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JOURNAL WATCH

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Effects of 12 weeks of treatment with fermented milk on blood pressure, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes

EDITOR'S VIEW

Previous studies have indicated a blood pressure (BP) - lowering effect of milk-derived peptides in non-diabetic individuals, but the cardiometabolic effects of such peptides in patients with type 2 diabetes (T2DM) are not known. This group investigated the effect of milk fermented with Lactobacillus helveticus on BP, glycaemic control and cardiovascular risk factors in T2D.

Ingestion of milk fermented with L. helveticus compared with placebo for 12 weeks did not significantly reduce BP in patients with T2DM. But there was lowering of heart rate and fasting plasma glucose levels in T2DM patients during ingestion of fermented milk. This is a small study and needs further confirmation.

This is a randomized double-blind placebo-controlled study. In one arm, 41 patients with T2DM were randomized to receive 300 ml milk fermented with L. helveticus (Cardi04 yogurt) (n=23) or 300 ml artificially acidified milk (placebo yogurt) (n=18) for 12 weeks. BPs were measured over 24-h, and blood samples were collected in the fasting state and during a meal test before and after the intervention.

The Cardi04 yogurt group did not reduce 24-h, daytime or nighttime systolic or diastolic BPs compared with placebo ($P>0.05$). Daytime and 24-h heart rate (HR) were significantly reduced in the group treated by Cardi04 yogurt compared with the placebo group ($P<0.05$ for both). There were no differences in HbA1c, plasma lipids, C-reactive protein, plasminogen activator inhibitor-1, tumour necrosis factor alpha, tissue-type plasminogen activator: Ag, and von Willebrand factor: Ag between the groups. The change in fasting blood glucose concentration differed significantly between the two groups with a larger increase in the placebo group ($P<0.05$).

Source: K D Hove, C Brøns, K Færch et al. Eur J Endocrinol January 1, 2015 172 11-20.

Sustained Prognostic Implications of Newly Detected Glucose Abnormalities in Patients with Acute Myocardial Infarction: Long Term Follow-Up of the Glucose Tolerance in Patients with Acute Myocardial Infarction cohort

EDITOR'S VIEW

If one OGTT is performed before hospital discharge after an AMI, it can disclose a high prevalence of glucose abnormalities and can identify individuals at a substantially increased risk for future major cardiovascular. In contrast, patients with NGT have a considerably more benign prognosis. The results strongly support that not only blood glucose should be monitored during AMI, but OGTT after AMI add important and independent prognostic information in patients without previously known glucose abnormalities.

This study investigated the long-term prognostic importance of newly discovered glucose disturbances in patients with acute myocardial infarction (AMI) during 1998–2001. Consecutive patients with AMI (n = 167) and healthy controls (n = 184) with no previously known diabetes were investigated with an oral glucose tolerance test (OGTT). Patients and controls were separately followed up for cardiovascular events (first of cardiovascular mortality/AMI/stroke/heart failure) during a decade.

In all, 68% of the patients and 35% of the controls had newly detected abnormal glucose tolerance (AGT). Cardiovascular event (n = 72, p = 0.0019) and cardiovascular mortality (n = 31, p = 0.031) were more frequent in patients with newly detected AGT. Regarding patients, a Cox proportional-hazard regression analysis identified AGT (hazard ratio (HR): 2.30; 95% confidence interval (CI): 1.24–4.25; p = 0.008) and previous AMI (HR: 2.39; CI: 1.31–4.35; p = 0.004) as prognostically important.

The conclusion was that, an OGTT at discharge after AMI disclosed a high proportion of patients with previously unknown AGT which had a significant and independent association with long-term prognosis.

Source: Viveca Ritsinger, Eleni Tanoglidi, Klas Malmberg et al. Diabetes & Vascular Disease Research 2015, Vol. 12(1) 23–32.

Glucose Counter regulation in Advanced Type 2 Diabetes: Effect of Beta-Adrenergic Blockade

This study examined the counter-regulatory glucose kinetics and tested the hypothesis that beta-adrenergic blockade impairs these in patients with type 2 diabetes mellitus (T2DM) and advanced beta cell-failure. Nine insulin-requiring T2DM subjects and six matched nondiabetic control subjects were studied. Beta-Cell function was assessed by the C-peptide response to arginine stimulation. Counter-regulatory hormonal responses and glucose kinetics were assessed by hyperinsulinemic euglycemic-hypoglycemic clamps with (3-3Hour) glucose infusion. T2DM subjects underwent two clamp experiments in a randomized crossover fashion: once with infusion of the b-adrenergic antagonist propranolol and once with infusion of normal saline.

Compared with the control subjects, T2DM subjects had threefold reduced C-peptide responses to arginine stimulation. During the hypoglycemic clamp, glucagon responses were markedly diminished (16.064.2 vs. 48.666.0 ng/L, P < 0.05),but other hormonal responses and the decrement in the required exogenous glucose infusion rate (GIR) from the euglycemic clamp were normal (210.4 6 1.1 vs. 27.861.9 mmol · kg21 · min21 in control subjects); however, endogenous glucose production (EGP) did not increase (20.8 6 1.0 vs. 2.2 6 0.7 mmol · kg21 · min21 in control subjects, P < 0.05), whereas systemic glucose disposal decreased normally. Beta-Adrenergic blockade in the T2DM subjects increased GIR <“20% during the euglycemic clamp (P < 0.01), but neither increased GIR during the hypoglycemic clamp or decreased its decrement from the euglycemic clamp to the hypoglycemic clamp.

EDITOR'S VIEW

The overall glucose counter-regulation is usually preserved in advanced T2DM, but the contribution of EGP is diminished. The Beta-Adrenergic blockade may increase insulin sensitivity at normoglycemia but does not impair glucose counter-regulation in T2DM patients, even those with advanced beta-cell failure.

Conventionally it is thought that beta blockers particularly the non-selective beta blockers block the counter regulation during hypoglycemia and lead to hypoglycaemia unawareness .But this small study reveals that nonselective beta-adrenergic blockade does not impair glucose counter-regulation, suggesting that beta-blocker therapy may not increase the risk of severe hypoglycemia in these patients.

Source: Syed Bokhari, Elena Plummer, Peter Emmerson et al. Diabetes Care 2014;37:3040–3046.

Dietary Intervention in Patients with Gestational Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Clinical Trials on Maternal and Newborn Outcomes

Diet is the pivotal treatment of patients with gestational diabetes mellitus (GDM), but its role in maternal and new born outcomes has not been convincingly studied. The study analysed the efficacy of dietary interventions on maternal or new born outcomes in patients with GDM.

A systematic review and meta-analysis of randomized clinical trials (RCTs) of dietary intervention in GDM or pregnancy with hyperglycemia was done. The main evaluated maternal outcomes were proportion of patients using insulin and proportion of cesarean delivery; the new born outcomes were proportion of macrosomia and hypoglycemia and new born weight.

From 1,170 studies, nine RCTs, including 884 women aged 31.5 years (28.7–33.2) with 27.4 weeks (24.1–30.3) of gestation, were eligible. They divided the RCTs according to the type of dietary intervention: low glycemic index (GI) (n = 4; 257 patients), total energy restriction (n = 2; 425 patients), low carbohydrates (n = 2;182 patients), and others (n = 1; 20 patients). Diet with low GI reduced the proportion of patients who used insulin (relative risk 0.767 [95% CI 0.597, 0.986];P = 0.039) and the new born birth weight (weight mean differences 2161.9 g [95%CI 2246.4, 277.4]; P = 0.000) as compared with control diet. Total restriction and low carbohydrate diets did not change either maternal or new born outcomes. A low GI diet was associated with less frequent insulin use and lower birth weight than control diets, suggesting that it is the most appropriate dietary intervention to be prescribed to patients with GDM.

EDITOR'S VIEW

There is no evidence based consensus regarding the nature of diet ideal in GDM. The investigators demonstrated that in GDM, the use of a low GI diet was associated with less frequent insulin use and lower birth weight than the control diets, without any detected adverse effects. Therefore, the present available evidence suggests that a low GI diet is the most appropriate dietary intervention to be prescribed to patients with GDM.

Source: Luciana Verçoza Viana, Jorge Luiz Gross, Mirela Jobim Azevedo. Diabetes Care 2014;37:3345–3355.

Pre-Pregnancy Fried Food Consumption and the Risk of Gestational Diabetes Mellitus: A Prospective Cohort Study

The health effects of different types of preparing food in gestational diabetes mellitus (GDM) are not well understood. The study aimed to prospectively examine the association between pre-pregnancy fried food consumption and risk of incident gestational diabetes mellitus (GDM). About 21,079 singleton pregnancies from15,027 women in the Nurses' Health Study II cohort were included. Since1991 and every 4 years thereafter, the diet information were collected, including consumption of fried foods at home and away from home, using a validated food frequency questionnaire.

The researchers documented 847 incident GDM pregnancies during10 years of follow-up. After adjustment for age, parity, dietary and non-dietary factors, the RRs (95% CIs) of GDM among women who consumed total fried foods 1–3, 4–6 ande"7 times/week, compared with those who consumed it less than once/week, were 1.13 (0.97, 1.32), 1.31 (1.08, 1.59) and2.18 (1.53, 3.09), respectively (p for trend <0.001). The association persisted after further adjustment for BMI (p fortrend=0.01). When analysed separately, it was found that there was a significant association of GDM with fried food consumption away from home, but not with fried food consumption at home.

Source: Wei Bao, Deirdre K, Tobias &Sjurdur F, Olsen, Cuilin Zhang. Diabetologia (2014) 57:2485–2491.

EDITOR'S VIEW

The probable detrimental effects of fried food consumption on GDM risk may be due to the modification of foods and frying medium, and generation of harmful by-products during the frying process. Frying deteriorates oils through the processes of oxidation and hydrogenation , leading to an increase in the absorption of oil degradation products by the foods being fried, and also a loss of unsaturated fatty acids such as linoleic and linolenic acids and an increase in the corresponding trans-fatty acids such as trans-linoleic acids and trans-linolenic acids.

Frequent fried food consumption has been shown to be significantly and positively associated with the risk of incident GDM in this prospective cohort study. This study indicates potential benefits of limiting fried food consumption in the prevention of GDM in women of reproductive age. But further studies are necessary to confirm these findings.

Pharmacokinetics and Pharmacodynamics of Insulin Glargine Given in Evening as Compared With in Morning in Type 2 Diabetes Mellitus

Porcellatiet al. compared the pharmacokinetics (PK) and pharmacodynamics (PD) of insulin glarginein type 2 diabetes mellitus (T2DM) after evening versus morning administration. Ten T2DM insulin-treated persons were studied during 24-h euglycemic glucoseclamp, after glargine injection (0.4 units/kg s.c.), either in the evening (2200 h) or the morning (1000 h).

The 24-h glucose infusion rate area under the curve (AUC [0-24h]) was similar in the evening and morning studies (995 6 691, 1,058 6 571 mg/kg 3 24 h, P =0.503), but the first 12 h (AUC [0-12h]) was lower with evening versus morning glargine (357 6 244 vs. 593 6 374 mg/kg 3 12h, P = 0.004), whereas the opposite occurred for the second 12 h (AUC [12-24] 7006396 vs. 4036343 mg/kg 324 h,P = 0.002). The glucose infusion rate differences were totally accounted for by different rates of endogenous glucose production, not utilization. Plasma insulin and C-peptide levels did not differ in evening versus morning studies. Plasmaglucagon levels ([AUC0–24h] 1,120 6 344 vs. 1,533 6 656 ng/L/h, P = 0.027) andlipolysis (free fatty acid AUC0–24h 7.561.6 vs. 8.961.9 mmol/L/h, P = 0.005; b-OHbutyrateAUC0–24h 6.8 6 4.7 vs. 17 6 12 mmol/L/h, P = 0.005; glycerol, P < 0.020)were overall more suppressed after evening versus morning glargine administration.

EDITOR'S VIEW

In this study, total insulin activity on glucose metabolism is similar with evening or morning glargine administration. However, with evening glargine administration, the suppression of nocturnal endogenous glucose production lipolysis, and glucagon concentration are more consistent. One explanation might be different, PK in the first 12-hperiod compared with the second 12-hperiod.The other explanation may be that insulin sensitivity might be greater during daytime hours compared with nighttime hours.

Regardless of the mechanisms, the differential insulin activity observed in the current study after morning glargine administration compared with evening glargine administration is meaningful in clinical practice. So targeting fasting euglycemia appears more convenient with evening glargine dosing compared with morning glargine dosing. Conversely, morning dosing may be preferable whenever greater protection against the risk for nocturnal hypoglycemia is needed.

Source: Francesca Porcellati, Paola Lucidi, Patrizia Cioli, et al. Diabetes Care Publish Ahead of Print, published online December 18, 2014.1-10.

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Moderate or Severe Renal Impairment: Observations from the SAVOR-TIMI 53 Trial

The glycemic management of patients with type 2 diabetes mellitus (T2DM)and renal impairment is challenging, with few treatment options. The Savor-Timitrial group investigated the effect of saxagliptin in the SAVOR-TIMI 53 trial according to baseline renal function. Patients with T2DM at risk for cardiovascular events were stratified as having normal or mildly impaired renal function (estimated glomerular filtration rate [eGFR] >50 mL/min/1.73 m2; n = 13,916), moderate renal impairment (eGFR30–50 mL/min/1.73 m2; n = 2,240), or severe renal impairment (eGFR<30mL/min/1.73 m2; n = 336) and randomized to receive saxagliptin or placebo.

The primary end point was cardiovascular death, myocardial infarction, orischemic stroke. After a median duration of 2 years, saxagliptin neither increased nor decreased the risk of the primary and secondary composite end points compared with placebo, irrespective of renal function (all P for interactions ‡0.19). Overall, the risk of hospitalization for heart failure among the three eGFR groups of patients was2.2% (referent), 7.4% (adjusted hazard ratio [HR] 2.38 [95% CI 1.95–2.91], P <0.001), and 13.0% (adjusted HR 4.59 [95% CI 3.28–6.28], P < 0.001), respectively .The relative risk of hospitalization for heart failure with saxagliptin was similar (P for interaction = 0.43) in patients with eGFR>50 mL/min/1.73m2 (HR 1.23 [95%CI 0.99–1.55]), eGFR 30–50 mL/min/1.73 m2 (HR 1.46 [95% CI 1.07–2.00]), and inpatients with eGFR<30 (HR 0.94 [95% CI 0.52–1.71]). Patients with renal impairment achieved reductions in microalbuminuria with saxagliptin (P = 0.041) that were similar to those of the overall trial population.

The study reveals that Saxagliptin did not affect the risk of ischemic cardiovascular events, increased the risk of heart failure hospitalization, and reduced progressive albuminuria, irrespective of baseline renal function.

EDITOR'S VIEW

Treatment of patients with T2DMand CKD is a problem to target both the hyperglycemia and prevention of progressive nephropathy. Intensive glucose management strategies and some anti-hyperglycemic medications lead to inherent risks, including adverse CV, renal, and hypoglycemic events.

In the SAVOR-TIMI 53 trial, the relative effects of saxagliptin on CV, renal, and glycemic end points were consistent in patients with moderate-to-severe renal impairment compared with patients with normal or mildly impaired renal function was seen. These findings highlight the increased CV risk of patients with diabetic nephropathy, and provide data on the efficacy and safety of saxagliptin to inform clinicians when formulating treatment strategies for their patients with concomitant T2DM and renal impairment.

Source: Jacob A. Udell, Deepak L. Bhatt, Eugene Braunwald et al. Diabetes Care Publish Ahead of Print, published online December 31, 2014.1-10.

FDA Approves New Weight-Management Drug on December 24, 2014

The US Food and Drug Administration (FDA) has approved liraglutide 3mg (rDNA origin [Saxenda]) injection as a treatment option for chronic weight management together with a reduced-calorie diet and physical activity. The drug is approved for use in adults with a body mass index (BMI) of e"30 or adults with a BMI of e"27 who have at least 1 weight-related condition such as hypertension, type 2 diabetes or dyslipidaemia.

Saxenda is a glucagon-like peptide-1 (GLP-1) receptor agonist. The safety and effectiveness of liraglutide were evaluated in 3 clinical trials including approximately 4,800 obese and overweight patients with and without significant weight-related conditions. All patients were following lifestyle modifications that consisted of a reduced-calorie diet and regular physical activity.

In the trial, patients without diabetes showed that

patients had an average weight loss of 4.5% from baseline compared with treatment with a placebo at 1 year. In this trial, 62% of patients treated with liraglutide lost at least 5% of their body weight compared with 34% of patients treated with placebo.

Another trial that enrolled patients with type 2 diabetes showed that patients had an average weight loss of 3.7% from baseline compared with treatment with placebo at 1 year. In this trial, 49% of patients treated with liraglutide lost at least 5% of their body weight compared with 16% of patients treated with placebo.

Patients using liraglutide should be evaluated after 16 weeks to determine if the treatment is working. If a patient has not lost at least 4% of baseline body weight, the drug should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Liraglutide should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

Serious side effects include pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts. Liraglutide can also raise heart rate and should be discontinued in patients who experience a sustained increase in resting heart rate. In clinical trials, the most common side effects observed in patients treated with liraglutide were nausea, diarrhoea, constipation, vomiting, hypoglycaemia, and decreased appetite. The cardiovascular safety of liraglutide is being investigated in an ongoing cardiovascular outcome trial.

EDITOR'S VIEW

Till date we are in dearth of an ideal anti-obesity drug. Preliminary results are promising. Liraglutide may be an answer. Future experience after its use in large number may answer properly.

Source: US Food and Drug Administration

Prevalence of Diabetes and Cardiovascular Risk Factors in Middle class Urban Participants in India

This Indian study attempted to determine the prevalence of diabetes and awareness, treatment and control of cardiovascular risk factors in population-based participants in India in 11 cities indifferent regions of India using cluster sampling. Participants were evaluated for demographic, biophysical, and biochemical risk factors. 6198 participants were recruited, and in 5359 participants (86.4%, men 55%), details of diabetes (known or fasting glucose >126 mg/dL), hypertension (known or blood pressure >140/>90 mm Hg), hypercholesterolemia (cholesterol>200 mg/dL), low high-density lipoprotein (HDL) cholesterol (men <40, women <50 mg/dL), hypertriglyceridemia (>150 mg/dL), and smoking/tobacco use were available. Details of awareness, treatment, and control of hypertension and hypercholesterolemia were also obtained.

The age-adjusted prevalence (%) of diabetes was 15.7 (95% CI 14.8 to 16.6; men 16.7, women 14.4)and that of impaired fasting glucose was 17.8 (16.8 to18.7; men 17.7, women 18.0). In participants with diabetes, 27.6% were undiagnosed, drug treatment was in 54.1% and control (fasting glucose d"130 mg/dL) in39.6%. Among participants with diabetes versus those without, prevalence of hypertension was 73.1 (67.2 to75.0) vs 26.5 (25.2 to 27.8), hypercholesterolemia 41.4(38.3 to 44.5) vs 14.7 (13.7 to 15.7),hypertriglyceridemia 71.0 (68.1 to 73.8) vs 30.2 (28.8 to31.5), low HDL cholesterol 78.5 (75.9 to 80.1) vs 37.1(35.7 to 38.5), and smoking/ smokeless tobacco use in26.6 (23.8 to 29.4) vs 14.4 (13.4 to 15.4; p<0.001). Awareness, treatment, and control, respectively, of hypertension were 79.9%, 48.7%, and 40.7% and those of hypercholesterolemia were 61.0%, 19.1%, and 45.9%, respectively.

Editor's view

This nationwide study shows that the prevalence of diabetes among the urban middle-class participants in India is greater than that reported by the International Diabetes Federation. More than a quarter of patients with diabetes in the Indian urban middle class are not diagnosed.

In patients with diabetes, cardiovascular risk factors—hypertension, hypercholesterolemia, low HDL and hypertriglyceridemia are very common. There is a poor status of treatment and control. The low status of control of hypertension and hypercholesterolemia in participants with known diabetes is a serious issue. Effective plans for early diagnosis, for improvement of risk factor management and control should be developed in India to prevent premature cardiovascular disease in diabetes and to save the younger generation.

Source: Arvind Gupta, Rajeev Gupta, Krishna Kumar Sharma et al. BMJ Open Diabetes Research and Care 2014; 2:e000048.

High-Intensity Statin Therapy Alters the Natural History of Diabetic Coronary Atherosclerosis: Insights from SATURN

This study tested the hypothesis that high intensity statin therapy may promote coronary atheroma regression in patients with diabetes. The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg oratorvastatin 80 mg for 24 months. This analysis compared changes in biochemistry and coronary percent atheroma volume (PAV) in patients with (n = 159) and without (n = 880) diabetes.

At baseline, patients with diabetes had lower LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels but higher triglyceride and CRP levels compared with patients without diabetes. At follow-up, diabetic patients had lower levels of LDL-C (61.0 6 20.5 vs. 66.4 6 22.9 mg/dL, P = 0.01) and HDL-C (46.3 6 10.6 vs.49.9612.0 mg/dL, P < 0.001) but higher levels of triglycerides (127.6 [98.8, 163.0]vs. 113.0 mg/dL [87.6, 151.9], P = 0.001) and CRP (1.4 [0.7, 3.3] vs. 1.0 [0.5, 2.1]mg/L, P = 0.001).

Both patients with and without diabetes demonstrated regression of coronary atheroma as measured by change in PAV (20.83 6 0.13 vs.21.15 6 0.13%, P = 0.08). PAV regression was less in diabetic compared with nondiabetic patients when on-treatment LDL-C levels were >70 mg/dL (20.31 60.23 vs. 21.01 6 0.21%, P = 0.03) but similar when LDL-C levels were £70 mg/dL(21.09 6 0.16 vs. 21.24 6 0.16%, P = 0.50).

Thus it is expected that high-intensity statin therapy alters the progressive nature of diabetic coronary atherosclerosis, yielding regression of disease in diabetic and nondiabetic patients.

EDITOR'S VIEW

Though not a very large study but this study establishes that, high-intensity statin therapy is associated with coronary atheroma regression in both diabetic and nondiabetic patients and alter the progressive nature of diabetic atherosclerosis. This response in diabetic individuals appears maximal if end point LDL-C levels are below a 70 mg/d. These observation support the use of high-intensity statin treatment in diabetic patients with atherosclerotic disease. But, further research is required to determine the specific LDL-C targets required to achieve plaque regression and lower clinical event rates in these high-risk diabetic patients with and without clinical atherosclerotic disease.

Source: Brian Stegman, Rishi Puri, Leslie Cho et al. Diabetes Care 2014;37:3114–20.