

## **The links between diabetes and cardiovascular disease**

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### **ABSTRACT**

The aim was to review current studies relevant to the link between IGT, diabetes and cardiovascular disease.

Cardiovascular disease is a major cause of the reduction in life expectancy in patients with diabetes. 75 % of diabetic patients die prematurely of cardiovascular complications. Both prediabetes and diabetes highly predispose to cardiovascular alterations. Impaired glucose tolerance and even the upper normal of non-diabetic glucose values are associated with an increased cardiovascular risk. The risk of heart disease is increased up to 15 years prior diagnosis of diabetes. Patients with chronic or acute cardiovascular disease and no previous diagnosis of diabetes frequently present with either impaired glucose tolerance or diabetes. Patients with cardiovascular disease and no previous diagnosis diabetes need to be screened for diabetes with an oral glucose tolerance test. In acute coronary syndromes, lowering glucose levels to the near-normal range with insulin is highly beneficial. Early and rigorous improvement of metabolic control is highly supportive in improving the cardiovascular outcome in patients with dysglycemia. Preventive treatment strategies, which include multiple approaches, are required to overcome the burden of cardiovascular disease in diabetes and IGT.

### **CVD AND GLUCOSE INTOLERANCE**

Diabetes mellitus is associated with a high risk for the development of coronary artery disease (1). It represents a risk for cardiac mortality of 20% over 7 years, which is comparable to the risk of non-diabetic patients after myocardial infarction (2). As evidenced by the Munich Myocardial Infarction Registry, mortality of diabetic patients after

acute myocardial is substantially enhanced (3). A twofold increased in-hospital mortality has been reported in the patients (4). Furthermore, the risk for cardiovascular mortality in diabetic patients with acute myocardial infarction over a time period of 7 years has been observed to be 45 % (2).

The association between the glucose status and cardiovascular disease extends far beyond the diabetic threshold. A relationship can be detected as early as in the presence of impaired glucose tolerance and the upper normal of both fasting and 2-h glucose levels (5). This is emphasized by the observation, that the increase in cardiovascular risk starts up to fifteen years before the diagnosis of diabetes and further augments closer to diagnosis of diabetes (6).

The silence of coronary alterations is indicated by the frequent presence of coronary calcifications, as assessed by tomographic techniques. Coronary calcium not only present in one third of patients with diabetes and without clinical coronary artery disease, but also in impaired fasting glucose tolerance, impaired glucose tolerance and insulin resistant patients (7,8).

The threat of impaired glucose tolerance to the cardiovascular system is present in subjects with both a fasting glucose of  $< 7$  mmol/l or  $\geq 7$  mmol/l. (8). This emphasizes the role of postprandial glycemia with regard to the pathogenesis of cardiovascular complications (9).

Insulin resistance as a key factor in pathogenesis of diabetes is also accompanied by an increased risk of cardiovascular disease (10).

The fact that, cardiovascular disease is promoted early in the course of metabolic abnormalities, requires earliest diagnosis of these abnormalities. Preventive strategies as a firm action against the accelerating cardiovascular cascade are needed.

## **SILENT DIABETES IN CARDIOVASCULAR DISEASE**

The presence of silent glucose abnormalities in cardiovascular disease has become visible more recently and underlines the need for screening with an oral glucose tolerance test:

The LURIC-Study demonstrated that diabetes is newly detectable in 18 % of the patients, who undergo coronary angiography (11). The Euro Heart Survey showed that 20 to 30 % of patients with either acute coronary syndrome or chronic coronary artery disease present with newly-detected glucose intolerance or diabetes (12). Nearly 70 % of patients with acute myocardial infarction and no previous diagnosis of diabetes show either impaired glucose tolerance or diabetes (13). Impaired glucose tolerance or diabetes are not only detectable in the subacute phase of myocardial infarction, but also three and twelve

months past the diagnosis of myocardial infarction (13). In view of these observations, the performance of an oral glucose tolerance test in all patients with cardiovascular disease and no previous diagnosis is recommended.

## EFFECTIVENESS OF TREATING GLUCOSE ABNORMALITIES IN CVD

Interventional studies such as the UKPDS (14) and the Diabetes Control and Complications Trial (15) have provided scientific evidence that good glycemic control is beneficial for the prevention of diabetes-related complications, as is appropriate therapy for hypertension and dyslipidemia. The UKPDS data relate myocardial infarction and cardiovascular disease to the updated mean glycated (14).

Glycemic levels associated with microvascular and arterial risk are summarized and outlined in Table 1 (16).

**Table 1**  
**Risk Associated With Glycemia in**  
**Patients With Type 2 Diabetes\***

<b>Biochemical index</b>	<b>Low risk</b>	<b>Arterial risk</b>	<b>Microvascular risk</b>
HbA1c (%)†	<6.5	>6.5	>7.5
FPG (venous plasma)			
mmol/L	<6.0	>6.0	>7.0
mg/dL	<110	>110	>125
SMBG fasting			
mmol/L	<5.5	>5.5	>6.0
mg/dL	<100	>100	>110
SMBG postprandial			
mmol/L	<7.5	>7.5	>9.0
mg/dL	<135	>135	>160

\*FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; SMBG = self-monitored blood glucose. †High-performance liquid chromatographic method; normal range, 4 to 6%. Data from European Diabetes Policy Group

In acute coronary syndromes, mortality reducing effects of advanced treatments like reperfusion strategies are equally beneficial in patients with and without diabetes (17). These approaches, however, have been shown to be underutilised in diabetic patients (17,18). This resistance to utilize treatment options has been suggested to partially contribute to the poorer outcome in diabetic patients compared to non-diabetic patients (17,18).

Furthermore, the need of optimized glycemic control in the critical phase of disease has

been underestimated (19). Emphasizing the importance of metabolic control, the DIGAMI-1 study reported a reduction of in-hospital-mortality in diabetic patients, who obtained a glucose-insulin-infusion followed by an intensified therapy of diabetes (20). The long-term outcome was also significantly improved in the glucose-insulin-infusion group (20). The DIGAMI-2 study obtained good metabolic control in all treatment arms (21). It failed, however, to achieve a superior glycemic control in any of the three groups and, therefore, did not observe differences in mortality (21).

In acute coronary complications, optimization of glucose control to the near-normal range with insulin is highly beneficial (3,20). The Munich Myocardial Infarction Registry analysed both therapeutic approaches and hospital mortality in diabetic and non-diabetic patients (3). It demonstrated, that an intensification of multiple advanced treatment strategies in diabetic patients with acute myocardial infarction enables a substantial reduction of hospital mortality in the patients (Figure 1; 3). The results emphasize the need for early intervention targeting both arterial occlusion and metabolic disturbances in an appropriate hospital setting.

The STOP-NIDDM Trial investigated the effects of lowering postprandial blood glucose with acarbose on the incidence of Type 2 diabetes and the development of cardiovascular events. It demonstrated that early intervention with acarbose in individuals with IGT significantly reduces the occurrence of newly diagnosed diabetes (22). The STOP-NIDDM Trial also showed that treatment of acarbose is associated with a significant reduction in cardiovascular endpoints (23).

Both changes in live style and administration of metformin can successfully prevent conversion from IGT to diabetes (24). The results of the meta-analysis MeRIA compare well to the results of STOP-NIDDM. The meta-analysis demonstrated a significant reduction of CV death, peripheral heart disease and stroke (25).

**Conclusion:** Diagnosis of early metabolic alterations is essential for the future prevention of cardiac complications in diabetes. Overcoming the underutilisation of treatment strategies in diabetes is a primary goal. The application of advanced treatment strategies in diabetes lightens the burden of cardiovascular complications in diabetes. In the future, both diagnosis and treatment of impaired glucose tolerance need to be stronger in the focus of diagnostic and therapeutic efforts.

## REFERENCES

1. Standl E, Schnell O. A new look at the heart in diabetes mellitus: from ailing to failing. *Diabetologia* 43: 1455-1469, 2000
2. Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339: 229-234, 1998
3. Schnell O, Schäfer O, Kleybrink S, Doering W, Standl E, Otter W. Intensification of therapeutic approaches reduce mortality in diabetic patients with acute myocardial infarction: The Munich Registry. *Diabetes Care* 2004, 27: 455-4604.
4. Otter W, Kleybrink S, Doering W, Standl E, Schnell O. Hospital outcome of acute myocardial infarction in patients with and without diabetes mellitus. *Diabetic Medicine* 2004, 21:183-187
5. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years, *Diabetes Care* 1999; 22:233-40
6. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 2002;25:1129–34
7. Thilo C, Standl E, Knez E, Reiser M, Steinbeck G, Haberl R, Schnell O. Coronary calcification in long-term type 1 diabetic patients – A study with Multi Slice Spiral Computed Tomography. *Exp Clin Endocrinol Diabetes* 2004, 112:561-565
8. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PW, O'Donnell CJ Coronary artery calcification in type 2 diabetes and insulin resistance: the framingham offspring study. *Diabetes Care* 2002;25:1313–19

8. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care* 2001;24:1397-402
9. Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. The DECODE-study group. European Diabetes Epidemiology Group. *Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe*. *Diabetologia*. 1999 42: 647-54.
10. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care* 2002;25:1177-1184
- 11 Taubert G, Winkelmann BR, Schleiffer T, Marz W, Winkler R, Gok R, Klein B, Schneider S, Boehm BO. Prevalence, predictors, and consequences of unrecognized diabetes mellitus in 3266 patients scheduled for coronary angiography. *Am Heart J* 2003; 145; 285-291
- 12 Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, Standl E, Soler-Soler J, Ohrvik J; Euro Heart Survey Investigators. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J*. 2004; 25:1880-90
- 13 Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J*. 2004; 25:1990-7.
- 14 Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
- 15 Diabetes Control and Complications Trial Research Group. The effect of intensive

treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.

16 European Diabetes Policy Group. A desktop guide to type 2 diabetes mellitus: European Diabetes Policy Group 1999. *DiabetMed*. 1999;16:716-730

17 Norhammar A, Malmberg K, Ryden L, Tornvall P, Stenestrand U, Wallentin L; Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. *Eur Heart J* 24:838-44, 2003

18 Loewel H, Koenig W, Engel S, Hormann A, Keil U. The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment? Results of a population-based myocardial infarction register follow-up study. *Diabetologia* 43: 218-226, 2000

19 Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med* 31: 359-66, 2003

20 Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction; long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study. *Circulation*. 1999;99:2626-2632.

21 Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, Macleod K, Laakso M, Torp-Pedersen C, Waldenstrom A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005; 26:650-61

- 22 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–7.
- 23 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290:486–94.
- 24 Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *N Engl J Med* 2002; 346:393-403
- 25 Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 2004;25:10–16.
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