Sugar-sweetened drinks increase cardiovascular risk in women

Women who drink two or more sugar-sweetened beverages daily experience increasing waist circumferences as well high triglycerides and elevated risk for type 2 diabetes when compared with women who drink fewer than one such beverage a day.

Christina Shay, Oklahoma Health Sciences Center in USA, et al compared adults (45-84 years) who drank two or more sugar-sweetened beverages a day with women who drank one or less daily.

The study included 4166 African American, Caucasian, Chinese, and Latino adults without cardiovascular disease and determined their consumption of sugar-sweetened beverages through use of a food frequency questionnaire. The cardiovascular risk factors were identified at three exams (2002-2003, 2004-2005, and 2005-2007). Cardiovascular risk factors included weight gain (>3 % higher than baseline), increased waist circumference (>3 % higher than baseline), low HDL (<40 mg/dL for men and <50 mg/dL for women), high triglycerides (>40 mg/dL for men and >50 mg/dL for women), impaired fasting glucose (101-126 mg/dL), and type 2 diabetes (fasting glucose >126 mg/dL or use of diabetes medication).

Conclusions: Women consuming two or more beverages per day were found to be nearly 4 times as likely to develop high triglycerides, and were significantly more likely to increase their waist sizes and develop impaired fasting glucose levels. The same associations were not observed in men.

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Children & Adolescents with Type 2 DM share Same Defects in Insulin Secretion as Adults

Type 2DM occurs in adults and is characterized by the inability of the β-cells to compensate for decreased insulin sensitivity. Data indicate that the same mechanisms are responsible for new forms of T2DM, which occur earlier in life, in obese children and adolescents.

In non-diabetics, β-cells adapt insulin secretion to compensate for insulin resistance. If this compensation fails, hyperglycaemia arises, resulting in IFG, IGT and T2DM. In this study, β-cell function decreased by nearly 40 % in those who progressed from normal to IGT, and by 20 % only in subjects whose glucose tolerance remained normal.

In youths, the same mechanisms for progression were seen, with emphasis on defects in insulin secretion rather than in insulin sensitivity. β-cell function was reduced by nearly 50 % in children. In another study from the same group, including 147 overweight young patients, aged 8-<20 years, mean BMI 35 to 37.5 kg/m², hyperinsulinaemic-euglycaemic clamps, hyperglycaemic clamps, and OGTT were performed. Youths with normal glucose tolerance presented with the highest β-cell function. β-cell function significantly declined by around 40 % in youths, and by around 75 % in youths with 2-h glucose levels in the diabetic range.

The data indicate a broad range of defects of insulin secretion in overweight youths, with a continuum from normal insulin secretion in patients with normal glucose tolerance to severely reduced insulin secretion in youth with T2DM. These results are close to those in adults with IGT and T2DM.

P-J. Guillausseau - Paris, France Jan 17, 2012
**A 2-Year Trial of Obesity Treatment in Primary Care Practice**

**BACKGROUND:** This randomized trial compared weight loss during a 2-year period in response to three lifestyle interventions, all delivered by Primary Care Physicians (PCPs) in collaboration with auxiliary health professionals (lifestyle coaches) in their practices.

**METHODS:** 390 obese adults in six primary care practices were randomly assigned to one of three types of intervention: usual care, consisting of quarterly PCP visits with education about weight management; brief lifestyle counselling, consisting of quarterly PCP visits combined with brief monthly sessions with lifestyle coaches who instructed participants about behavioural weight control; or enhanced brief lifestyle counselling, which provided the same care as described for the previous intervention but included meal replacements or weight-loss medication (orlistat or sibutramine), chosen by the participants in consultation with the PCPs, to potentially increase weight loss.

**RESULTS:** Of the 390 participants, 86 % completed the 2-year trial, at which time, the mean (±SE) weight loss with usual care, brief lifestyle counselling, and enhanced brief lifestyle counselling was 1.7±0.7, 2.9±0.7, and 4.6±0.7 kg, respectively. Enhanced lifestyle counselling was superior to usual care on both these measures of success (P=0.003 and P=0.02, resp.), with no other significant differences among the groups. The benefits of enhanced lifestyle counselling remained even after participants given sibutramine were excluded from the analyses. There were no significant differences between the intervention groups in the occurrence of serious adverse events.

**CONCLUSIONS:** Enhanced weight-loss counselling helps about one third of obese patients achieve long-term, clinically meaningful weight loss.


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**Effect of Two Intensive Statin Regimens on Progression of Coronary Disease**

**BACKGROUND:** Statins reduce adverse CV outcomes and slow the progression of coronary atherosclerosis in proportion to their ability to reduce LDL cholesterol. However, few studies have either assessed the ability of intensive statin treatments to achieve disease regression or compared alternative approaches to maximal statin administration.

**METHODS:** Serial intravascular ultrasonography (IVUS) was performed in 1039 patients with CAD, at baseline and after 104 weeks of treatment with either atorvastatin 80 mg daily, or rosuvastatin 40 mg daily, to compare effects of the two intensive statin regimens on progression of coronary atherosclerosis, and to assess their safety and side-effect profiles.

**RESULTS:** After 104 weeks of therapy, the rosuvastatin group had lower levels of LDL-C than the atorvastatin group [1.62 vs. 1.82 mmol/l], P<0.001), and higher levels of HDL-C [1.30 vs. 1.26 mmol/l], P=0.01). The primary efficacy end point, percent atheroma volume (PAV), decreased by 0.99 % (95 % confidence interval [CI], −1.19 to −0.63) with atorvastatin and by 1.22 % (95 % CI, −1.52 to −0.90) with rosuvastatin (P=0.17). The effect on the secondary efficacy end point, normalized total atheroma volume (TAV), was more favourable with rosuvastatin than with atorvastatin: −6.39 mm³ (95 % CI, −7.52 to −5.12), as compared with −4.42 mm³ (95 % CI, −5.98 to −3.26) (P=0.01). Both agents induced regression in the majority of patients: 63.2 % with atorvastatin and 68.5 % with rosuvastatin for PAV (P=0.07) and 64.7 % and 71.3 %, resp., for TAV (P=0.02). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

**CONCLUSIONS:** Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups.

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Among obesity parameters, including body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR), a high predictive value of WHR for MI has been shown by the INTERHEART study in whole populations from 70 countries. No association was found with BMI and WC. The value of WHR as a marker of CV risk has been confirmed by results of a meta-analysis of prospective cohort studies and randomized clinical trials of CV risk and markers of abdominal obesity. For any 0.01 U increase in WHR, the relative risk (RR) for CV events increased by 5 % (95 % CI: 4-7 %), the results being consistent in both genders. Is it the same in type 2 diabetes (T2DM)?

Recently published results of the ADVANCE trial cohort provide important information on this point. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial included 11 140 patients with T2DM. The aim of ADVANCE was to compare the effect of an intensive vs. conventional glucose control strategy (HbA1c 6.5 % vs. 7.3 %) on micro- and macrovascular complications, and deaths. The first part of the trial was completed in 2008, with a 5-year prolongation (ADVANCE-ON) now in progress. After a mean 5-year follow-up duration, a 10 % reduction ($P=0.013$) in the primary criteria (major micro- and macrovascular events and deaths), a 14 % reduction in microvascular events ($P=0.015$), and a trend toward a reduction in CV deaths (12 %, $P=0.12$) were observed in the intensive group.

The present analysis aimed at investigating in T2DM the association of BMI, WC, and WHR with CV risk and establishing the predictive value of the indices for this purpose. Hazard ratios (HR), and 95 % confidence intervals (95 % CI) were calculated by Cox proportional hazard models with multiple adjustments for 1 standard deviation (SD) increase in baseline BMI (5 kg/m²), WC (13 cm), and WHR (0.08 U) with CV outcome (CV events, coronary events, and CV deaths). No association was found between BMI and the three predefined outcomes. HRs for WC were 1.10 (CI 1.03-1.18) for CV events, 1.13 (CI 1.03-1.24) for coronary events, and 1.08 (CI 0.98-1.19) for CV deaths. HRs for WHR were 1.12 (CI 1.05-1.19) for CV events, 1.17 (CI 1.08-1.28) for coronary events, and 1.19 (1.09-1.31) for CV deaths. Further statistical analysis indicated that WHR had the best discriminative value, except for cerebrovascular outcomes.

**Conclusion:** The analysis of the ADVANCE cohort is the first study to assess the relative value of the different adiposity markers for predicting CVD risk and deaths in a large population of patients with T2DM. The results indicate that markers of abdominal obesity, and particularly WHR, possess the best predictive value for future CVD events.

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**Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy**

**BACKGROUND:** In patients with established CVD, residual CV risk persists despite the achieving target LDL-C with statin therapy. Would extended-release niacin added to simvastatin raise low levels of HDL-C and be superior to simvastatin alone in reducing such residual risk?

**METHODS:** Patients received extended-release niacin, 1500 to 2000 mg daily, or placebo. All received simvastatin, 40-80 mg daily, plus ezetimibe 10 mg/day, if needed, to maintain an LDL-C of 1.03 to 2.07 mmol/l. The primary end point was the first event of the composite of death from CAD, nonfatal MI, ischemic stroke, hospitalization for ACS, or revascularization.

**RESULTS:** 3414 patients were randomly assigned to niacin (1718) or placebo (1696). The trial was stopped after 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased HDL-C from 0.91 to 1.08 mmol/l, lowered TGs 1.85 to 1.38 mmol/l, and lowered the LDL-C 1.91 to 1.60 mmol/l. The primary end point occurred in 282 patients on niacin (16.4 %) and in 274 patients on placebo (16.2 %) (HR 1.02; 95 % confidence interval, 0.87 to 1.21; $P=0.79$ by the log-rank test).

**CONCLUSIONS:** Among patients with CVD and LDL-C <1.81 mmol/l, there was no clinical benefit from addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.

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Islet Inflammation impairs Insulin Secretion in Type 2 diabetes

Type 2 diabetes (T2DM) is characterized by an activation of the innate immune system. This is reflected in the circulation by increased levels of CRP, leukocytes and cytokines and chemokines, including IL-6, IL-1Ra, and MCP-1. At tissue level, inflammation is apparent through changes in cytokines, chemokines, immune cell infiltration, apoptosis, and tissue fibrosis. Such changes can be detected in adipose tissue, the liver, pancreatic islets, and the vasculature. Animal and clinical studies suggest that these inflammatory processes play an important role in the pathogenesis of T2DM. An understanding of the mechanisms may open the door to novel therapeutic approaches aiming at improvement of insulin production and action. The article focuses on islet inflammation as a cause of β-cell failure.

Several mechanisms have been proposed to explain islet β-cell dysfunction in T2DM. These include oxidative stress, endoplasmic reticulum stress, pancreatic amyloid deposition, lipotoxicity, and glucotoxicity. Each of these cellular stresses is also thought to either induce an inflammatory response or to be promoted by inflammation. Thus, these factors should be viewed as part of the multiple causes of islet dysfunction and not as separate mechanisms.

Initially, islet inflammation was shown to be a mechanism underlying glucotoxicity. Indeed, increased glucose levels induce β-cell production of IL-1β, a key cytokine regulating immunity. This induces cytokines and chemokines which recruit immune cells. Free fatty acid (FFA)-induced islet-derived IL-1β has also been observed, in combination with increased glucose levels. Accordingly, antagonism of IL-1β decreases tissue inflammation and improves β-cell function. Of note, clinical studies failed to demonstrate improvement in insulin resistance, only enhanced insulin secretion. However, based on a number of animal studies, IL-1β antagonism under certain conditions is expected to improve also insulin sensitivity.

A major advance was the discovery of the Inflammasome by Jürg Tschopp. Inflammasome is a molecular complex that, when activated, results in the production of IL-1β. It appears to be a sensor of danger molecules such as increased levels of glucose, cholesterol, FFA, and uric acids. Conceptually, this means that innate immunity is an integral part of the adaptation to changes in metabolism. Therefore it may have beneficial roles and only when chronically activated leads to a deleterious inflammatory process.

Several studies modulating the IL-1 system or a downstream factor, NF-κB, have convincingly shown that inflammation is a possible therapeutic target to improve insulin secretion and action. A large outcome study with CVD and diabetes end-points using an anti-IL-1β antibody has been recently launched. Many questions remain unanswered. What is the durability of the effects? What is the best therapeutic modality: short-term interventions aiming at breaking inflammatory flare-ups or continuous treatment? Which patients will benefit best from this treatment? Will serious side effects emerge? What are the interference with other drugs displaying anti-inflammatory effects (e.g., statins, thiazolidinediones, gliclazide)? Although many questions remain open, it is exciting that for the first time drugs may be able to interfere with the pathogenesis of the disease.

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