β-Cell failure is a major and constant determinant of type 2 diabetes mellitus (T2DM), aside from defects in insulin sensitivity due to environmental factors (excess body weight and lack of physical exercise). According to most work in the field, insulin secretory defects have been currently explained by a severe decrease in β-cell mass in T2DM, β-cell death being due to increased apoptosis. However, some new data suggest that other mechanisms may be also involved in β-cell failure.

A recent study from Piero Marchetti et al. provides some new insights in the field. In addition to estimation of β-cell mass, the authors performed morphological, ultrastructural, and functional studies of β-cells from islets of T2DM and non-diabetic controls. For this purpose, age and sex matched pancreata from 10 non-diabetic and 10 organ donors with T2DM were studied by immune-cytochemistry and electron microscopy. Insulin secretion was measured from isolated diabetic and non-diabetic islets after stimulation of insulin secretion by glucose. Insulin release was also measured in non-diabetic islets after 24-hour exposure to high glucose concentrations (22.2 mmol/L). Compared with non-diabetic islet samples, fractional pancreatic and fractional islet areas positive for insulin staining were reduced in T2DM (0.47±0.13 % vs. 1.02±0.43 and 54.9±6.3 % vs. 72.1±8.7 % respectively; P<0.01), confirming previous results. No difference was observed between groups either for glucagon nor chromogranin A staining. Electron microscopy indicated a 10 % decrease (P=0.05) in the proportion of β-cells and a mean 45 % reduction in insulin granules in islets from T2DM pancreata. These last findings were similarly observed in non-diabetic islets after a 24-hour exposure to high glucose levels. Insulin degranulation may be responsible for an overestimation of β-cell loss, when β-cell number is assessed by standard immunochemistry staining for insulin. This dedifferentiation may also contribute to β-cell failure. Finally, marked insulin secretion defects were evidenced in T2DM islets. Glucose-induced insulin release was reduced by 50 % in T2DM isolated islets when compared with fresh non-diabetic islets (0.24±0.03% vs. 0.52±0.33; P=0.04). This reduction was also present in non-diabetic islets after pre-culture in a high glucose medium.

These results confirm previous data, which consistently indicated a significant reduction in β-cell mass, as well as severe functional insulin secretory defects in islets of T2DM patients when compared with non-diabetic islets. They also suggest that, at least in part, loss of β-cells may have been overestimated in T2DM pancreata, possibly due to dedifferentiation of β-cells. Finally, they may explain why insulin secretion is preserved for years when T2DM patients are treated with sulphonylureas.
A ccording to the results of a British Study, eating yoghurt could reduce the risk of developing type 2 diabetes by 28 percent, compared to not eating any yoghurt. Additionally, eating some other fermented dairy products, such as low-fat cheeses, could cut the risk by 24 percent.

"What our study shows is that yoghurt should be part of a healthy diet," said Dr. Nita Forouhi, group leader of the nutritional epidemiology program at the MRC at the University of Cambridge. "Although this study did not directly address the nutrients in yoghurt or low-fat fermented dairy products that are most beneficial, previous information suggests what they're likely to be. These include calcium, magnesium, vitamin D [in fortified dairy products] and potentially beneficial fatty acids, which are present in dairy products. Fermented dairy products, including yoghurt, are likely to have the further benefits of specific types of vitamin K and probiotic bacteria."

She added that the study "does not prove a cause-and-effect relationship, but highlights the importance of considering food group subtypes associations. Past research has focused on overall total dairy products intake, whereas our research was able to examine subtypes of dairy products."

The university-funded study appeared in the journal *Diabetologia*.

Samantha Heller, a senior clinical nutritionist at NYU Langone Medical Center, in New York City, said the new study "appears to echo what some studies, but not all, have found, which is that low-fat dairy foods may help reduce the risk of type 2 diabetes. Emerging research suggests that gut microbes play important roles in the development of type 2 diabetes, inflammation and other diseases".

For the study, Forouhi and colleagues collected data on 4,255 men and women who were part of a larger British study. This group included 753 people who developed type 2 diabetes over 11 years of follow-up and 3,502 randomly selected people for comparison.

Looking at these people's diets, the researchers found that the amount of high-fat dairy or total low-fat dairy was not linked to the risk of developing diabetes, once factors like healthy lifestyles, education, obesity, other eating habits and total calorie intake were taken into account.

Milk and cheese consumption was also not associated with the risk of developing diabetes. But what was significant was the amount of low-fat fermented dairy products, such as yoghurt, fromage frais (a fresh, low-fat curd cheese similar to cottage cheese), and low-fat cottage cheese participants ate, Forouhi's group found.

For those who ate the most of these foods, the risk of developing diabetes shrank 24 percent, compared with those who didn't eat any, the study found.

When the investigators looked specifically at yoghurt, the risk of developing diabetes was reduced by 28 percent. The lowered risk was seen among people who ate about 4.5 standard 125-gram cups of yoghurt a week. This was also the case for other low-fat fermented dairy products, such as low-fat unripened cheeses, including fromage frais and low-fat cottage cheese.

In addition, eating yoghurt instead of other snacks, such as chips, further cut the risk of developing type 2 diabetes, they noted.

Including fermented foods like yoghurt as part of an overall healthy diet is a good idea but is not the whole story, nutritionist Heller said.

"A primary risk factor for type 2 diabetes is being overweight or obese," Heller said. "Regular exercise, shifting to a more plant-based diet and reaching and maintaining a healthy weight will go a long way in helping to prevent type 2 diabetes."

© HealthDay, 25 Feb 2014
Hypoglycaemia and vascular risk in diabetes: where do we stand?

Ronan ROUSSEL, INSERM, UMR 872, Paris, France. 19 November, 2013

In the hours following the premature halt of the ACCORD study due to an excess in fatality cases in the glucose intensive arm, one obvious sequence of events was randomization to intensive glucose objectives, aggressive escalation of anti-diabetes drugs, including sulfonylurea and insulin, increased hypoglycaemic events rates parallel to a sharp fall in mean blood glucose values and many sudden deaths related to low blood glucose in frail persons.¹

Five years later, we simultaneously know that hypoglycaemia is undoubtedly associated with increased mortality, and that this sequence is not based on evidence. How can we reconcile these observations? Recent reports by the Ceriello’s group suggest things are not so simple; low glucose matters, but how you leave the red zone is also of importance.

Hypoglycaemia definitively means a poor prognosis in patients with diabetes and high cardiovascular risk. In the ADVANCE study, Zoungas et al concluded that severe hypoglycaemia was strongly associated with increased risks of a range of adverse clinical outcomes; indeed, risk of macrovascular events was roughly doubled for patients with a history of severe hypoglycaemia, but it was also the case for the risk of microvascular complications, or even the risk of cancer or diseases of the skin.² It is possible that severe hypoglycaemia sometimes contributes to adverse outcomes, but “these analyses indicate that hypoglycaemia is just as likely to be a marker of vulnerability to such events.”

The authors of the ACCORD study published a fascinating post-hoc analysis about the increased mortality in the intensive group.³ According to the commonly repeated sequence described above, we should expect that the more the HbA₁c decreased in the first months of the trial in the patients randomized to the intensive arm, the higher the mortality rate. Interestingly, just the opposite happened. That is, the increased risk of death was observed in the “non-responders” to the intensification, the patients whose HbA₁c level remained high despite their randomization group (intensive objectives). We can speculate that these patients received more and more anti-diabetes treatments, were noncompliant, gained weight, etc. The bottom line is that their increased risk of death was not related to a sharp fall in their mean glucose values. Actually, episodes of hypoglycaemia were of lower prognostic value (regarding mortality) in the intensive arm, relative to their value in the conventional arm, as if “expected hypoglycaemic episodes” (such as those that happen in tightly controlled type 1 diabetes) did not have the same meaning as “unexpected” or even “spontaneous” ones. Nevertheless, neither patients nor physicians had been waiting for these results to consider the reduction of the rates of hypoglycaemia as a major issue. But should we alter the focus of therapeutic education in that field?

Wang and others investigated the effect of low blood glucose levels in patients with diabetes, and found oxidative stress to be exaggerated in that setting. Endothelial function was impaired for hours, even after recovery. Recently, Ceriello’s group provided more details with their finding that the time course of circulating oxidative stress markers and of endothelial dysfunction was markedly different according to the post-hypoglycaemic phase. Patients who experienced a glycaemic rebound well over euglycaemia after the hypoglycaemic period had a much more severe and prolonged increase in oxidative stress.

Thus, at this stage, we are more aware of the danger announced, if not carried, by severe hypoglycaemia. Moreover, we know it is not a good reason to renounce intensive objectives, as far as they are attained 1) without pushing to a fault a patient who is in failure; 2) with appropriate therapeutic education related to hypoglycaemic episodes, which will be inevitably more frequent and should not be overcorrected.

“Hypoglycaemia definitively means a poor prognosis in patients with diabetes and high cardiovascular risk.”
Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

White, WB, Cannon, CP, Heller, SR, Nissen, SE, et al. For the EXAMINE Investigators

BACKGROUND
To assess potentially elevated cardiovascular risk related to new antihyperglycaemic drugs in patients with type 2 diabetes, regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies. We assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome.

METHODS
We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycaemic and cardiovascular drug therapy. The study design was a double-blind, non-inferiority trial with a pre-specified non-inferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS
A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8 %) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for non-inferiority). Glycated haemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; P<0.001). Incidences of hypoglycaemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

CONCLUSIONS
Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo. (Funded by Takeda Development Center Americas; EXAMINE ClinicalTrials.gov number, NCT00968708.)

October 3, 2013 DOI: 10.1056/NEJMoa1305889