PATOGÉNESIS DM2

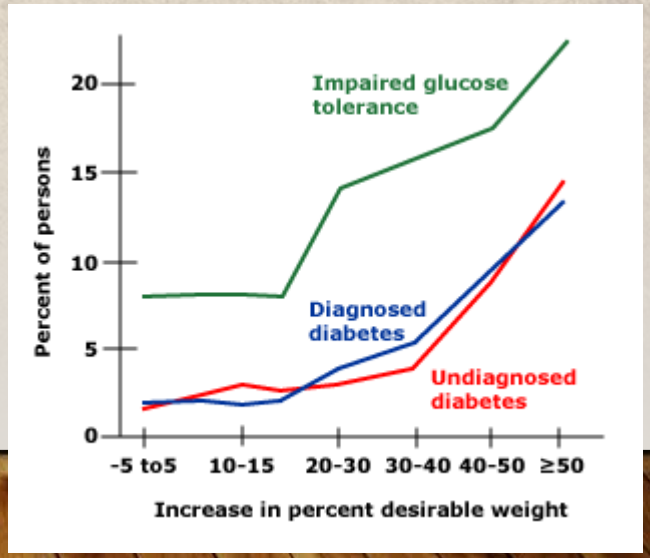
DRA. JENNIFER RODRIGUES BOOCK – RESIDENTE PEDIATRÍA USS HPM

HOJA DE RUTA

- Introducción
- Fisiopatogenia
  - Secreción de insulina e insulinoresistencia
  - Susceptibilidad genética
  - Dieta, obesidad e inflamación
  - Desarrollo intrauterino
  - Hiperglicemia inducida por drogas
- Conclusión
- Bibliografía

INTRODUCCIÓN

- La Diabetes Mellitus tipo 2 se caracteriza por la hiperglicemia, resistencia a la insulina y alteración en la secreción de insulina
- Prevalencia directamente relacionada al aumento de peso (obesidad)
- Incidencia en aumento relacionada al aumento a nivel mundial de la obesidad y estilo de vida sedentario
- Patogénesis compleja y multifactorial

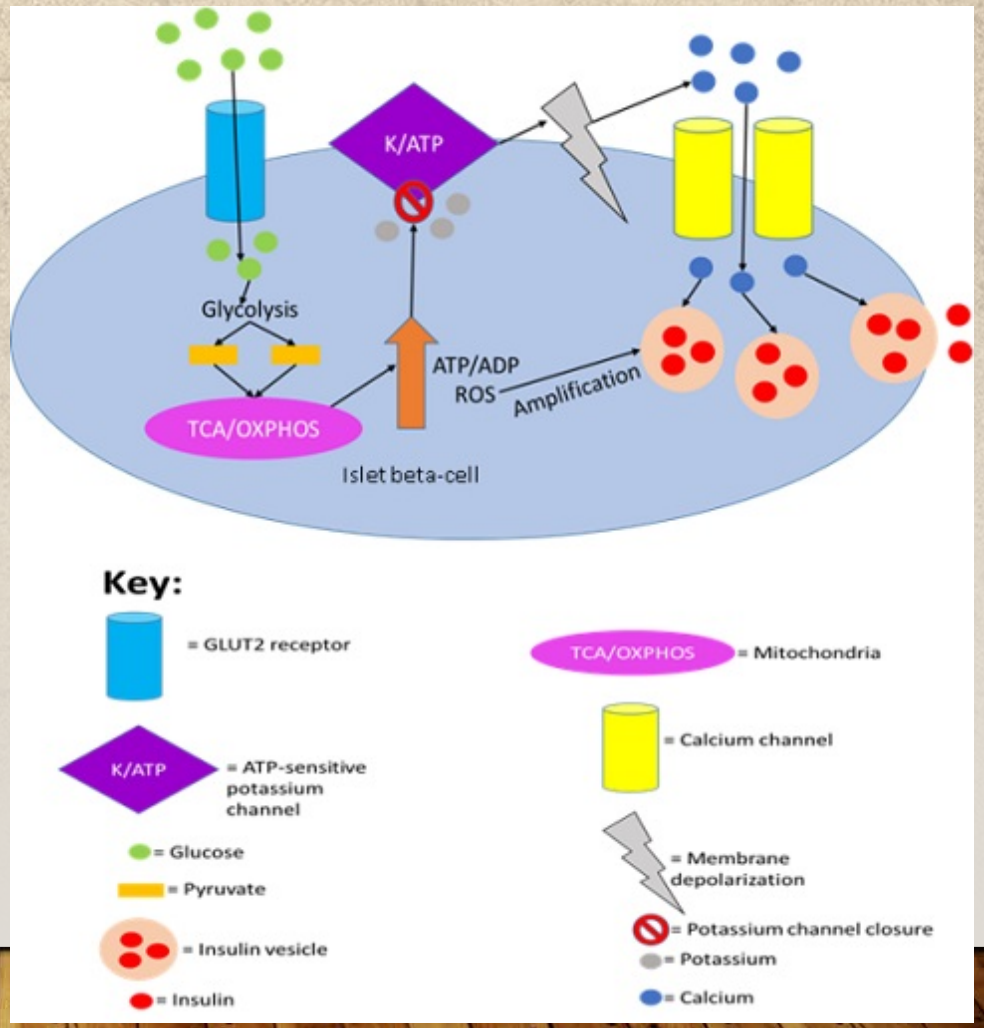


FISIOPATOGENIA

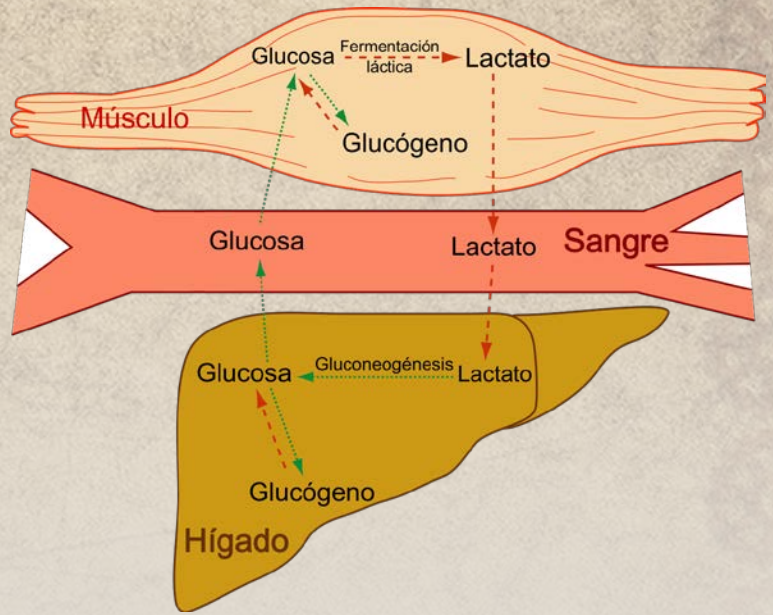
- Grados variables de resistencia a la insulina y déficit relativo de insulina
- Influencia genética o ambiental
- Hiperglicemia → alteración función célula beta → resistencia a la insulina → hiperglicemia
- Condiciones concomitantes: Sd metabólico
  - HTA
  - LDL elevado y HDL bajo

SECRECIÓN DE INSULINA E INSULINORESISTENCIA

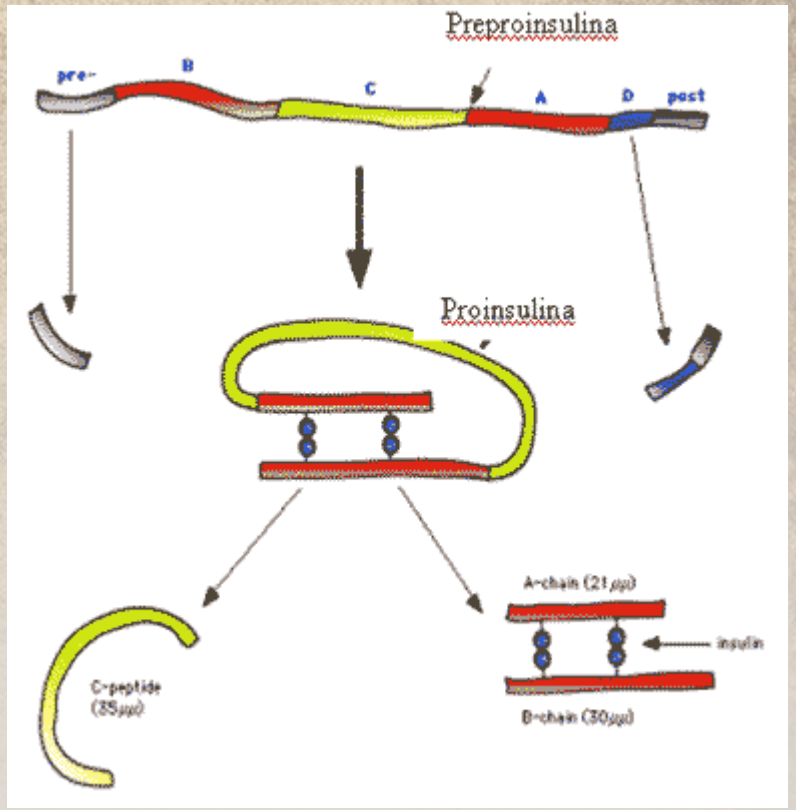
- Factores de riesgo independientes para DM2
- Secreción de insulina
  - Glucose transporter 2 (GLUT-2) en células beta
  - Abca1 – transporte celular de colesterol en cels beta



- Resistencia a la insulina
  - Mejor predictor de DM2
  - Susceptibilidad genética
  - Hiperglicemia: efecto tóxico en células beta
  - "Adipokinas": leptina, adiponectina, TNFa, y resistina
  - Metabolismo no oxidativo de la glucosa reducido
    - Predisposición genética
  - Diminución de glucógeno muscular

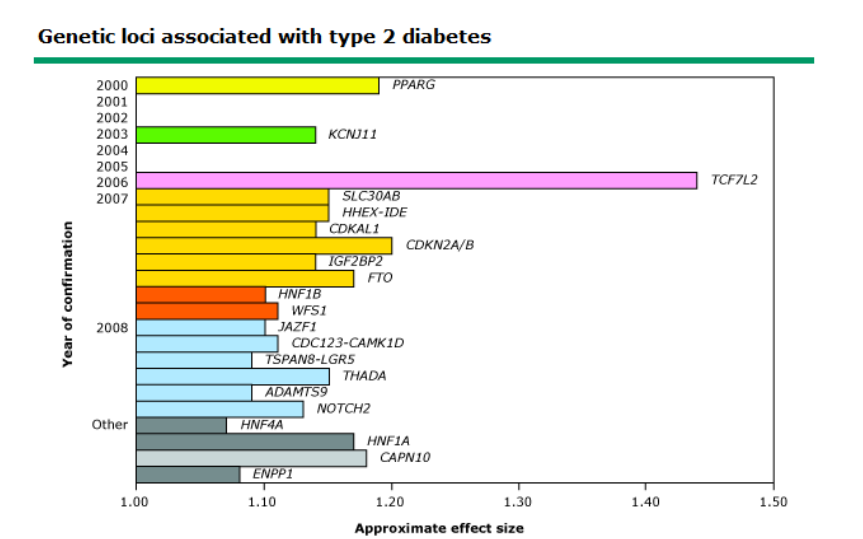


- Procesamiento de la insulina alterado
  - Aumento en la proporción de proinsulina secretada en comparación a sujetos normales.
  - Disfunción de célula beta
- Amilina
  - Polipeptido amiloide del islote – almacenado en los gránulos secretorios de insulina de las células beta
  - Cosecretado con la insulina: aumentado en DM2
  - Disminuye absorción de glucosa e inhibe secreción de insulina endógena



SUSCEPTIBILIDAD GENÉTICA

- Prevalencia variable entre distintas etnias en ambiente similar
- 39% al menos 1 padre afectado
- 90% gemelos monocigóticos
- 5-10x más riesgo de desarrollar DM2 en familiares de primer grado
- Más de 100 locus genéticos identificados
  - Desarrollo pancreático y función de células beta
  - Factores de transcripción: liberación de insulina
  - MODY2 y MODY4
  - Factores nucleares hepatociticos (MODY 1, 3 y 5)



Chronological accounting of the discovery of type 2 diabetes-associated genes, plotted by year of definitive publication and approximate effect size. Within each group, *darker colors* indicate biological candidate genes *(PPARG, KCNJ11, HNF1B, WFS1, HNF4A, HNF1A, and ENPP1)*, and *lighter colors* denote loci identified via agnostic genome-wide approaches. In *gray* are genes implicated in type 2 diabetes by considerable functional and genetic evidence but for which genome-wide statistical evidence of association has not been reached.

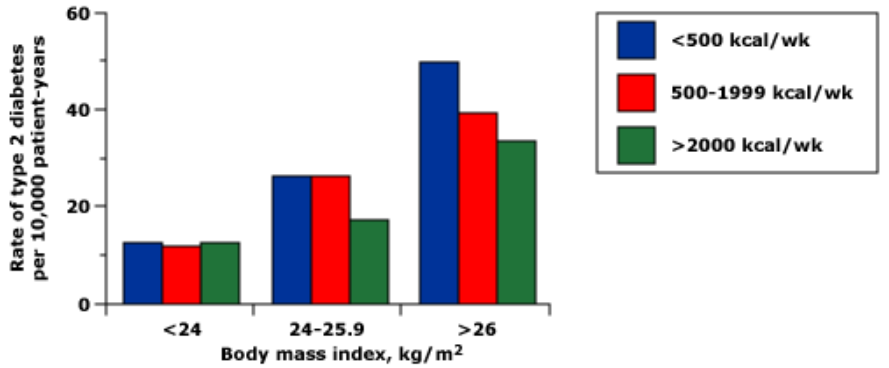
Reproduced with permission from: Florez JC. The genetics of type 2 diabetes: A realistic appraisal in 2008. J Clin Endocrine Metab 2008; 93:4633. http://jcem.endojournals.org/. Copyright © 2008 The Endocrine Society.

UpToDate®

DIETA, OBESIDAD E INFLAMACIÓN

- La obesidad causa resistencia periférica a la insulina y disminuye la sensibilidad de células beta a la glucosa – revertida por baja de peso
- Aumento de marcadores inflamatorios: PCR, IL-6, PAI-1, TNFa, y recuento de leucocitos
- Adipokinas
- Ácidos grasos libres

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 BMI (in kg/m^2) and the level of physical activity (in kcal/week). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for in men with a BMI below 24.

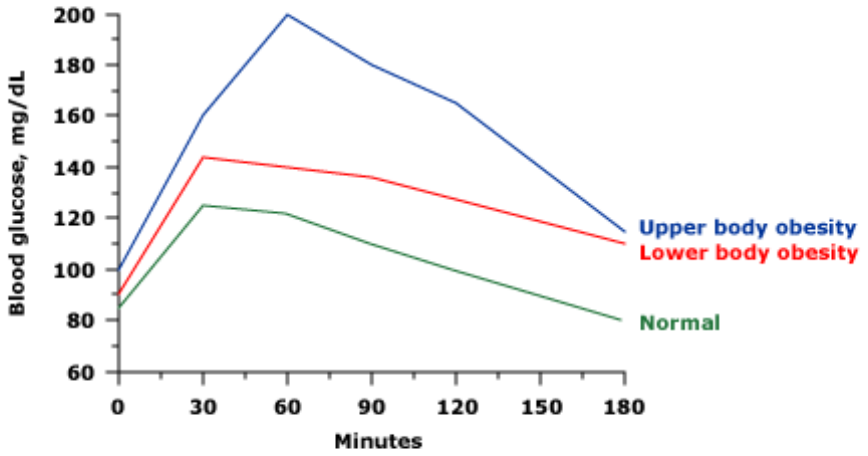
BMI: body mass index.

Data from: Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991; 325:147.

UpToDate®

- Factores liberados por el tejido adiposo
  - Leptina
  - Adiponectina
  - TNFa
  - Quimiocinas
  - PAI-1
  - Resistina
  - RBP4

Obesity and fat distribution impair glucose tolerance



Serial changes in blood glucose concentrations during an oral glucose tolerance test in nine patients with upper body obesity, 16 patients with lower body obesity, and nine normal subjects. Both obese groups had impaired glucose tolerance, but the abnormality was more pronounced in the group with upper body obesity. The degree of glucose intolerance underestimated the degree of insulin resistance, since peak serum insulin concentrations were also much higher in the group with upper body obesity (225 µU/mL versus 115 and 65 µU/mL in the other two groups). To convert blood glucose to mmol/L, divide by 18; to convert serum insulin to pmol/L, multiply by 6.

Data from: Kissebah A, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982; 54:254.

UpToDate®

DESARROLLO INTRAUTERINO

- Bajo peso de nacimiento
  - Malnutrición durante vida fetal o temprana – especialmente RCIU
    - Riesgo elevado de resistencia a la insulina, intolerancia a la glucosa, DM2, dislipidemia e hipertensión
  - Bajo peso al nacimiento y sobrepeso en adultez tienen el mayor riesgo de DM2 y la resistencia a la insulina más severa
- Peso alto al nacer
  - >4kg
  - Tan relacionada con la DM2 cuando el bajo peso
  - Hiperglicemia materna durante el embarazo
- Prematuridad
  - Aumento de riesgo dm2 y otras patologías relacionadas a la resistencia a la insulina

HIPERGLICEMIA INDUCIDA POR DROGAS

Drugs that can impair glucose tolerance or cause overt diabetes mellitus

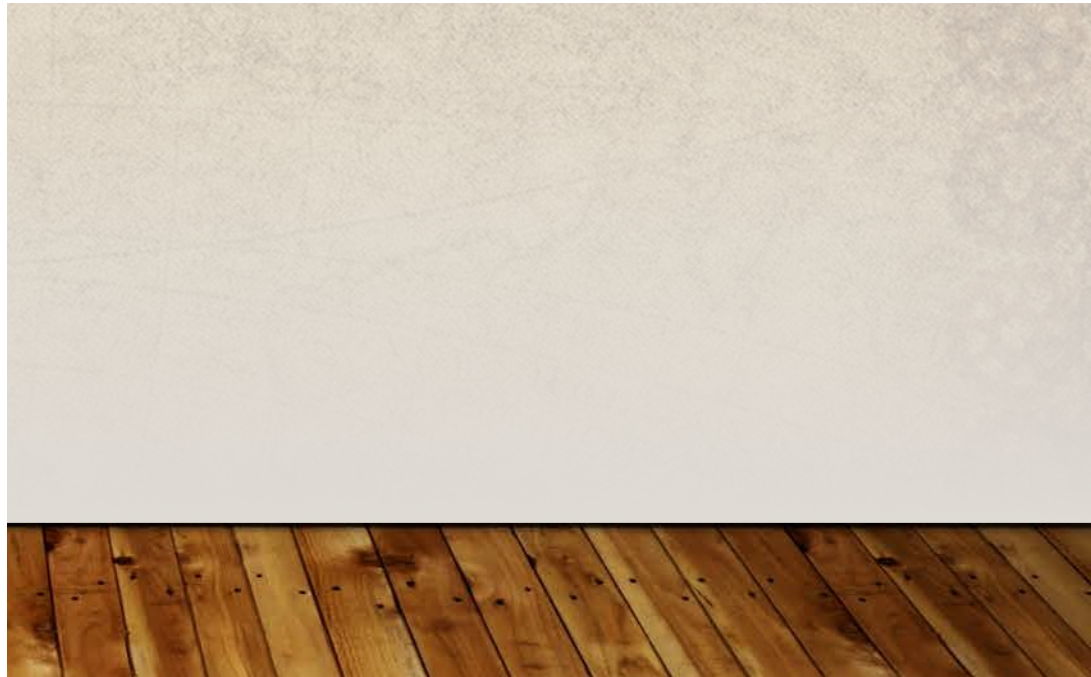
Category	Agents	Mechanism*
Anti-infectives		
Fluoroquinolones	Gatifloxacin¶ (not available in United States), moxifloxacin	Altered insulin secretion. Association with moxifloxacin is rare.
HIV antiretrovirals	Protease inhibitors Nucleoside reverse transcriptase inhibitors (NRTIs)	Increased peripheral insulin resistance. Part of antiretroviral-associated metabolic syndrome.
Other anti-infectives	Pentamidine	Altered pancreatic beta cell function. Following initial hypoglycemic effect, beta cell destruction can occur.
Antipsychotics		
First-generation	Chlorpromazine¶, perphenazine, other phenothiazines	Mechanism not established. Appears to involve increased insulin resistance and diminished insulin secretion.
Second-generation	Clozapine¶, iloperidone, olanzapine¶, paliperidone, quetiapine, risperidone	Mechanism not established. Appears to involve increased insulin resistance and diminished insulin secretion.
Cardiovascular		
Beta blockers	Atenolol, metoprolol, propranolol[1]	Decreased insulin sensitivity (moderate effect). Carvedilol does not appear to impair glucose tolerance. Refer to UpToDate topic on treatment of hypertension in patients with diabetes mellitus.
Hypolipidemic	Niacin (nicotinic acid)¶, statins	Niacin – Altered hepatic glucose metabolism, probably greater with extended-release form. Statins – Evidence of impaired glucose tolerance due to statins is conflicting, and overall risk appears low.
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide	Reduced total-body potassium, decreased insulin secretion, and increased insulin resistance[2]. Infrequent with low dosages (ie, hydrochlorothiazide ≤25 mg or equivalent). Potassium supplementation may decrease thiazide-associated glucose intolerance.
Vasodilators	Diazoxide	Reduced insulin secretion and sensitivity, increased hepatic glucose production.
Vasopressors	Epinephrine¶, norepinephrine[3]	Activation of glycogenolysis, increased hepatic gluconeogenesis, stimulation of glucagon and cortisol, inhibition of insulin secretion.
Gonadotropin-releasing hormone agonists	Class effect in men receiving androgen deprivation therapy for metastatic prostate cancer	Refer to UpToDate topic on side effects of androgen deprivation therapy.
Glucocorticoids, systemic* NOTE: Glucocorticoids are a particularly common cause of clinically significant drug-induced hyperglycemia	Class effect	Multifactorial, including increased hepatic glucose production, increased insulin resistance, increased expression of peroxisome proliferator activated gamma receptors (PPAR-gamma). Refer to UpToDate topic on major side effects of systemic glucocorticoids.
Hormones, sex		
Oral contraceptives	Combination estrogen-progestin oral contraceptives, progestin-only contraceptives	Altered hepatic glucose metabolism, increased peripheral insulin resistance. Low-dose pills (≤35 mcg ethinyl estradiol) have little effect on carbohydrate metabolism in most women.
Progestin	Megestrol acetate	Refer to UpToDate topics on pregnancy evaluation and management of women with diabetes mellitus.
Hormones, growth	Somatropin, tesamorelin	Increased counterregulatory responses. Refer to UpToDate topics on treatment of growth hormone deficiency and treatment of HIV-associated lipodystrophy.
Immunosuppressants	Cyclosporine (cyclosporin), sirolimus, tacrolimus	Decreased insulin synthesis and release. Refer to UpToDate topic on new-onset diabetes after transplant in renal transplant recipients.

* Degree or incidence of hyperglycemia is generally related to dose.
¶ Among agents listed, these have been more frequently associated with hyperglycemia and/or diabetes mellitus.

Data from:

1. *Sarafidis PA, Bakris GL. Antihypertensive treatment with beta-blockers and the spectrum of glycaemic control. QJM 2006; 99:431.*
2. *Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA 2001; 286:1945.*
3. *Thomas Z, Bandali F, McCowen K, Malhotra A. Drug-induced endocrine disorders in the intensive care unit. Crit Care Med 2010; 38:S219.*

UpToDa



CONCLUSIÓN

- La diabetes tipo 2 esta causada por una combinación de grados variables de resistencia a la insulina y déficit relativo de insulina
- Interacción compleja de factores genéticos y ambientales
- Genes identificados relacionados principalmente al desarrollo pancreático, síntesis de insulina, su secreción o acción
- Principales factores de riesgo ambientales: obesidad y sedentarismo
- Un gran numero de fármacos puede alterar tolerancia a la glucosa al disminuir secreción de insulina, aumentar gluconeogénesis hepática, o produciendo resistencia a la acción de la insulina.

BIBLIOGRAFÍA

- Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005; 365:1333.
- Merino J, Udler MS, Leong A, Meigs JB. A Decade of Genetic and Metabolomic Contributions to Type 2 Diabetes Risk Prediction. Curr Diab Rep 2017; 17:135.
- McCulloch, D. K., & Robertson, R. P. (2019, 10 octubre). *Pathogenesis of type 2 diabetes mellitus*. Up To Date. https://www.uptodate.com/contents/pathogenesis-of-type-2-diabetes-mellitus
- Pearson E. R. (2019). Type 2 diabetes: a multifaceted disease. *Diabetologia*, *62*(7), 1107–1112. https://doi.org/10.1007/s00125-019-4909-y
- Laakso M. (2019). Biomarkers for type 2 diabetes. *Molecular metabolism*, *27S*(Suppl), S139–S146. https://doi.org/10.1016/j.molmet.2019.06.016