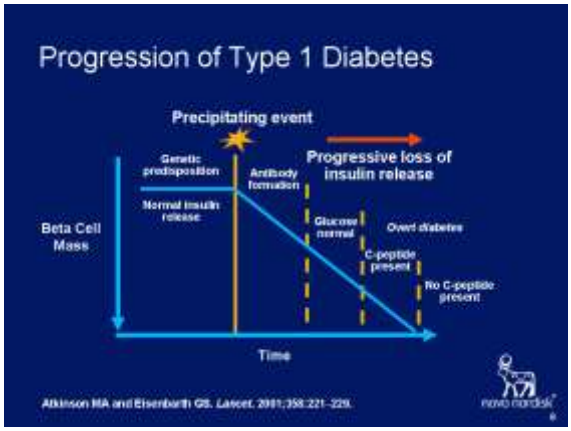
Major Metabolic Effects of Insulin and Consequences of Insulin Deficiency

Insulin effects: inhibits breakdown of triglycerides (lipolysis) in adipose tissue
- Consequences of insulin deficiency: elevated FFA levels



Insulin effects: inhibits ketogenesis
- Consequences of insulin deficiency: ketoacidosis, production of ketone bodies

Insulin effects in muscle: stimulates amino acid uptake and protein synthesis, inhibits protein degradation, regulates gene transcription
- Consequences of insulin deficiency: muscle wasting



Clinical Presentation of Type 2 Diabetes

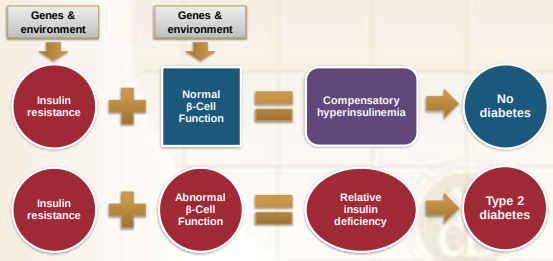
Risk Factors for Prediabetes and Type 2 Diabetes

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C <35 mg/dL and/or triglycerides >250 mg/dL)
- History of gestational diabetes
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Chronic glucocorticoid exposure
- Sleep disorders
  - Obstructive sleep apnea
  - Chronic sleep deprivation
  - Night shift work

BP, blood pressure; HCL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Development of Type 2 Diabetes Depends on Interplay Between Insulin Resistance and β-Cell Dysfunction



Gerich JE. *Mayo Clin Proc.* 2003;78:447-456.

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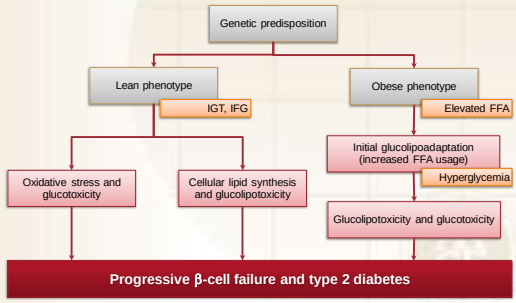
Etiology of β-cell Dysfunction



Poitout V, Robertson RP. *Endocrine Rev.* 2008;29:351-366.

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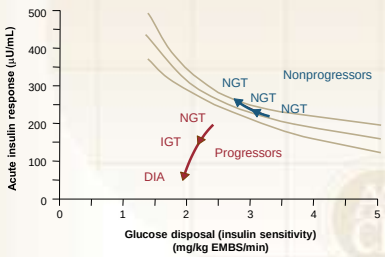
Progression to Type 2 Diabetes: "Falling Off the Curve"



EMBS, estimated metabolic body size; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Weyer C et al. *J Clin Invest.* 1999;104:787-794.

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Pathophysiology of Type 2 Diabetes

Organ System	Defect
Major Role	
Pancreatic beta cells	Decreased insulin secretion
Muscle	Inefficient glucose uptake
Liver	Increased endogenous glucose secretion
Contributing Role	
Adipose tissue	Increased FFA production
Digestive tract	Decreased incretin effect
Pancreatic alpha cells	Increased glucagon secretion
Kidney	Increased glucose reabsorption
Nervous system	Neurotransmitter dysfunction

DeFronzo RA. *Diabetes.* 2009;58:773-795

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Tissues Involved in T2D Pathophysiology

Organ System	Normal Metabolic Function	Defect in T2D
Major Role		
Pancreatic beta cells	Secrete insulin	Decreased insulin secretion
Muscle	Metabolizes glucose for energy	Inefficient glucose uptake
Liver	Secretes glucose during fasting periods to maintain brain function; main site of gluconeogenesis (glucose production in the body)	Increased endogenous glucose secretion
Contributing Role		
Adipose tissue (fat)	Stores small amounts of glucose for its own use. When fat is broken down, glycerol is released, which is used by the liver to produce glucose	Increased FFA production
Digestive tract	Digests and absorbs carbohydrates and secretes incretin hormones	Decreased incretin effect
Pancreatic alpha cells	Secrete glucagon, which stimulates hepatic glucose production between meals and also helps suppress insulin secretion during fasting periods	Increased glucagon secretion
Kidney	Reabsorbs glucose from renal filtrate to maintain glucose at steady-state levels; also an important site for gluconeogenesis (glucose production)	Increased glucose reabsorption
Brain	Utilizes glucose for brain and nerve function Regulates appetite	Neurotransmitter dysfunction

T2D, type 2 diabetes.

DeFronzo RA. *Diabetes.* 2009;58:773-795

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Natural History of Type 2 Diabetes

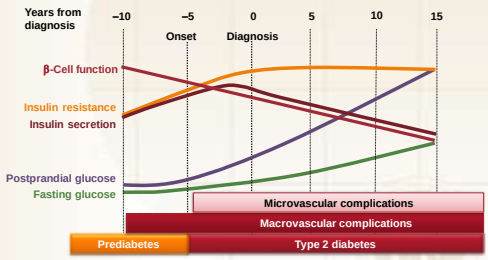

Figure courtesy of CADRE.

Adapted from Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25; Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789; Nathan DM. *N Engl J Med.* 2002;347:1342-1349; UKPDS Group. *Diabetes.* 1995;44:1249-1258

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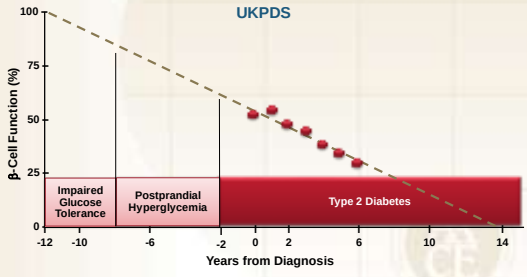
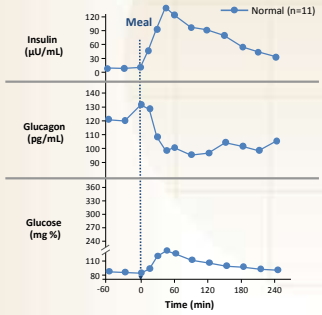
β-cell Loss Over Time



Dashed line = extrapolation based on Homeostasis Model Assessment (HOMA) data.
Data points from obese UKPDS population, determined by HOMA model.
Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.

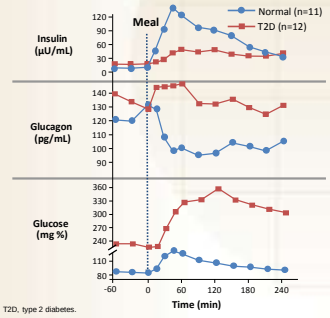
Normal Glucose Homeostasis and Pre- and Postmeal Insulin and Glucagon Dynamics



Premeal	Postmeal
↓ Insulin	↑ Insulin
↑ Glucagon ↑ HGP	↓ Glucagon ↓ HGP
Just enough glucose to meet metabolic needs between meals	Modest postprandial increase with prompt return to fasting levels

Müller WA, et al. *N Engl J Med.* 1970;283:109-115.

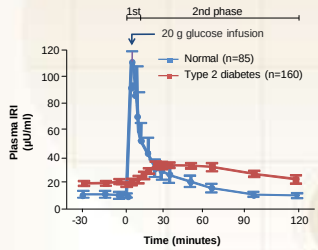
Hyperglycemia in Type 2 Diabetes Results from Abnormal Insulin and Glucagon Dynamics



Premeal	Postmeal
↓ Insulin	↓ Insulin
↑ Glucagon ↑ HGP	↑ Glucagon ↑ HGP
↑ FPG	↑↑ PPG

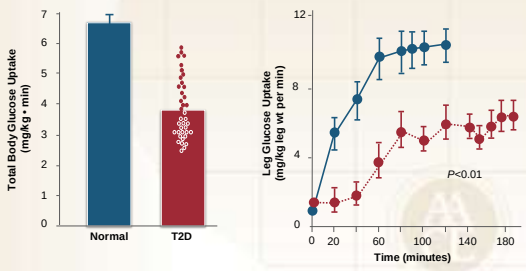
T2D, type 2 diabetes.
Müller WA, et al. *N Engl J Med.* 1970;283:109-115.

Acute Insulin Response Is Reduced in Type 2 Diabetes



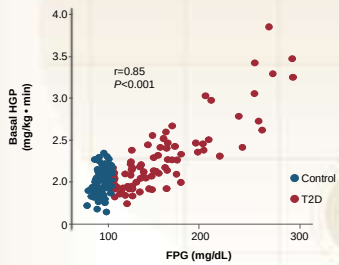
IRI, immunoreactive insulin.
Pfeifer MA, et al. *Am J Med.* 1981;70:579-588.

Defective Insulin Action in Type 2 Diabetes



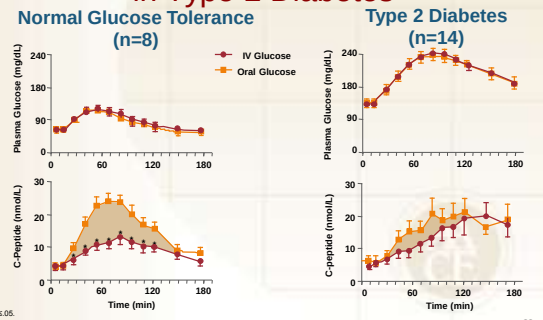
T2D, type 2 diabetes.
DeFronzo RA. *Diabetes.* 2009;58:773-795; DeFronzo RA, et al. *J Clin Invest.* 1985;76:149-155.

Elevated Fasting Glucose in Type 2 Diabetes Results From Increased HGP



FPG, fasting plasma glucose; HGP, hepatic glucose production; T2D, type 2 diabetes.
DeFronzo RA, et al. *Metabolism.* 1989;38:387-395.

The Incretin Effect Is Diminished in Type 2 Diabetes



*Ps.05.

Nauck M, et al. *Diabetologia*. 1986;29:46-52.

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Actions of GLP-1 and GIP

GLP-1

- Released from L cells in ileum and colon
- Stimulates insulin release from β-cell in a glucose-dependent manner
- Potent inhibition of gastric emptying
- Potent inhibition of glucagon secretion
- Reduction of food intake and body weight
- Significant effects on β-cell growth and survival

GIP

- Released from K cells in duodenum
- Stimulates insulin release from β-cell in a glucose dependent manner
- Minimal effects on gastric emptying
- No significant inhibition of glucagon secretion
- No significant effects on satiety or body weight
- Potential effects on β-cell growth and survival

Drucker DJ. Diabetes Care 2003;26:2929-2940.

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Renal Glucose Reabsorption in Type 2 Diabetes

- Sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) reabsorb glucose in the proximal tubule of kidney
  - Ensures glucose availability during fasting periods
- Renal glucose reabsorption is increased in type 2 diabetes
  - Contributes to fasting and postprandial hyperglycemia
  - Hyperglycemia leads to increased SGLT2 levels, which raises the blood glucose threshold for urinary glucose excretion

Wright EM, et al. *J Intern Med*. 2007;261:32-43.

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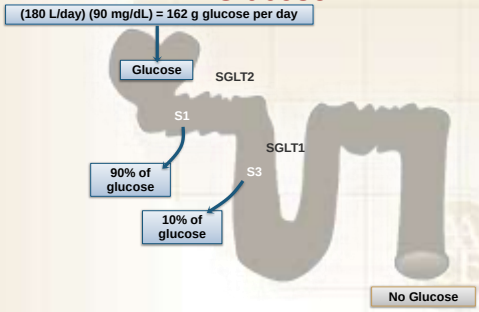
Normal Renal Handling of Glucose



Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790.

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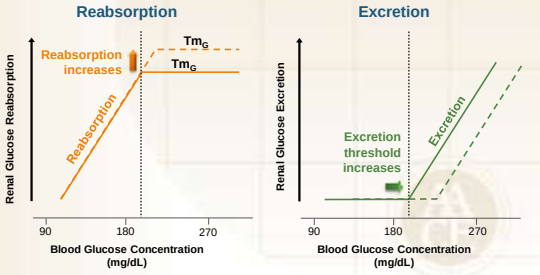
Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds



Tm$_G$, glucose transport maximum.

Abdul-Ghani MA, DeFronzo RA. Endocr Pract. 2008;14:782-790.

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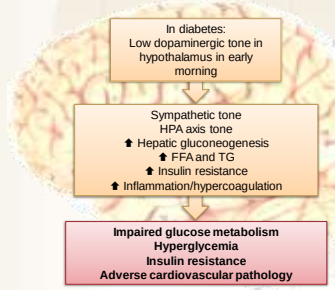
Hypothalamic Dopaminergic Tone and Autonomic Imbalance



Fonseca V. *Dopamine Agonists in Type 2 Diabetes*. New York, NY: Oxford University Press; 2010.
Cincotta AH. In: Hansen B, Shafrir E, eds. *Insulin Resistance and Insulin Resistance Syndrome*. New York, NY: Taylor & Francis; 2002:271-312.

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ADDICTION

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DSM-5

Changes to DSM in new edition: no longer dichotomy between abuse and dependence

Addiction now the preferred term instead of dependence.

Addiction now seen as a continuum.

Substance use disorder requires 2 of following:

tolerance	inability to stop
withdrawal problems	excessive spending or effort
use more than intended	to obtain
reduced involvement	continued use

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What is addiction?

- heroin addiction
- cocaine addiction
- alcohol addiction (“alcoholism”)
- marijuana addiction
- amphetamine addiction
- nicotine addiction

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What is addiction?

- sex addiction??
- gambling addiction??
- food addiction??
- shopping addiction????
- internet addiction????
- cell phone addiction????

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Vulnerability

Why do some people become addicted while others do not?

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True or False

Prescription medications are the most abuse substances in the United States?

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True or False

It is safer to abuse prescription medications than street drugs?

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True or False

Most people who abuse prescription drugs get them from a drug dealer?

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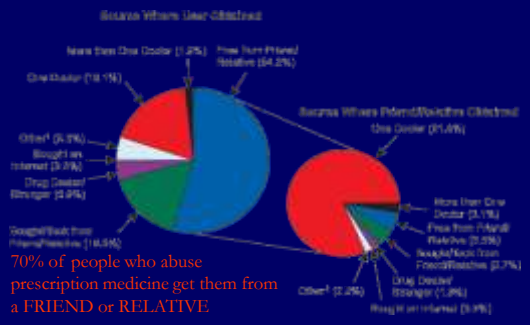
Where do People Obtain Prescription Drugs?



70% of people who abuse prescription medicine get them from a FRIEND or RELATIVE

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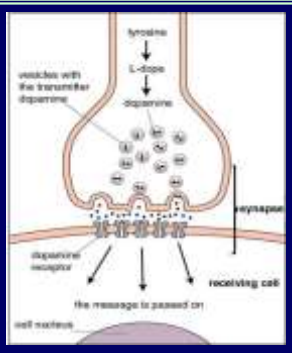
DA Neurotransmiter



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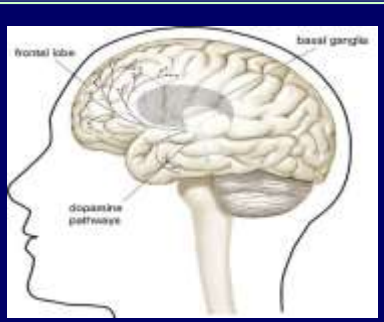
DA Pathway



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DOPAMINE RECEPTOR

1) Decreased in DM2
2) Control Food Intake
3) Energy Expenditure
4) Glucose Metabolism
5) Increase Resistance
6) Control Insulin Secretion (acute +, chronic -)
7) Insulin and DA ReUptake (acute +, chronic -)
8) Increase Liver Production Glucose
9) Lipid Metabolism Increase Lipolysis, FFA

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Dopamine Related

1) Schizophrenia/ Depression
2) Restless Leg Syndrome
3) ADHD
4) Prolactinoma
5) Nausea, Vomiting
6) Parkinson and other Movement disorders
7) Obesity?
8) Metabolic Syndrome?

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Pharmacologic Use

1) Movement Disorders
2) Prolactinomas
3) Nausea, Vomiting
4) Motility Disorders
5) Mood Disorders
6) Psychotic Disorders
7) ADHD
8) Pain

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ALCOHOL

1) Increase in CARB intake
2) Increased Hypoglycemia
3) Decrease hypoglycemia awareness
4) Confusion over hypoglycemia
5) Chronic use increase nerve damage
6) Blurry vision Vasodilation of eye vessels
7) Decrease activity of secretague
8) Dyslipidemia

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SMOKING

1) Increase Vascular Disease
2) Increase Cancer
3) Decrease Control
4) Increase Renal Disease
5) Increase Neuropathic Pain
6) Increased Amputations

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STIMULANTS

1) Hyperglycemia
2) Hypoglycemia
3) Weight Loss
4) Insulin Resistance
5) Increase MI and CVA

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Benzodiazepine

1) Insulin Resistance
2) Increase Sedentary Life
3) Increase Metabolic Syndrome
4) Weight Gain

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Narcotics

1) Increase Insulin Resistance
2) Decrease Insulin Secretion
3) Change in appetite
4) Memory Change
5) Mood change
6) Weight Change
7) Bowel Habit Change

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CANABIS

1) Decrease in Glucose in Intoxication
2) Increase in Fat Deposition
3) Increase Appetite
4) Short Term Memory Loss with Decrease compliance
5) Decrease coordination

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ANTIPSYCHOTICS

1) Increase Insulin Resistance
2) Decrease Insulin secretion
3) Increase Weight Mainly Central
4) Dyslipidemia
5) Increase Prolactin
6) Increase DM
7) Cardiovascular Disease

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ACTION POINTS

1) Avoid Dopamine Altering Medication
2) Aggressive Life Intervention to Minimize Effects
3) Pharmacologic Therapy
4) Seek Professional and Spiritual Help

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- OPEN DISCUSION

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