Cardiovascular Complications in Diabetes

Targets and interventions

ALIN O. STIRBAN, MD
DIETHELM TSCHOEPE, MD

Cardiovascular complications are mainly responsible for the high morbidity and mortality in people with diabetes. The awareness of physicians for the importance of primary prevention increased lately and numerous strategies have been developed. The spectrum ranges from pharmacologic treatment to vitamins and dietetic interventions. Some interesting concepts such as focusing on exogenous advanced glycation end products have emerged, but definitive results on their clinical relevance are still lacking. A major problem of the primary prevention is the choice of the method applied for screening, the criteria used to classify risk patients, as well as the choice of therapy. Guidelines provide goals to be achieved and offer alternatives for treatment, but the medical decision has to be made on an individualized basis. In this overview, we will comprehensively focus on the most important pathomechanisms and clinically relevant approaches, aiming at the early diagnosis and treatment of diabetes along with coronary heart disease. When primary prevention fails, we advocate a more aggressive treatment of critically ill patients, followed by optimal secondary prevention meeting on-target goals precisely.

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Genetic background and lifestyle are not only determinants of the metabolic syndrome, but also influence the rate at which risk factors degenerate into metabolic disorders (e.g., diabetes) and/or coronary heart disease (CHD). The Adult Treatment Panel III regards diabetes as a CHD risk equivalent (1). Indeed, people with diabetes have a three to five times higher risk for CHD death than nondiabetic subjects (2,3) and similar to that of patients without diabetes after a myocardial infarction (4).

Atherosclerotic plaque rupture and subsequent thrombocyte aggregation are the trigger for major cardiovascular events, and their prevention by lipid lowering and thrombocyte aggregation inhibition is a major therapeutic goal.

A first step in the screening for CHD is to detect people with incipient atherosclerosis, e.g., with endothelial dysfunction ("functional atherosclerosis"). This enables the physician to initiate lifestyle and pharmaceutical prevention of morphological changes early ("primordial prevention"). If atherosclerosis already exists, but has no clinical consequences so far, screening and treatment of these patients already at high-risk is an important task ("primary prevention"). Thus, risk factor elimination in patients with manifest CHD to prevent (re)occurrence of acute occlusive events (e.g., myocardial infarction, stroke, death, etc.) appears as the ultimate goal ("secondary prevention").

THE PATIENT WITH DIABETES IN THE GENERAL PRACTITIONER'S OFFICE

—Data from the U.S. show that 9.3% of the population has diabetes (6.5% diagnosed and 2.8% undiagnosed) and an additional 26.0% has impaired fasting glucose, totaling 35.3% (73.3 million) with either diabetes or impaired fasting glucose (5). Of note, people with normal fasting glucose but impaired glucose tolerance could further increase the incidence of metabolic abnormalities. This qualifies any patient with risk factors for a proper diabetes screening. Detailed recommendations for screening and management of diabetes have already been made available (6). Optimal blood glucose control is important in the long term for reducing diabetes complications (7). Increased blood glucose might be particularly devastating in people with diabetes, but there is certainly far more to treat. Reducing blood pressure at values <130/80 mmHg (systolic/diastolic) (6), especially with ACE inhibitors and angiotensin II type 1 receptor blockers, should be also considered.

Alterations of platelets from insulin-resistant subjects with or without type 2 diabetes explain platelet hyperactivation and enhanced risk of thrombosis in these patients (8,9). Therefore, aspirin is recommended primarily for prevention in this group (10).

Recommendations for decreasing LDL cholesterol <100 mg/dl (<70 mg/dl in people with overt CHD) already exist (6). We sometimes tend to accept values slightly over this threshold, but we should consider that the LDL level might not reflect the entire risk. People with diabetes have an increased amount of small dense LDL, known for their increased atherogenicity (11). We therefore advocate a consequent lipid-lowering policy. Increasing HDL cholesterol to over 40/50 mg/dl (men/women) (6) for example with niacin (12) and decreasing triglycerides <150 mg/dl (e.g., with fibrates) is a further important goal.

Currently, we have multiple medications to treat and prevent diabetes and its complications. Nevertheless, we should not forget that lifestyle changes and motivation added to pharmacological treatment impressively reduce end points (13). However, lifestyle changes have a maximum impact during the first 6 months and a progressively decreasing compliance is noted afterward (14), highlighting the need for continuous empowerment of our patients.

THE PATIENT AT RISK FOR CARDIOVASCULAR DISEASE: EARLY RECOGNITION

— Endothelial dysfunction ("the functional atherosclero-

From the Heart and Diabetes Center, Ruhr-University Bochum, Bad Oeynhausen, Germany.
Address correspondence and reprint requests to Prof. Dr. Diethelm Tschoepe, Heart and Diabetes Center NRW, Georgstrasse 11, 32545 Bad Oeynhausen, Germany. E-mail: dtschoepe@hdz-nrw.de.
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Abbreviations: AGE, advanced glycation end products; CHD, coronary heart disease; RAGE, receptors for AGE.
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sis") precedes by decades morphological atherosclerosis and cardiovascular complications (15). People with diabetes have an early altered endothelial function (16,17). Measurements of endothelial dysfunction can be performed either directly on the coronary arteries or at the level of peripheral macrocirculation (brachial or femoral artery) and microcirculation (forearm, hand, or foot). Several noninvasive or invasive methods for the assessment of endothelial dysfunction are available (18).

As one of the invasive methods, the intracoronary infusion of acetylcholine is the gold standard for the assessment of endothelial function of the coronary arteries and allows the response assessment of the artery diameter, blood flow, and vessel resistance (19). An unaltered endothelial function will result after acetylcholine administration in vasodilation, increase in blood flow, and decrease in resistance. Impaired endothelial function is characterized by blunted vasodilation or even vasoconstriction.

Further invasive methods assessing endothelial dysfunction in the peripheral arteries are the strain-gauge plethysmography (20) and the thermodilution method (21). Endothelial dysfunction can be assessed noninvasively with ultrasound measurements of the flow-mediated dilation (22), laser Doppler (23), plethysmography (24), magnetic resonance imaging measurements of the blood oxygen level–dependent (BOLD) signal (25), or positron emission tomography (26).

The ultrasound measurement of flow-mediated dilation (22) is the most common method for the indirect assessment of endothelial function. The diameter of the brachial artery is measured before and after a 4.5-min ischemia of the forearm. The extent of vasodilation after ischemia (flow-mediated dilation) reflects the integrity of endothelial function. This method offers the advantage of being a noninvasive, low-cost, and trustworthy method in the hands of a skilled investigator. It is especially valuable in the early detection of risk patients, as well as for the assessment of therapeutic success.

Adding laboratory markers of endothelial dysfunction to the functional parameters, the picture of vascular impairment can be completed (23). Some of the common markers that mirror endothelial dysfunction and have a good predictive value for CHD are listed below: plasminogen activator inhibitor 1 (27), von Willebrand factor (28), cell adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin (endothelial-leukocyte adhesion molecule 1) (29,30), and endothelin 1 (31).

The measurement of endothelial function has revolutionized the testing for cardiovascular effects of medications. End point studies (still the gold standard for the assessment of cardiovascular effects) require many years and numerous patients. For shortening the investigation period, morphological changes of vessels were used as surrogate parameters. One of them is the intima-media thickness usually measured at the level of the carotid artery. But even in this case, results of interventions can be seen no earlier than 6 months (32). Endothelial function is the first to react to positive or negative influences targeting the vessels, and usually only prolonged impairment of endothelial function will result in morphological changes of the vessel wall. Therefore, assessment of endothelial function will reveal the earliest changes. Pharmacological interventions can positively affect endothelial function as early as after 3 days (23,33).

Interventional studies that have as the main parameter endothelial function cannot replace the clinical significance of end point studies, but can prove enormous utility in studies conducted as "proof of principle" and as precursors of larger intervention trials.

Having the ability of looking at early signals from the endothelium and drawing therapeutic consequences, we might prevent numerous cardiovascular complications. Therefore, it is our strong belief that methods assessing endothelial function will penetrate progressively into clinical routine.

ADVANCED GLYCATION END PRODUCTS AND DIABETES COMPLICATIONS

— Recent data suggest that advanced glycation end products (AGEs) might also play an important role in the development of endothelial dysfunction (34), leading to the long-term complications of diabetes and aging (35). AGEs are a heterogeneous group of moieties with carboxymethyllysine being one of the most representative. They form by nonenzymatic reaction between glucose, lipids, and/or certain amino acids on proteins, lipids, and nucleic acids (36).

The reaction finally leading to AGE formation was first described by the French scientist Louis Camille Maillard almost one century ago and was named in his honor. It is also known as the browning reaction of sugar-containing substances, which are exposed to heating. Several intermediate reactions have been described. Glucose reacts with a free amino group of a protein and forms reversible intermediates of a Schiff base and an Amadori product. One known representative of the latter class is A1C. Rearrangements of internal structure with development of irreversible covalent bindings finally form AGEs (36). Alternate mechanisms leading to AGE formation have been described elsewhere and imply the formation of highly reactive dicarbonyl intermediates, with methylglyoxal being the most studied (36).

AGEs are formed endogenously intra- and extracellularly by reactions that have been believed to take days to weeks. Recent data show that the endogenous formation of AGEs and their intermediates might be more rapid (minutes to hours) when environmental conditions such as hyperglycemia and oxidative stress are present (23,37).

But beyond endogenous generation, there are also important exogenous sources of AGEs such as smoking and food. The latter is a major AGE provider. AGE content is highly dependent on food nutrient composition, as well as on temperature, method, and duration of heat application during cooking (38). About 10% of ingested AGEs are rapidly absorbed into the body, from where they are cleared by different cell types (such as macrophages) or excreted by the kidneys: around 30% within 48 h if the renal function is preserved and 5% if renal function is impaired (e.g., diabetic nephropathy) (39).

Still, an important amount of exogenous AGEs (70–95%) is retained into the body, where they exert different pathological effects (39) including binding with and activation of receptors for AGE (RAGE) (40). Multiple cell types present RAGE: endothelial cells, monocytes, denditric cells, and macrophages. Especially the latter are implicated in the clearance of AGEs.

Not only AGEs but also AGE precursors such as methylglyoxal can activate RAGE. There are two main pathomechanisms of AGE, one of them RAGE independent and another dependent on activated RAGE. The latter determines oxidative stress, inflammation, and endothelial dysfunction.

Increased AGE concentrations were

found in atherosclerotic plaques and collagen structures, suggesting the implication of AGEs in vascular disease. Administration of AGE precursors (methylglyoxal) induces in animal models microvascular changes and perturbation of wound healing (41). AGE-rich collagen proves decreased turnover and increased rigidity. Summarizing, AGE-modified proteins or enzymes partly lose their function and can be cleared only with difficulty.

By all the above-mentioned mechanisms, AGEs contribute to impaired endothelial function and change in vessel wall properties, leading to basement membrane thickening, increased vascular permeability, prothrombotic state, and decreased blood flow. The results are damage to retina, nephron, peripheral, and central nerves and atherosclerosis (42–44).

People with uncomplicated diabetes were shown to have ~30% higher AGE levels than their nondiabetic counterparts (45)—an amount that rises to 100% when complications such as coronary artery disease or microalbuminuria are present (46,47). This increase can be explained mainly by three mechanisms: *1*) hyperglycemia and increased oxidative stress promote endogenous AGE synthesis; 2) decreased AGE clearance occurs, especially when impaired renal function coexists; and *3*) increased exogenous AGE supply occurs. Indeed, people with diabetes have been suggested to consume more AGEs than nondiabetic subjects (48).

The AGE content of 250 different food types has been measured by Goldberg et al. (38). Interestingly, foods of the fat group were shown to have the highest amount of AGE content (+100/−19 kU/g) followed by the meat and meat-substitute group (+43/−7 kU/g) and the carbohydrate group, which contained the lowest values of AGEs (+3.4/−1.8 kU/g). The amount of AGEs in the final product is dependent on cooking temperature, length of cooking time, and presence of moisture. Goldberg et al. propose that broiling (225°C) and frying (177°C) resulted in the highest levels of AGEs, followed by roasting (177°C) and boiling (100°C). Taking the same ingredients (e.g., chicken breast, potatoes, vegetables, and oil) fried/broiled at 230°C for 20 min, a high concentration of AGEs was obtained (15.100 kU AGE/meal), while steaming/boiling at 100°C for 10 min resulted in a more than fivefold lower AGE concentration (2.750 kU AGE) (48a).

The conclusion is that one accessible intervention aiming at reducing exogenous AGE supply is to choose the appropriate cooking methods. It is therefore not only important *what* we eat, but also *how* we eat.

Limitation of endogenous production of AGEs can be achieved by reducing hyperglycemia (with oral antidiabetic agents or insulin [37]) and oxidative stress or by specific blockade with benfotiamine (23,49) or aminoguanidine. A comprehensive overview on therapeutic agents that can reduce AGEs and/or their effects has been published (36).

Reducing AGE availability, a reduction of their effects, has been postulated. Indeed, interventions aiming at reducing AGEs were shown to partly prevent diabetes complications in animal models (49–51). Still, large and especially long-term interventional studies in humans are lacking.

POSTPRANDIAL STATE AND ATHEROSCLEROSIS — Much attention has been paid lately to the link between increased postprandial oxidative stress and endothelial dysfunction (23). The postprandial state in people with diabetes is paralleled by hyperglycemia, hypertriglyceridemia, oxidative stress, and endothelial dysfunction, and distinctive and cumulative effects of hyperglycemia and hypertriglyceridemia on postprandial endothelial dysfunction have been shown (33). Because the postprandial state covers most of our daytime, interventions aiming at reducing postprandial changes might play a decisive role in the prevention of complications.

Several therapeutic approaches have been suggested for the treatment of postprandial endothelial dysfunction, including insulin (52), folic acid (53), tetrahydrobiopterin (54), vitamins C and E (55), benfotiamine (23), and statins (33). They aim at reducing postprandial oxidative stress (vitamins C and E, statins, and partly folic acid), postprandial hyperglycemia (insulin), and postprandial hypertriglyceridemia (statins) or have a direct effect on endothelial nitric oxide (NO) production (folic acid, insulin, and tetrahydrobiopterin).

But a significant increase in AGEs also occurs after a meal (23). Endogenous methylglyoxal synthesis was proven to increase in parallel with hyperglycemia in vivo (37). Postprandially, the absorbed and endogenously generated AGEs and methylglyoxal act synergistically to decrease vascular function through direct NO scavenging or increase in oxidative stress. Part of these effects might be counteracted by benfotiamine, a liposoluble vitamin B_1 with much higher bioavailability than thiamine (56). Benfotiamine, commonly used in the treatment of diabetic neuropathy (57), is a transketolase activator that directs glucose substrates to the pentose phosphate pathway. Thus, it blocks several hyperglycemia-induced pathways, one of them being endogenous AGE and dicarbonyl formation (49). Benfotiamine was shown to prevent experimental diabetic retinopathy (49) and in vitro hyperglycemia-induced endothelial dysfunction (58,59).

We have recently shown that a meal with a high AGE content can reduce vascular function up to 60% and that this effect can be counteracted by a 3-day pretreatment with benfotiamine (23).

To develop strategies for the prevention of atherosclerosis, we have to focus not only on the reduction of postprandial hyperglycemia, hypertriglyceridemia, and oxidative stress, but also on preventing postprandial AGE increase and endothelial dysfunction.

SCREENING OF PATIENTS — Numerous people with diabetes have myocardial perfusion disturbances (60). These are partly due to endothelial dysfunction, but also to already morphological changed arteries. While we dealt earlier with the recognition of the first condition, we will focus here on diagnosis of overt atherosclerosis.

Asymptomatic people with diabetes have myocardial perfusion abnormalities similar to symptomatic ones (61), stressing the fact that symptoms are unreliable for the diagnosis of CHD in these patients. In light of this fact and taking into consideration that subclinical coronary artery stenoses are often responsible for complications such as myocardial infarction and sudden death, screening for CHD in this patient group is of major importance.

Noninvasive stress tests play a major role in diagnosing CHD, with different degrees of sensitivity and specificity, with the lowest for the exercise electrocardiogram (sensitivity and specificity 61 and 70% in women and 72 and 77% in men, respectively). Stress echocardiography (sensitivity 81% and specificity 86%) and single photon emission computed tomography (91% sensitivity and 86% specific-

ity) have the highest accuracy (62), with the first being highly dependent on the experience of the investigator and the second on the availability. Both offer the advantage that they can be performed either by exercise or pharmacological stress testing. Although invasive methods (e.g., coronary angiography, intravascular ultrasound) remain the gold standard for the diagnosis of CHD, noninvasive methods such as positron emission tomography (quantitative measurement of blood flow and myocardial vitality), magnetic resonance imaging (morphology and perfusion), and computer tomography (calcium score and morphology) have exponentially evolved in recent years (63). Combined devices (e.g., computed tomography + single photon emission computed tomography, computed tomography + magnetic resonance imaging) are also available and increase image accuracy (64,65).

To assess morphological vascular changes, the measurement of intima-media thickness of the carotid artery offers a simple and validated method predicting the risk for future cardiovascular events (66).

In the light of these numerous possibilities, the choice of the diagnosis method depends on local availability, experience, and costs.

PEOPLE WITH DIABETES AND CHD RECEIVING PERCUTANEOUS CORONARY INTERVENTION OR CORONARY ARTERY BYPASS GRAFT (CABG)

Whether people with diabetes and CHD should be primarily treated with coronary artery bypass graft or percutaneous coronary intervention is still a matter of debate. In these patients, coronary artery disease is more often complex and diffuse, left ventricular function is depressed, and concomitant multiple risk factors are present. Whereas older studies comparing bare metal stents with coronary artery bypass graft showed clear benefits of the latter, the introduction of drug-eluting stents markedly reduced the handicap. Even though studies still suggest better results with coronary artery bypass graft (67), especially concerning repeated revascularization, no clear data on significant differences exist with respect to the 12-month rate of death (68), myocardial infarction, and cerebrovascular events in patients treated with drug-eluting stents compared with coronary artery bypass graft.

The decision to chose one of the two methods must be made according to the morphology of coronary lesions and surgical risk (68).

Drug-eluting stents have definitely improved the outcome of percutaneous coronary intervention in people with diabetes (69), but led to premature euphoria. Recent studies suggest that the rate of cardiac death and nonfatal myocardial infarction was higher in patients treated with a drug-eluting stent than a bare metal stent. An excess of noncardiac death from cancer and infectious diseases has also been mentioned with drug-eluting stents (70,71).

At present, the analysis of local stenose morphology should guide the decision of which kind of stent should be used: short stenoses of a large vessel can be treated by bare metal stent implantation, whereas long stenoses of small caliber vessels would be more suitable for drug-eluting stents.

THE CRITICALLY ILL PATIENT

— Hyperglycemia accompanying acute cardiovascular complications has been incriminated in worsening outcome (72), and treatment of critically ill patients with intravenous insulin has proven efficacy (73). Dandona et al. (72) have comprehensively reviewed the mechanisms responsible for these effects. Acute myocardial infarction, surgical interventions, and septicemia are characterized by inflammation and the catabolic state. The latter is partly modulated by sympathetic activation and results in hyperglycemia and increased concentrations of free fatty acids. Especially the latter are made responsible for deteriorated NO production by endothelial cells, prostacyclin availability, and increased oxidative stress. All these mechanisms taken together contribute to an impairment of endothelial function, thus promoting vascular damage. Free fatty acids can also induce insulin resistance by at least two mechanisms: the induction of protein kinase C and promotion of inflammation. On the other hand, hyperglycemia itself is accompanied by increased oxidative stress and deterioration of endothelial function (33). Insulin treatment might counteract several pathogenic mechanisms by reducing free fatty acid concentration, decreasing hyperglycemia, and increasing glucose availability for insulin-responsive organs, including the myocardium. Independently of these mechanisms, insulin itself has been suggested to have a potent anti-inflammatory effect (72) and to stimulate NO production (74).

Hypotheses on the genesis of hyperglycemia that accompanies acute events have been raised, and we believed for many years that this is a transient state. But recent data prove that there is a persistent metabolic disorder in most of these patients that is unveiled during the acute phase of the complication rather than being a completely new metabolic feature. Approximately 25–30% of patients admitted with an acute coronary syndrome have diabetes and ~57% show abnormalities of glucose metabolism. About 66% of those who met criteria for diabetes were not diagnosed or treated as such by their physicians (75). These data should increase our awareness in critically ill patients, independently of the presence or absence of a previous diabetes diagnosis. Hyperglycemia accompanying acute coronary syndrome is associated with increased mortality (76). Peri-interventional insulin-glucose treatment improved long-term survival after acute coronary syndrome in patients with diabetes in the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study (77). The results of the DIGAMI-II trial are questionable because of major inaccuracies, but further concern is raised by recently published data showing no survival benefit in people with known diabetes on intensive care unit on intensive insulin treatment (78). Further studies are warranted to bring light to this important topic.

Data showing decreased short-time mortality after intensive insulin treatment (IIT) in critically ill patients on a surgical (73) and a medical intensive care unit (79) have been made available. This suggests that there is a broad spectrum of patients who will benefit from this treatment and that there are not only acute coronary events that have to increase our awareness for treating glucose metabolism disturbances.

Still, the optimal blood glucose level for critically ill patients remains a matter of debate. As published by Van den Berghe et al. (78), a blood glucose target <110 mg/dl seems to be the most effective, but also carries the highest risk of hypoglycemia with a potential harmful effect that cannot be neglected. A further noteworthy statement of the authors was that differences in mortality have reached

significant differences in long-stayers (patients treated ≥3 days in the intensive care unit) only. This highlights the importance of being consequent in lowering blood glucose with insulin in intensive care unit patients.

In our opinion, if possibilities of tight monitoring of blood glucose are given (hourly at the beginning of insulin treatment and every 2–4 h after achievement of a steady state), a blood glucose target <110 mg/dl should be used. Otherwise, blood glucose should be kept between 110 and 150 mg/dl.

In light of the above-mentioned data, we advocate the performance of an oral glucose tolerance test in all nondiabetic patients before or immediately after discharge from a hospital where they were treated for an acute ischemic event, independently of their blood glucose level during the hospitalization. Even though data on survival benefit in critically ill patients with known diabetes on intensive insulin treatment are lacking, we have reason to believe that, in these patients, blood glucose targets should be set at least as stringent as for people without known diabetes.

Many aspects of diabetes therapy are still far from being clarified, but our first task is to improve awareness for diabetes and its cardiovascular consequences. The development of more aggressive prevention strategies instead of treatment for manifest complications can reduce cost and improve the quality of life in our patients.

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