Tema: Diabetes Mellitus.

La diabetes mellitus es una compleja y heterogénea enfermedad metabólica caracterizada por altas concentraciones de glucosa en sangre, asociadas a un deterioro de la producción de insulina (tipo I) o de su acción (tipo II) que resulta en una incapacidad del organismo para utilizar los nutrientes. Factores genéticos y ambientales, así como el estilo de vida, parecen relacionados con la etiología y el pronóstico, además de importantes diferencias en la frecuencia y las complicaciones.

La diabetes mellitus es una de las 10 principales causas de muerte en la mayoría de los países de América; es una causa importante de ceguera, insuficiencia renal, infarto de miocardio, accidente cerebrovascular y amputación de los miembros inferiores.

Entre 2000 y 2016, se ha registrado un incremento del 5% en la mortalidad prematura por diabetes. Se estima que en 2019 la diabetes fue la causa directa de 1,5 millones de defunciones y que, en 2012, 2,2 millones de personas fallecieron como consecuencia de la hiperglucemia.

La dieta saludable, la actividad física regular, el mantenimiento de un peso corporal normal y la evitación del consumo de tabaco previenen la diabetes de tipo 2 o retrasan su aparición. La alimentación saludable, la actividad física, la medicación y las pruebas periódicas permiten tratar la diabetes y prevenir, retrasar y tratar sus complicaciones.

El surgimiento del programa del Médico de Familia nos permitió caracterizar a nivel primario las distintas facetas de la diabetes mellitus en cuanto a edad, duración, tipo, control, tratamiento, así como las complicaciones, y se logró establecer un control más estricto que permitiera contribuir con acciones básicas al esfuerzo del Sistema Nacional de Salud para enfrentar el reto de la epidemia del nuevo milenio.
REFERENCIAS BIBLIOGRÁFICAS:


RESUMEN:

Background Some studies have suggested that in people with type 2 diabetes, Roux-en-Y gastric bypass has therapeutic effects on metabolic function that are independent of weight loss. Methods We evaluated metabolic regulators of glucose homeostasis before and after matched (approximately 18%) weight loss induced by gastric bypass (surgery group) or diet alone (diet group) in 22 patients with obesity and diabetes. The primary outcome was the change in hepatic insulin sensitivity, assessed by infusion of insulin at low rates (stages 1 and 2 of a 3-stage hyperinsulinemic euglycemic pancreatic clamp). Secondary outcomes were changes in muscle insulin sensitivity, beta-cell function, and 24-hour plasma glucose and insulin profiles.

Results Weight loss was associated with increases in mean suppression of glucose production from baseline, by 7.04 μmol per kilogram of fat-free mass per minute (95% confidence interval [CI], 4.74 to 9.33) in the diet group and by 7.02 μmol per kilogram of fat-free mass per minute (95% CI, 3.21 to 10.84) in the surgery group during clamp stage 1, and by 5.39 (95% CI, 2.44 to 8.34) and 5.37 (95% CI, 2.41 to 8.33) μmol per kilogram of fat-free mass per minute in the two groups, respectively, during clamp stage 2; there were no significant differences between the groups. Weight loss was associated with increased insulin-stimulated glucose disposal, from 30.5±15.9 to 61.6±13.0 μmol per kilogram of fat-free mass per minute in the diet group and from 29.4±12.6 to 54.5±10.4 μmol per kilogram of fat-free mass per minute in the surgery group; there was no significant difference between the groups. Weight loss increased beta-cell function (insulin secretion relative to insulin sensitivity) by 1.83 units (95% CI, 1.22 to 2.44) in the diet group and by 1.11 units (95% CI, 0.08 to 2.15) in the surgery group, with no significant difference between the groups, and it decreased the areas under the curve for 24-hour plasma glucose and insulin levels in both groups, with no significant difference between the groups. No major complications occurred in either group.

Conclusions In this study involving patients with obesity and type 2 diabetes, the metabolic benefits of gastric bypass surgery and diet were similar and were apparently related to weight loss itself, with no evident clinically important effects independent of weight loss.

RESUMEN:

Background Higher serum urate levels are associated with an increased risk of diabetic kidney disease. Lowering of the serum urate level with allopurinol may slow the decrease in the glomerular filtration rate (GFR) in persons with type 1 diabetes and early-to-moderate diabetic kidney disease. Methods In a double-blind trial, we randomly assigned participants with type 1 diabetes, a serum urate level of at least 4.5 mg per deciliter, an estimated GFR of 40.0 to 99.9 ml per minute per 1.73 m² of body-surface area, and evidence of diabetic kidney disease to receive allopurinol or placebo. The primary outcome was the baseline-adjusted GFR, as measured with iohexol, after 3 years plus a 2-month washout period. Secondary outcomes included the decrease in the iohexol-based GFR per year and the urinary albumin excretion rate after washout. Safety was also assessed. Results A total of 267 patients were assigned to receive allopurinol and 263 to receive placebo. The mean age was 51.1 years, the mean duration of diabetes 34.6 years, and the mean glycated hemoglobin level 8.2%. The mean baseline iohexol-based GFR was 68.7 ml per minute per 1.73 m² in the allopurinol group and 67.3 ml per minute per 1.73 m² in the placebo group. During the intervention period, the mean serum urate level decreased from 6.1 to 3.9 mg per deciliter with allopurinol and remained at 6.1 mg per deciliter with placebo. After washout, the between-group difference in the mean iohexol-based GFR was 0.001 ml per minute per 1.73 m² (95% confidence interval [CI], −1.9 to 1.9; P= 0.99). The mean decrease in the iohexol-based GFR was −3.0 ml per minute per 1.73 m² per year with allopurinol and −2.5 ml per minute per 1.73 m² per year with placebo (between-group difference, −0.6 ml per minute per 1.73 m² per year; 95% CI, −1.5 to 0.4). The mean urinary albumin excretion rate after washout was 40% (95% CI, 0 to 80) higher with allopurinol than with placebo. The frequency of serious adverse events was similar in the two groups. Conclusions We found no evidence of clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with type 1 diabetes and early-to-moderate diabetic kidney disease.


RESUMEN:
**Background** A closed-loop system of insulin delivery (also called an artificial pancreas) may improve glycemic outcomes in children with type 1 diabetes. **Methods** In a 16-week, multicenter, randomized, open-label, parallel-group trial, we assigned, in a 3:1 ratio, children 6 to 13 years of age who had type 1 diabetes to receive treatment with the use of either a closed-loop system of insulin delivery (closed-loop group) or a sensor-augmented insulin pump (control group). The primary outcome was the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter, as measured by continuous glucose monitoring. **Results** A total of 101 children underwent randomization (78 to the closed-loop group and 23 to the control group); the glycated hemoglobin levels at baseline ranged from 5.7 to 10.1%. The mean (±SD) percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter increased from 53±17% at baseline to 67±10% (the mean over 16 weeks of treatment) in the closed-loop group and from 51±16% to 55±13% in the control group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; P<0.001). In both groups, the median percentage of time that the glucose level was below 70 mg per deciliter was low (1.6% in the closed-loop group and 1.8% in the control group). In the closed-loop group, the median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95). No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either group. **Conclusions** In this 16-week trial involving children with type 1 diabetes, the glucose level was in the target range for a greater percentage of time with the use of a closed-loop system than with the use of a sensor-augmented insulin pump.


**RESUMEN:**

Dr. Max C. Petersen (Medicine): A 34-year-old woman was evaluated in the diabetes clinic of this hospital for hyperglycemia. Eleven years before this presentation, the blood glucose level was 126 mg per deciliter (7.0 mmol per liter) on routine laboratory evaluation, which was performed as part of an annual well visit. The patient could not recall whether she had been fasting at the time the test had been performed. One year later, the fasting blood glucose level was 112 mg per deciliter (6.2 mmol per liter; reference range, <100 mg per deciliter [<5.6 mmol per liter]).
RESUMEN:

**Background**  El perfil cardiovascular de seguridad de dapagliflozin, un inhibidor selectivo de la cotransportadora de sodio-glucosa 2 que promueve la glucosuria en pacientes con diabetes tipo 2, es indeterminado. **Methods**  Se asignaron al azar a los pacientes con diabetes tipo 2 que tenían o estaban en riesgo de enfermedad cardiovascular aterosclerótica, dapagliflozin o placebo. El resultado primario de seguridad fue un composite de eventos cardiovasculares adversos mayores (MACE), definido como muerte cardiovascular, infarto del miocardio o accidente cerebrovascular isquémico. Los resultados primarios de eficacia fueron MACE y un composite de muerte cardiovascular o hospitalización por insuficiencia cardíaca. Los objetivos secundarios de eficacia fueron un composite renal (≥40% disminución en filtración glomerular estimada a <60 ml por minuto por 1.73 m2 de superficie corporal, nuevo estadio renal terminal, o muerte por fallo renal o cardiovascular) y muerte por cualquier causa. **Results**  Evaluamos a 17,160 pacientes, incluyendo 10,186 sin enfermedad cardiovascular aterosclerótica, que fueron seguidos durante un promedio de 4.2 años. En el análisis del resultado primario de seguridad, dapagliflozin cumplió el criterio prespecífico para no inferioridad con respecto a MACE (límite superior del intervalo de confianza del 95% [IC], <1.3; P<0.001 para no inferioridad). En los dos análisis de eficacia primarios, dapagliflozin no resultó en una menor tasa de MACE (8.8% en el grupo dapagliflozin y 9.4% en el grupo placebo; razón de riesgo, 0.93; IC del 95%, 0.84 a 1.03; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; razón de riesgo, 0.83; IC del 95%, 0.73 a 0.95; P = 0.005), which reflected a lower rate of hospitalization for heart failure (razón de riesgo, 0.73; IC del 95%, 0.61 a 0.88); there was no between-group difference in cardiovascular death (razón de riesgo, 0.98; IC del 95%, 0.82 a 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (razón de riesgo, 0.76; IC del 95%, 0.67 a 0.87), and death from any cause occurred in 6.2% and 6.6%, respectivamente (razón de riesgo, 0.93; IC del 95%, 0.82 a 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001). **Conclusions**  En pacientes con diabetes tipo 2 que tenían o estaban en riesgo de enfermedad cardiovascular aterosclerótica, el tratamiento con dapagliflozin no resultó en una tasa mayor o menor de MACE que el placebo, pero sí resultó en una tasa más baja de muerte cardiovascular o hospitalización por insuficiencia cardíaca, un hallazgo que refleja un menor rate of hospitalización for heart failure.
Background Metformin is the regulatory-approved treatment of choice for most youth with type 2 diabetes early in the disease. However, early loss of glycemic control has been observed with metformin monotherapy. Whether liraglutide added to metformin (with or without basal insulin treatment) is safe and effective in youth with type 2 diabetes is unknown. Methods Patients who were 10 to less than 17 years of age were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide (up to 1.8 mg per day) or placebo for a 26-week double-blind period, followed by a 26-week open-label extension period. Inclusion criteria were a body-mass index greater than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin (with or without insulin). All the patients received metformin during the trial. The primary end point was the change from baseline in the glycated hemoglobin level after 26 weeks. Secondary end points included the change in fasting plasma glucose level. Safety was assessed throughout the course of the trial. Results Of 135 patients who underwent randomization, 134 received at least one dose of liraglutide (66 patients) or placebo (68 patients). Demographic characteristics were similar in the two groups (mean age, 14.6 years). At the 26-week analysis of the primary efficacy end point, the mean glycated hemoglobin level had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo, for an estimated treatment difference of −1.06 percentage points (P<0.001); the difference increased to −1.30 percentage points by 52 weeks. The fasting plasma glucose level had decreased at both time points in the liraglutide group but had increased in the placebo group. The number of patients who reported adverse events was similar in the two groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and gastrointestinal adverse events were higher with liraglutide. Conclusions In children and adolescents with type 2 diabetes, liraglutide, at a dose of up to 1.8 mg per day (added to metformin, with or without basal insulin), was efficacious in improving glycemic control over 52 weeks. This efficacy came at the cost of an increased frequency of gastrointestinal adverse events.


RESUMEN:
**Background** Observational studies support an association between a low blood 25-hydroxyvitamin D level and the risk of type 2 diabetes. However, whether vitamin D supplementation lowers the risk of diabetes is unknown. **Methods** We randomly assigned adults who met at least two of three glycemic criteria for prediabetes (fasting plasma glucose level, 100 to 125 mg per deciliter; plasma glucose level 2 hours after a 75-g oral glucose load, 140 to 199 mg per deciliter; and glycated hemoglobin level, 5.7 to 6.4%) and no diagnostic criteria for diabetes to receive 4000 IU per day of vitamin D3 or placebo, regardless of the baseline serum 25-hydroxyvitamin D level. The primary outcome in this time-to-event analysis was new-onset diabetes, and the trial design was event-driven, with a target number of diabetes events of 508. **Results** A total of 2423 participants underwent randomization (1211 to the vitamin D group and 1212 to the placebo group). By month 24, the mean serum 25-hydroxyvitamin D level in the vitamin D group was 54.3 ng per milliliter (from 27.7 ng per milliliter at baseline), as compared with 28.8 ng per milliliter in the placebo group (from 28.2 ng per milliliter at baseline). After a median follow-up of 2.5 years, the primary outcome of diabetes occurred in 293 participants in the vitamin D group and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). The hazard ratio for vitamin D as compared with placebo was 0.88 (95% confidence interval, 0.75 to 1.04; P= 0.12). The incidence of adverse events did not differ significantly between the two groups. **Conclusions** Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo.


**RESUMEN:**

Dr. Rachel Wood (Obstetrics and Gynecology): A 35-year-old pregnant woman was admitted to the labor and delivery unit of this hospital at 36 weeks 4 days of gestation for a planned repeat cesarean section because of placenta previa. At 6 weeks 4 days of gestation, the patient had been seen at a community health center because of a positive pregnancy test. She was gravida 4, 1-0-2-1. Her first pregnancy, 5 years earlier, had resulted in the need for a cesarean section because the fetus was in the breech presentation; the baby was delivered at full term without complications. The second and third pregnancies had been electively terminated. The patient reported that her husband had human immunodeficiency virus type 1 (HIV-1) infection and that he had been taking antiretroviral therapy; he had had undetectable plasma levels of HIV-1 RNA during the 5 months before this visit. Blood testing in the patient for HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen with the use of a fourth-generation combination assay was negative.
Preexposure prophylaxis with a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate was prescribed.


RESUMEN:

Background Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear. Methods We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer. Results A total of 15,480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P = 0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P= 0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned. Conclusions Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.
RESUMEN:

**Background**

El consumo aumentado de ácidos grasos n−3 se ha asociado con un reducido riesgo de enfermedad cardiovascular en estudios observacionales, pero este hallazgo no ha sido confirmado en ensayos aleatorizados. Se permanece incierto si la suplementación con ácidos grasos n−3 (también conocidos como omega-3) tiene beneficio cardiovascular en pacientes con diabetes mellitus.

**Methods**

Se asignó aleatoriamente a 15,480 pacientes con diabetes pero sin evidencia de enfermedad cardiovascular aforrosa a recibir 1 g de cápsulas que contenían ácidos grasos n−3 (grupo de ácidos grasos) o placebo (aceite de oliva) diariamente. La principal cuestión fue un primer evento vascular serio (es decir, infarto de miocardio no letal o accidente cerebrovascular transitorio, o muerte por enfermedad arterial, excepto en caso de hemorragia intracraneal confirmada). La cuestión secundaria fue un primer evento vascular serio o cualquier revascularización arterial.

**Results**

Durante un seguimiento medio de 7.4 años (adherencia del 76%), se produjo un evento vascular serio en 689 pacientes (8.9%) en el grupo de ácidos grasos y en 712 (9.2%) en el grupo de placebo (razón de riesgo, 0.97; intervalo de confianza [IC] del 95%, 0.87 a 1.08; P= 0.55). El composite outcome de un primer evento vascular serio o revascularización ocurrió en 882 pacientes (11.4%) y 887 (11.5%), respectivamente (razón de riesgo, 1.00; IC del 95%, 0.91 a 1.09). La muerte de cualquier causa ocurrió en 752 pacientes (9.7%) en el grupo de ácidos grasos y en 788 (10.2%) en el grupo de placebo (razón de riesgo, 0.95; IC del 95%, 0.86 a 1.05). No hubo diferencias significativas entre las tasas de eventos adversos no letales entre los grupos.

**Conclusions**

Entre los pacientes con diabetes sin evidencia de enfermedad cardiovascular, no hubo diferencia significativa en el riesgo de eventos vasculares serios entre aquellos asignados a recibir suplementación con ácidos grasos n−3 y aquellos asignados a recibir placebo.

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**Background**

El sobrepeso en la infancia se asocia con un aumento del riesgo de diabetes de tipo 2 en la edad adulta. Investigamos si la remisión del sobrepeso en la adolescencia temprana reduce este riesgo.

**Methods**

Realizamos un estudio que involucró a 62,565 hombres daneses cuyos pesos y alturas habían sido medidas a los 7 y 13 años de edad y en la edad adulta temprana (17-26 años de edad). El sobrepeso se definió en conformidad con los criterios de CDC. Datos sobre el estado de diabetes tipo 2 (edad ≥30 años, 6710
persons) were obtained from a national health registry. **Results** Overweight at 7 years of age (3373 of 62,565 men; 5.4%), 13 years of age (3418 of 62,565; 5.5%), or early adulthood (5108 of 62,565; 8.2%) was positively associated with the risk of type 2 diabetes; associations were stronger at older ages at overweight and at younger ages at diagnosis of type 2 diabetes. Men who had had remission of overweight before the age of 13 years had a risk of having type 2 diabetes diagnosed at 30 to 60 years of age that was similar to that among men who had never been overweight (hazard ratio, 0.96; 95% confidence interval [CI], 0.75 to 1.21). As compared with men who had never been overweight, men who had been overweight at 7 and 13 years of age but not during early adulthood had a higher risk of type 2 diabetes (hazard ratio, 1.47; 95% CI, 1.10 to 1.98), but their risk was lower than that among men with persistent overweight (hazard ratio [persistantly overweight vs. never overweight], 4.14; 95% CI, 3.57 to 4.79). An increase in body-mass index between 7 years of age and early adulthood was associated with an increased risk of type 2 diabetes, even among men whose weight had been normal at 7 years of age. **Conclusions** Childhood overweight at 7 years of age was associated with increased risks of adult type 2 diabetes only if it continued until puberty or later ages.


**RESUMEN:**

**Background** Pacientes con diabetes están a un mayor riesgo de muerte y eventos cardiovascular que la población general. Se investigó si el exceso de riesgo de muerte y eventos cardiovascular en pacientes con diabetes tipo 2 podría reducirse o eliminarse. **Métodos** En un estudio cohorte, se incluyeron 271,174 pacientes con diabetes tipo 2 que se registraron en el Registro Nacional de Diabetes de Suecia y se los equilibraron con 1,355,870 controles según edad, sexo y condado. Se evaluaron a los pacientes con diabetes según categorías de edad y según la presencia de cinco factores de riesgo (niveles elevados de glucosa en sangre, colesterol de baja densidad, albúmina, fumador, y presión arterial elevada). La regresión de Cox se usó para estudiar el exceso de riesgo de eventos (muerte, infarto agudo de miocardio, ictus y hospitalización por insuficiencia cardíaca) asociado con el consumo de tabaco y el número de variables fuera del rango objetivo. Se examinó también la relación entre varios factores de riesgo y eventos cardiovascular. **Resultados** El seguimiento medio entre todos los participantes del estudio fue de 5.7 años, durante los cuales ocurrieron 175,345 muertes. Entre los pacientes con diabetes tipo 2, el exceso de riesgo de muerte disminuyó de forma gradual para cada variable dentro del rango objetivo. Entre los pacientes con diabetes tipo 2 cuyos cinco factores se encontraban dentro del rango objetivo, el ratio de riesgo de muerte para cualquier causa, en comparación con los controles, fue 1.06 (IC del 95% 0.82 a 1.38).
interval [CI], 1.00 to 1.12), the hazard ratio for acute myocardial infarction was 0.84 (95% CI, 0.75 to 0.93), and the hazard ratio for stroke was 0.95 (95% CI, 0.84 to 1.07). The risk of hospitalization for heart failure was consistently higher among patients with diabetes than among controls (hazard ratio, 1.45; 95% CI, 1.34 to 1.57). In patients with type 2 diabetes, a glycated hemoglobin level outside the target range was the strongest predictor of stroke and acute myocardial infarction; smoking was the strongest predictor of death. **Conclusions** Patients with type 2 diabetes who had five risk-factor variables within the target ranges appeared to have little or no excess risk of death, myocardial infarction, or stroke, as compared with the general population.


**RESUMEN:**

**Background** Obesity is associated with an increased risk of adverse pregnancy outcomes. Lifestyle-intervention studies have not shown improved outcomes. Metformin improves insulin sensitivity and in pregnant patients with gestational diabetes it leads to less weight gain than occurs in those who do not take metformin. **Methods** In this double-blind, placebo-controlled trial, we randomly assigned pregnant women without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 35 to receive metformin, at a dose of 3.0 g per day, or placebo (225 women in each group) from 12 to 18 weeks of gestation until delivery. The BMI was calculated at the time of study entry (12 to 18 weeks of gestation). The primary outcome was a reduction in the median neonatal birth-weight z score by 0.3 SD (equivalent to a 50% reduction, from 20% to 10%, in the incidence of large-for-gestational-age neonates). Secondary outcomes included maternal gestational weight gain and the incidence of gestational diabetes and of preeclampsia, as well as the incidence of adverse neonatal outcomes. Randomization was performed with the use of computer-generated random numbers. The analysis was performed according to the intention-to-treat principle. **Results** A total of 50 women withdrew consent during the trial, which left 202 women in the metformin group and 198 in the placebo group. There was no significant between-group difference in the median neonatal birth-weight z score (0.05 in the metformin group [interquartile range, −0.71 to 0.92] and 0.17 in the placebo group [interquartile range, −0.62 to 0.89], P = 0.66). The median maternal gestational weight gain was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2], P<0.001), as was the incidence of preeclampsia (3.0% vs. 11.3%; odds ratio, 0.24; 95% confidence interval, 0.10 to 0.61; P = 0.001). The incidence of side effects was higher in the metformin group than in the placebo group.
There were no significant between-group differences in the incidence of gestational diabetes, large-for-gestational-age neonates, or adverse neonatal outcomes. **Conclusions** Among women without diabetes who had a BMI of more than 35, the antenatal administration of metformin reduced maternal weight gain but not neonatal birth weight.


RESUMEN:

A 22-year-old woman reports having hirsutism and irregular menses. She describes unpredictable and infrequent menses (five or six per year) since menarche at 11 years of age. Dark, coarse facial hair began to develop at 13 years of age. The symptoms worsened after she gained weight in college. The physical examination includes a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 29, blood pressure of 135/85 mm Hg, and moderate hirsutism without virilization. Laboratory tests reveal a total testosterone level of 65 ng per deciliter (2.3 nmol per liter) (assay reference range, 14 to 53 ng per deciliter [0.5 to 1.8 nmol per liter]), calculated free testosterone level of 15.3 pg per milliliter (53.1 pmol per liter) (assay reference range, 0.6 to 6.8 pg per milliliter [2.1 to 23.6 pmol per liter]), and glycated hemoglobin level of 5.7% (normal value, ≤5.6%). How should this case be evaluated and managed?


RESUMEN:

A 64-year-old man presented with a 2-year history of asymptomatic, widespread, erythematous-to-violaceous papules that were distributed symmetrically on his trunk, arms, and legs (Panel A). The papules coalesced to form annular plaques, especially on the forearms and dorsal surfaces of the hands (Panel B). Skin biopsy revealed palisading granulomatous inflammation that surrounded degenerating collagen within the dermis, findings that were consistent with a diagnosis of granuloma annulare. Laboratory tests revealed a fasting glucose level of 7.9 mmol per liter (142 mg per deciliter; normal range, 3.6 to 6.1 mmol/liter [65 to 110 mg per deciliter]) and a postprandial glucose level of 12.1
mmol per liter (218 mg per deciliter; normal value, <7.8 mmol per liter [140 mg per deciliter]), findings that were consistent with a diagnosis of diabetes mellitus. Thyroid hormone levels and the blood-lipid profile were normal. Granuloma annulare is a benign, noninfectious, granulomatous skin disease that is usually asymptomatic and self-limited. Granuloma annulare is often localized and not associated with systemic disease, although it can be triggered by trauma, infection, drugs, and metabolic derangement. This patient presented with the less common generalized variant of granuloma annulare, which is often associated with diabetes mellitus or thyroid disease. Four months after the patient began tight glucose control and treatment with oral hydroxychloroquine, the skin lesions had markedly regressed, without scarring.


RESUMEN:

The prevalence of diabetes is increasing rapidly, and type 2 diabetes now accounts for 20 to 50% of cases of new-onset diabetes in young people. Electrolyte disturbances are common in patients with diabetes and may be the result of an altered distribution of electrolytes related to hyperglycemia induced osmotic fluid shifts or of total-body deficits brought about by osmotic diuresis. Complications from end-organ injury and the therapies used in the management of diabetes may also contribute to electrolyte disturbances. In this review, we highlight the ways in which specific electrolytes may be influenced by dysregulation in glucose homeostasis.


RESUMEN:

Background The cardiovascular safety and efficacy of many current antihyperglycemic agents, including saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, are unclear. Methods We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications,
including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke. **Results** A primary endpoint event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P= 0.99 for superiority; P<0.001 for noninferiority); the results were similar in the “on-treatment” analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P= 0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P= 0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively). **Conclusions** DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.


**RESUMEN:**

A 42-year-old asymptomatic man with hypertension presents for his annual physical examination. His medications include atenolol combined with chlorthalidone (at doses of 50 mg and 25 mg, respectively, per day). Both parents had type 2 diabetes mellitus later in life. He does not smoke cigarettes. His body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 32.3, and his blood pressure is 130/80 mm Hg. Would you screen the patient for diabetes, and if so, how?

RESUMEN:

A 39-year-old man with a 2-year history of type 2 diabetes mellitus presents for care. He has no microvascular or macrovascular complications. His family history is positive for type 2 diabetes and cardiovascular disease in his mother and older brother. On examination, his weight is 99.8 kg (220 lb), with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 37, and his blood pressure is 125/85 mm Hg. His glycated hemoglobin level is 8.9%, serum creatinine level 1.0 mg per deciliter (88.4 μ mol per liter), low-density lipoprotein (LDL) cholesterol 88 mg per deciliter (2.3 mmol per liter), high-density lipoprotein (HDL) cholesterol 45 mg per deciliter (1.2 mmol per liter), and triglyceride level 130 mg per deciliter (1.5 mmol per liter); he does not have microalbuminuria. His medications include metformin (500 mg twice daily), glipizide (5 mg twice daily), simvastatin (20 mg daily), and lisinopril (10 mg daily). What would you recommend to improve his glycemic control?


RESUMEN:

Dr. Kimberly G. Blumenthal (Medicine): A 34-year-old woman, 2.5 months post partum, was admitted to this hospital because of episodes of altered mental status. The patient had been well until approximately 3 months before admission, near the end of her pregnancy, when periodic numbness of the lower lip occurred, which resolved after approximately 30 minutes. She gave birth to a healthy baby by normal spontaneous vaginal delivery 2.5 months before admission and had been breastfeeding since then. After delivery, the patient began to have intermittent numbness in the pelvis and thighs while walking, without pain or burning. Seven weeks before admission, she began to have episodes of unusual behavior in the morning after she awakened, including pouring cereal from one container to another and making growling noises; these resolved after approximately 30 minutes, and she had minimal recollection of the episodes. She also began to have panic attacks, insomnia, episodes of crying, and increasing feelings of anxiety and hopelessness; diagnoses of anxiety and postpartum depression were made. Clonidine was administered briefly, followed by clonazepam and, 2 weeks before admission, sertraline, without improvement. Three weeks before this admission, intermittent blurring of her vision developed, associated with “wooziness” and feeling “out of it.” She had periods of numbness of the lower lip, arms, and legs and had difficulty performing routine activities, such as typing. Ten days before admission, during a 2-hour...
period, she had trouble conversing, folding a stroller, and fastening her seatbelt; she later had difficulty recalling the events. Similar symptoms occurred the next day, lasting approximately 1 hour. Eight days before this admission, she saw a neurologist. She was asymptomatic, and the examination was normal; additional testing and follow-up were scheduled.


RESUMEN:

A 42-year-old asymptomatic man with hypertension presents for his annual physical examination. His medications include atenolol combined with chlorthalidone (at doses of 50 mg and 25 mg, respectively, per day). Both parents had type 2 diabetes mellitus later in life. He does not smoke cigarettes. His body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 32.3, and his blood pressure is 130/80 mm Hg. Would you screen the patient for diabetes, and if so, how?


RESUMEN:

Dr. Jennifer C. Hensley (Pediatrics): A 16-year-old boy was admitted to this hospital because of abdominal pain and a mediastinal mass. The patient had been well until 4 days before admission, when he began to feel vaguely ill. The next day, nonbloody emesis occurred. Two days before admission, epigastric pain, nausea, decreased appetite, and constipation developed. On the morning of admission, he took laxatives and acetaminophen, without relief. He saw his pediatrician; a tentative diagnosis of pancreatitis was made, and the patient was sent to the emergency department at an affiliated hospital. On arrival, he rated the pain at 10 on a scale of 0 to 10 (with 10 indicating the most severe pain). He had not had fever, additional episodes of vomiting, or diarrhea. On examination, the weight was 138.5 kg, the temperature 36.7°C, the blood pressure 155/75 mm Hg, the pulse 88 beats per minute, the respiratory rate 36 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The
abdomen was soft, with moderate tenderness in the epigastrium and right upper quadrant; the remainder of the examination was normal. Levels of platelets, electrolytes, albumin, alkaline phosphatase, calcium, creatine kinase isoenzymes, and troponin I were normal, as were tests of renal function; other test results are shown in Table 1. An electrocardiogram was normal. Computed tomography (CT) of the abdomen after the administration of intravenous contrast material revealed a cystic mass, 12.4 cm by 6.1 cm by 6.2 cm, in the posterior mediastinum above the gastroesophageal junction, which displaced the inferior vena cava, the heart, and the distal esophagus; hepatic steatosis and trace bilateral pleural effusions were also present. Morphine (5 mg) was administered intravenously with transient improvement (the patient rated the pain at 3 out of 10) within 4 minutes; ranitidine and normal saline were also given. The patient was transferred to this hospital by ambulance for further evaluation; morphine (4 mg) was administered for recurrent pain enrooted.


RESUMEN:

A 39-year-old man with type 1 diabetes of 27 years’ duration visits his endocrinologist for review of his blood glucose control. He is overweight (body-mass index [the weight in kilograms divided by the square of the height in meters], 28.4). The overall glycemic control has been suboptimal, with glycated hemoglobin values of 7.5 to 8.0% in recent years. He reports unpredictable swings in self-monitored blood glucose concentrations and frequent episodes of severe hypoglycemia, which markedly disrupt his work and home life. He also reports that he now has fewer warning symptoms of hypoglycemia than he had previously. These findings are present despite the patient’s best efforts to achieve glycemic control with intensified insulin-injection therapy, regular visits to a diabetes clinic, and input from diabetes nurse educators. He attended a structured diabetes education course 1 year previously, which he found to be useful and which led to slight improvements in glycated hemoglobin levels; however, the frequency of hypoglycemic episodes was unchanged. His endocrinologist has ruled out coexisting illnesses, including celiac disease and Addison’s disease, as causes of poor glycemic control and wonders whether a trial of insulin-pump therapy is appropriate. Since the endocrinologist has little experience with this type of therapy himself, he refers the patient to a center with a specialized insulin-pump clinic.
RESUMEN:

**Background** The 65-kD isoform of glutamic acid decarboxylase (GAD65) is a major autoantigen in type 1 diabetes. We hypothesized that alum-formulated GAD65 (GAD-alum) can preserve beta-cell function in patients with recent-onset type 1 diabetes. **Methods** We studied 334 patients, 10 to 20 years of age, with type 1 diabetes, fasting C-peptide levels of more than 0.3 ng per milliliter (0.1 nmol per liter), and detectable serum GAD65 autoantibodies. Within 3 months after diagnosis, patients were randomly assigned to receive one of three study treatments: four doses of GAD-alum, two doses of GAD-alum followed by two doses of placebo, or four doses of placebo. The primary outcome was the change in the stimulated serum C-peptide level (after a mixed meal tolerance test) between the baseline visit and the 15-month visit. Secondary outcomes included the glycated hemoglobin level, mean daily insulin dose, rate of hypoglycemia, and fasting and maximum stimulated C-peptide levels. **Results** The stimulated C-peptide level declined to a similar degree in all study groups, and the primary outcome at 15 months did not differ significantly between the combined active-drug groups and the placebo group (P= 0.10). The use of GAD-alum as compared with placebo did not affect the insulin dose, glycated hemoglobin level, or hypoglycemia rate. Adverse events were infrequent and mild in the three groups, with no significant differences. **Conclusions** Treatment with GAD-alum did not significantly reduce the loss of stimulated C peptide or improve clinical outcomes over a 15-month period.

RESUMEN:

A 27-year-old woman was admitted to a hospital in Ethiopia because of severe abdominal pain during labor, with cessation of contractions. She had been in labor at home, pushing for 24 hours. On arrival at the hospital 3 hours later, she was in shock. A procedure was performed.

RESUMEN:

Evaluation and treatment (with psychotherapy, antidepressant therapy, or both) of women with depression during pregnancy are described. Data on potential benefits and risks of antidepressant medications in pregnancy are reviewed; overall, the absolute risks are small.


RESUMEN:

A recent study by Smith and colleagues shows that the transcription factor Rfx6 is mandatory for the development of pancreatic endocrine cells. These investigators carried out experiments in a mouse model and in human tissue specimens and obtained highly concordant results (Fig. 1). They showed that, in mice, Rfx6 is expressed in the definitive endoderm early during development and is then restricted to the gut and pancreatic bud, reactivated in endocrine progenitors, and ultimately restricted to pancreatic islets in adults. They also found that RFX6 is expressed in human pancreatic tissue with an expression pattern consistent with that of Rfx6 in adult mice. Rfx6-deficient mice exhibited gross bowel distention due to small-bowel obstruction and died within 2 days post partum. Although the pancreas was present, with many endocrine cells positive for chromogranin, these cells did not express the hormones insulin, glucagon, somatostatin, or ghrelin.


RESUMEN:

**Background** We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease. **Methods** We randomly assigned 5518 patients with type 2 diabetes who were being...
treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. **Results**

The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79 to 1.08; P= 0.32). There were also no significant differences between the two study groups with respect to any secondary outcome. Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.10; P= 0.33). Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P= 0.01 for interaction), and a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol (P = 0.057 for interaction). **Conclusions** The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.


**RESUMEN:**

**Background** There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events. **Methods** A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. **Results** After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P= 0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P= 0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively.
(hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P= 0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001). **Conclusions** In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.


**RESUMEN:**

Dr. Elizabeth Guancial (Medicine): A 32-year-old woman was evaluated because of oligomenorrhea and difficulty becoming pregnant. Menarche had occurred at 12 years of age and menses were regular until the patient began taking oral contraceptives at 20 years of age. At 25 years of age, she discontinued oral contraceptives and irregular menstrual cycles developed, ranging from 31 to 51 days, with menstrual flow of 7 days' duration. Between the ages of 28 and 32 years, she had unprotected coitus with her husband but did not conceive. At 32 years of age, her primary care provider referred her to a gynecologist because of infertility. The patient reported that testing with over-the-counter ovulation-predictor kits did not show evidence of ovulation. Pelvic examination revealed no abnormalities. Clomiphene citrate was administered (100 mg on days 5 through 9 of the menstrual cycle). Laboratory-test results are shown in Table 1. A hysterosalpingogram was normal.