Current therapeutical options in diabetes mellitus type 2 and coronary artery disease: intensive secondary prevention with focus on exercise training versus percutaneous or surgical revascularization

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ABSTRACT

Diabetes mellitus is one of the major risk factors for coronary artery disease. The disease progresses faster in diabetic patients and is associated with a worse prognosis. Although bypass surgery or percutaneous interventions with stent implantation provide quick symptomatic relief for patients with stable coronary artery disease, it has no substantial prognostic benefit. A multifactorial intervention including dietary measures, blood-glucose control, antihypertensive treatment, and regular physical exercise does have a positive influence on the modifiable risk factors, and improves among others cardiovascular fitness and angina-free exercise tolerance.

EPIDEMIOLOGY

Diabetes mellitus type 2 is one of the most common diseases in industrialized countries and is one of the main risk factors for the development of micro- and macrovascular diseases. Vascular complications are causes of death in up to 80% of these patients and 75% of deaths are due to coronary artery disease[1,2].

Patients with diabetes mellitus type 2 develop more often diffuse multivessel coronary disease and heart failure. After a myocardial infarction their outcome is worse and mortality is higher than in normoglycemic patients[3]. Currently, it is being discussed controversially which therapy is best for these patients (see table 1).

TABLE 1
Therapeutical options and their influences on cardiac risk factors and prognosis in patients with non insulin-dependent diabetes mellitus and stable coronary heart disease

	Hyperglycemia	Cholesterol	Blood pressure	Prognosis
PTCA	–	–	–	?
ACB	–	–	–	?
Weight reduction	+	+	+	+
Physical exercise	+	+	+	+
Blood glucose control	+	(+)	(+)	+
Blood pressure control	–	–	+	+
Lipid lowering therapy	–	+	–	+

PTCA = percutaneous transluminal coronary angioplasty, ACB = aorto-coronary bypass graft, ? = uncertain, – = no influence, + = positive influence.

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AORTO-CORONARY BYPASS GRAFT

There have been great achievements and new developments in cardiac surgery over the last years. Today, arterial grafts (A. mammaria interna, A. radialis) are used as bypasses, and this is supported among others by a subgroup analysis of the BARI 1 study[4], which could show that diabetic patients who underwent bypass surgery after a myocardial infarction had a better survival rate when arterial instead of venous grafts were used[5,6].

Also a growing number of operations is being performed minimal invasively and without heart-lung-machine whenever possible. These break-throughs minimize operation-induced trauma and thus lower postoperative complication rates as well as faster mobilization. As was shown in recent studies these modern surgical techniques result in faster symptomatic relief but do not improve the survival rate when compared to percutaneous treatment (PTCA)[1,5].

CORONARY ANGIOPLASTY AND STENT IMPLANTATION

Percutaneous coronary intervention is the therapy of choice for patients with unstable angina pectoris or an acute myocardial infarction[7]. If the stenosis is located in the left main stem or the left anterior descending artery revascularization is associated with a significantly higher survival rate. Therefore, from a prognostic point of view surgical or interventional revascularization is mandatory in these patients[8]. For patients with stable coronary artery disease and a stenosis in other segments of the coronary vascular system clear evidence is lacking[9,10].

It was shown in the RITA-2 study that benefit from PTCA is greatest in highly symptomatic patients in terms of angina and reduced cardiorespiratory fitness. Patients with fewer and milder symptoms do not profit from revascularization. No improved performance on stress tests after PTCA could be shown in patients with a good pre-interventional performance. Additionally, not only could no prognostic benefit be documented in the PTCA group for asymptomatic or only mildly symptomatic patients, but there was even a significantly higher risk for cardiac death or myocardial infarction after an average of 2.7 years[11].

Therefore, PTCA with stent implantation in patients with stable coronary artery disease must be seen as a strictly symptomatic therapy providing fast relief of symptoms without any prognostic benefit[12]. Although no restenosis was initially found in studies on sirolimus-eluting stents[13], more recent data shows a restenosis rate of up to 9% (18% for diabetics and up to 38% for insulin-dependent diabetics) in stented coronary arteries with complex lesions[14].

MULTIFACTORIAL SECONDARY PREVENTION

In patients with stable coronary artery disease and no hemodynamically relevant stenoses of the coronary main stem or left anterior descending artery conservative therapy is a therapeutic option. This treatment strategy takes into account the multifactorial pathogenesis of the disease and aims for a positive influence on all modifiable risk factors (figure 1).
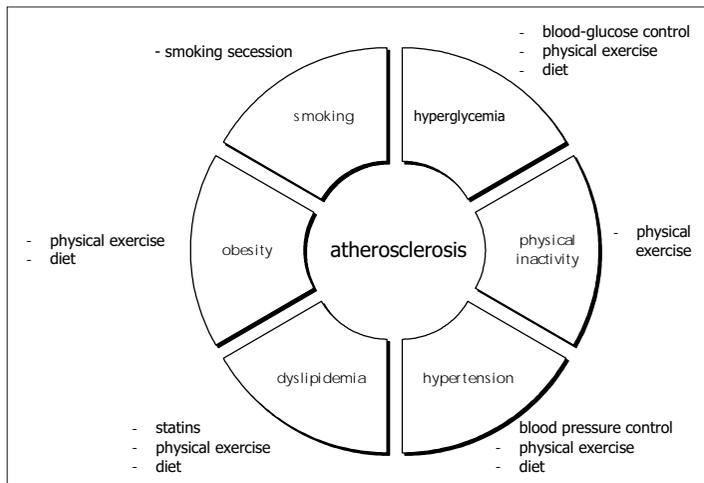

Fig. 1 – *Therapeutical options aiming at minimizing modifiable risk factors*

BLOOD-GLUCOSE CONTROL

The importance of an early diagnosis of diabetes was shown in the United Kingdom Prospective Diabetes Study (UKPDS). The results show that it is necessary to keep HbA1c levels < 6.0 mmol/l in order to reduce the incidence of cardiovascular events[1]. These data were confirmed by a study by Hu *et al.* in 84941 nurses where it could be demonstrated in a subgroup with a low risk profile (body mass index < 25, healthy diet, > 30 min physical exercise/d, non-smokers, > half a drink/d) that the incidence of diabetes mellitus type 2 was significantly lower than for the rest of the nurses[15]. It was also shown that 91% of the newly developed diabetics could have been prevented by a life-style common to the subgroup of nurses with a low risk profile.

Tuomilehto *et al.*[16] studied 522 overweight patients with impaired glucose tolerance to find out the influence of diet counselling and the recommendation to exercise regularly on the incidence of type 2 diabetes mellitus. After 4 years the incidence of newly developed diabetes was significantly lower in the intervention group (11%) as compared to the control group (23%).

Another study compared the influence of a healthy life-style with prevention or delay of the occurrence of diabetes by metformin[16]. After an average of 2.8 years it was shown that a healthy life-style could prevent diabetes mellitus type 2 more effectively (58%) than a metformin therapy (31%).

The STENO-2 study investigated the influence of conservative therapy and an intensified therapy (behavioral changes aiming at weight reduction, increased physical activity and intensified pharmacological therapy) on type 2 diabetic patients with micro-albuminuria[17]. After an average study time of 7.8 years intensified therapy was able to reduce cardiovascular and microvascular events by 50%[17] (see table 2).

In the studies mentioned physical training was only recommended but never conducted under supervision[17]. Future studies must show whether increased exercise compliance due to group exercise sessions or supervision of home exercise with the help of telemedicine can even further augment these beneficial effects. Our own data show that not only stationary but also ambulatory group training in addition to daily home exercise can further improve the risk factor profile[29].

TABLE 2
Therapeutical options in treating coronary disease in patients with diabetes mellitus

Author/study	Therapeutical option	Result
BARI I[4]	ACB vs. PTCA	Reduction of mortality to 5.8% vs. 20.6% after 5 years
Moses *et al.*[14]	Sirolimus-Stent	Restenosis rate of up to 35%
ARTS[5]	ACB vs. PTCA/stent implantation	Freedom from angina 84.4% vs. 63.4%
Turner *et al.*[1]	Consequent blood glucose control	Reduction of cardiovascular complication rate
UKPDS 38[18]	Consequent blood glucose control	Significant reduction of risk for micro- and macrovascular complications
Gaede *et al.*[17]	Multifactorial intervention	50% reduction of cardiovascular complications
Hu *et al.*[19]	Weight watch, diet, physical activity	Successful prevention of diabetes mellitus by ahealthier life-style
Hu *et al.*[20]	Physical activity	Significant reduction of risk for developing diabetes mellitus (50%)
Tanasescu *et al.*[21]	Physical activity	Significant reduction of risk for CAD (33%) and mortality (40%)
Wei *et al.*[22]	Good physical condition	Reduction of risk for developing diabetes mellitus by 25%
Hu *et al.*[23]	Physical activity	Reduction of risk for cardiovascular events inversely proportional to increasing physical activity
Batty *et al.*[24]	Physical activity	Reduction of risk for cardiovascular events and mortality depending on running speed and leisure time activity
Wei *et al.*[25]	Physical activity	Reduction of mortality through physical work out by 50%
HPS[26]	Statins as primary prevention	Reduction of cardiovascular disease incidence by 33%
4 S[27]	Statins as secondary prevention	Significant reduction of relative risk for cardiovascular events and mortality
CARE[28]	Statins as secondary prevention	Significant reduction of cardiovascular events by 5.2% (Death, MI, ACB, PTCA)

CAD = coronary heart disease, MI = myocardial infarction, ACB = aorto-coronary bypass graft, PTCA = percutaneous transluminal coronary angioplasty.

PHYSICAL EXERCISE

The incidence of diabetes mellitus correlates inversely with the degree of physical activity. This is best documented for patients with a very high risk of developing diabetes[30]. Regular physical exercise (e.g. 30 min/d of aerobic exercise at a moderate intensity) can cut the risk for impaired glucose tolerance by half and the diabetes risk by up to three quarters[19,22].

Endurance training is possible for patients with stable coronary artery disease. It increases exercise performance, improves the cardiovascular risk profile[31-33], reduces the cardiovascular complication rate[34,35], improves myocardial perfusion[33], and also slows the progression of coronary artery disease[32,36]. Although there is no proof that endothelial dysfunction leads to atherosclerosis to date, it was shown that endothelial dysfunction is associated with increased cardiovascular mortality[37]. Endothelial dysfunction can be improved by intensive physical exercise[37-41]. Not only does nitric oxide (NO) act anti-atherogenically but also a lack of NO has a pro-atherogenic effect[40-42]. Whether or not this applies to diabetics is currently being examined by us in different studies.

A meta-analysis could show that normoglycemic patients[43] profit from endurance training as part of a rehabilitation program for patients with coronary heart disease with a reduction of mortality by 31%. The importance of physical exercise, especially for diabetic patients, and the prognostic effect was demonstrated by several studies[24,30] (see table 2). Regular physical training reduces the risk for coronary artery disease by 33% and the mortality rate by 40%[21]. Energy consumption should ideally be between 1000 and 2000 kcal/week which corresponds to 3-5 hours of sub-maximal endurance training per week[20].

LIPID-LOWERING TREATMENT

A lipid lowering therapy with statins is only recommended if LDL cholesterol levels are > 3.0 mmol/l[44]. For patients with diabetes mellitus type 2 triglyceride levels are often increased and HDL serum levels are often reduced in spite of good metabolic control[42]. Stammler et al. could already show that both diabetics and non-diabetics profit from a reduction of LDL cholesterol by 1 mmol/L by a linear reduction of the risk for developing coronary artery disease regardless of their initial LDL levels[45]. However, the mortality rate for diabetics was 3 to 5 times higher when compared to the group of non-diabetics.

The data from UKPDS could confirm this linear correlation between LDL cholesterol levels and the risk for coronary heart disease[46].

In spite of a higher risk for cardiovascular complications in diabetic patients only a small number of diabetic patients were included in randomized studies with statins[27,28]. The Heart Protection Study compared the effects of simvastatin versus placebo on 5963 type 2 diabetics with regard to cardiovascular complications[26]. Over an average time of 4.8 years simvastatin increased the time until first myocardial infarction, cerebrovascular event or need for revascularization by 22%. New manifestations of cardiovascular diseases were reduced by 33%. A reduction of cholesterol levels by 1.0 mmol/L coincided with a reduced rate of all cardiovascular complications by one quarter.

Another study performed a multifactorial intervention with intensified blood-glucose control, blood pressure reduction by 11 mmHg and lowering of LDL cholesterol by 0.9 mmol/L. When compared to standard therapy a significant reduction of cardiovascular (20%) and microvascular (50%) complications could be documented[17].

Risk factors for normoglycemic patients with coronary artery disease such as dyslipoproteinemia, hypertension and obesity can be treated successfully with intensified physical exercise and individually adapted diet. However, only the impact of lipid control has been assessed so far and resulted in a reduction of cardiovascular mortality[47,48].

CONCLUSION

Diabetic patients with acute myocardial infarction, a stenosis of the left main stem or left anterior descending artery, or severe angina benefit from revascularization, which is associated with immediate relief of symptoms and a better prognosis.

There is no such evidence for diabetic patients with stable coronary heart disease and stenosis in other cardiovascular segments, whereas more recent studies increasingly underline the importance of an intensive multifactorial intervention. Although the multifactorial approach is the only intervention that results in a slowed progression of the disease, superiority with regard to relief of symptoms or even an improved prognosis remains to be demonstrated in prospective, randomized trials, which are currently under way.

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