UDC 616–018:616:379–008.64:512:108.2

E. Zander[1], K.-D. Kohnert[2], Chr. Allwardt[1], J. Reindel[1], J. Schmidt[1], W. Kerner[1], W. Motz[3]

[1]*Clinic for Diabetes and Metabolic Diseases, Karlsburg, Germany;*
[2]*Institute of Diabetes «Gerhardt Katsch», Karlsburg, Germany;*
[3]*Center of Heart Diseases and Diabetes, Karlsburg, Germany*
(E-mail: kohnert@diabetes-karlsburg.de)

Hyperglycemia and Cardiovascular Risk in Diabetes mellitus Type 1 and Diabetes mellitus Type 2

Diabetes mellitus is a chronic disease that through its complications seriously reduces quality of life and life expectancy in diseased people. There is a worldwide increase in the prevalence in diabetes mellitus type 2. Our understanding in reducing the micro- and macrovascular risk has increased in the last time. But, in contrast to microvascular morbidity the most persistent menace to the health in diabetic patients of both types remains atherosclerosis with increased cardiovascular morbidity and mortality when compared with the non-diabetic population. In the past, the role of hyperglycemia on CVD was not completely elucidated. It was the aim to review and to compare the role of hyperglycemia on cardiovascular morbidity and mortality both in type 2 and type 1 diabetes. Results from ADVANCE and UKPDS Studies in type 2 diabetes have shown that the effect of intensive glucose control was associated with decreased risk of cardiovascular disease and death from any cause in addition to reduction of microvascular disease. HbA1c targets lower than 7.5 % and near to 6.5 % and avoiding of hypoglycemia are recommended. DCCT-EDIC Study data in type 1 diabetes have demonstrated that an early intensive metabolic control near to normal level initiated in patients with short diabetes duration and without microangiopathic complications such as nephropathy significantly reduced micro- and macrovascular morbidity. The long lasting effect of intensive control is called «memory effect». Near normal HbA1c levels at least < 7.5 % and individually targeted in order to avoid hypoglycemia are required. When comparing both types of diabetes, in type 1 as well as type 2 diabetes intensified glucose control resulted in long-lasting effects, reducing significantly cardiovascular morbidity and mortality. Treatment has to be initiated early in the course of the disease. But considering meta-analyses of large randomized controlled trials of intensive vs. conventional glycemic control in type 2 diabetes, hyperglycemia has shown to be a weaker cardiovascular risk factor than increased cholesterol levels or hypertension.

Key words: diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, glycemic control, cardiovascular disease.

Abbreviations:

ACCORD	—	Action to Control Cardiovascular Risk in Diabetes;
ADVANCE	—	Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation;
DCCT/EDIC	—	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications;
CAC	—	coronary artery calcification;
CVD	—	cardiovascular disease;
CHD	—	coronary heart disease;
CAD	—	coronary artery disease;
EURODIAB	—	European Prospective Complications Study IDDM Complications Study;
ROS	—	reactive oxygen species;
UKPDS-PTM	—	United Kingdom Prospective Diabetes Study-Post trial monitor;
VADT	—	Veterans Affairs Cooperative Study;
WESDR	—	Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Diabetes mellitus is a chronic disease that through its complications seriously influences the quality of life by shortening the life expectancy of people suffering from diabetes. A worldwide diabetes expansion from 285 million diseased people to expected 438 million in 2030 demands strengthening efforts to control and to prevent the disease expansion [1–3]. The worldwide accelerating increase in the prevalence of type 2 diabetes [4] enhances the risk for diabetic complications, indeed when considering also an alarming rise of type 2 diabetes already in young people. In the young populations there is also an increase of the type 1 diabetes incidence by about 2 % to 5 % per year worldwide [5, 6].

In the last years, our understanding about cardiovascular risk of hyperglycemia and other risk factors in reducing the micro- and macrovascular morbidity has enlarged. Prospective epidemiological studies have

shown to reduce the micro- and macrovascular morbidity and mortality by intensive metabolic control both in type 1 and type 2 diabetic patients [7, 8]. Over the past 40 years, a reduction in the mortality due to cardiovascular disease and coronary heart disease by about 70 % both in diabetic and in non-diabetic population has been reported [9].

But diabetic patients have not equally benefited from advances in reducing the coronary risk as the non-diabetic have. The traditional risk factors do not fully explain the excess risk for increased cardiovascular morbidity in diabetes [10]. In both types of diabetes an increased CVD risk in men and women has been reported. A significant increase in CVD mortality in diabetic patients compared to people without diabetes related to increasing HbA1c levels has been shown [10].

In the past the role of hyperglycemia as an independent risk factor for cardiovascular disease in both types of diabetes was still not fully enlightened [11, 12].

In previous cross-sectional studies we had found that cardiovascular risk factors are working also in type 1 diabetes [13]. We found CVD in type 1 diabetes to be associated with age, disease duration, increased insulin requirement, hyperglycemia, nephropathy, hypertension, lipid abnormalities, retinopathy and neuropathy [14]. As cardiovascular risk factor in type 1 diabetes were further considered arterial stiffness, coronary artery calcification, cardiac autonomic neuropathy and hypoglycemia [15].

Today our understanding about the cardiovascular risk of hyperglycemia in both types of diabetes has enlarged [8, 16].

Therefore, it was the aim of the present survey to compare the impact of the risk of hyperglycemia on the cardiovascular morbidity and mortality both in type 2 and in type 1 diabetes.

What is a risk factor?

A risk factor is an attribute or an exposure that is associated with increased probability of occurrence of a disease. This is not necessarily a causal factor. A risk factor represents more the likelihood that people who are exposed to certain factors subsequently develop a particular disease [17].

Hyperglycemia as mediator of cardiovascular complications in type 1 und type 2 diabetes

The pathogenesis of micro- and macrovascular complications in type 1 and type 2 diabetes is still not completely elucidated. The concept of an unifying mechanism of hyperglycemia in this process has been proposed by M. Brownlee in 2005 [18].

In diabetes, hyperglycemia is washing round all cells of every tissue, but there is a tissue damaging effect of hyperglycemia to a particular cell type, i.e. capillary endothel cells in the retina, mesangial cells in the renal glomerulus, neurons and Schwann cells in the peripheral nerves, and on endothel cells by generating diabetic macrovascular disease. These cells are not able to reduce the transport of glucose into the cells when they are exposed to hyperglycemia [19].

The increased glucose flux goes through the polyol pathway. When the glucose concentration in the cells becomes too high, glucose will be converted to sorbitol, which later will be oxidized to fructose.

Aldose reductase consumes the cofactor NADH, an essential cofactor for regeneration of antioxidants as glutathione, and thereby increases intracellular oxidative stress [20].

Increased intracellular production of AGE precursors appears to damage cells by modification of proteins involved in the regulations of gene transcription [21] and thereby causing cellular dysfunction [22]. The activation of PKC effects gene expression and leads to endothelial nitric oxid synthesis (eNOS) and increased vasoconstrictor endothelin-1 [23, 24].

An increased hexosamin pathway activity flux results from metabolizing glucose by glycolysis and the formation of UDP N-acethyl-glucoseamin.

This results in increased expression of transforming growth factor-β1 and plasminogen activator inhibitor-1 which is detrimental to blood vessels function [25, 26]. Hyperglycemia increases superoxide production by the mitochondria. The mitochondrial electron transport chain is the source of the hyperglycemia induced superoxide generation, as formation of reactive oxygen species (ROS) [18].

An increased FFA-oxidation in diabetic patients causes overproduction of ROS by the same mechanisms as it has been described for hyperglycemia, thus causing the same damaging pathways [18].

Hyperglycemia and CVD in type 2 diabetes

Regarding the worldwide increase in the prevalence of type 2 diabetes, we are faced with obesity, physical inactivity and aging as the main pathogenetic factors [27]. The most persistent menace to diabetic patients health and life has remained atherosclerosis. Type 2 diabetes is one of the pathological consequences of the metabolic syndrome with CHD, obesity, dyslipidemia and hypertension [28]. On the other hand, today

people with diabetes can live with growing confidence a complications free life. This, however, is requiring significant modifications in life style and a regular correction of risk factors for complications [29].

Cardiovascular morbidity and mortality are significantly increased in type 2 diabetes when compared with the age- and sex-matched non-diabetic population [30]. Classic cardiovascular risk factors are hypertension, hyperlipoproteinemia and smoking [31]. In addition to the classic risk factors, other factors are contributing to the increased cardiovascular mortality in type 2 diabetes, such as microalbuminuria [32], hemostatic abnormalities [33], endothelial dysfunction and chronic inflammation [34].

However, cardiovascular risk of hyperglycemia in type 2 diabetes was not fully supported [35–37]. Some studies have reported an increase of cardiovascular risk with the increase of hyperinsulinemia and glycated hemoglobin [38, 39]. But in prospective population based observational studies the effect of hyperinsulinemia on the development of CVD in type 2 diabetes was less pronounced than that of conventional risk factors [35]. The UKPD-PTM-Study was established to definitely answer the glycemic control controversy and to answer questions about the class of antidiabetic agents used to achieve control [40].

The UKPDS results have shown that the microvascular complications such as retinopathy, nephropathy, and possibly neuropathy were reduced by lowering blood glucose levels in type 2 diabetes with intensive treatment. A median HbA1c of 7.0 % was achieved in intensive treated patients when compared with conventional therapy with a median HbA1c of 7.9 %. Hereby, the overall microvascular complications decreased by 25 % [41, 42].

These data have provided statistical evidence that hyperglycemia causes these complications [43]. There, a continuous relationship between the risk of microvascular complications and glycemia was found. Every percentage point decrease in HbA1c showed a 35 % reduction in the risk of complications [43]. The risk of complications significantly decreased in the range of glycemic levels of HbA1 c <8.0 %. There was no evidence of any glycemic threshold for any of the microvascular complications above normal glucose level [43]. A significant effect of lowering blood glucose on cardiovascular complications was not found. There was a 16 % reduction of combined fatal and nonfatal myocardial infarction and of sudden death (P = 0.052) [41, 42]. Epidemiological analysis demonstrated a continuous association between the risk of cardiovascular complications and glycemia. Every percentage point decrease in HbA1c was associated with a 25 % reduction in diabetes related deaths, a 7 % reduction in all-cause mortality, and a 18 % reduction in combined fatal and nonfatal myocardial infarction [43]. Again, there was no glycemic threshold above normal glucose levels [43].

While lowering of blood pressure to a mean of 144/82 mm Hg reduced significantly strokes, diabetes related deaths, heart failure, microvascular complications and visual loss, there was no threshold for the complications above blood pressure of 130 mm Hg [44, 45].

The UKPDS-PTM-Study aimed to definitely answer the glycemic control controversy in type 2 diabetes:

Despite an early loss of glycemic differences between intensive and conventional therapy, a continued reduction in microvascular risk was registered, and a further risk reduction for myocardial infarction and death from any cause could be observed during 10 years of post trial follow-up. There was also a continuous decrease in complications among overweight patients undergoing metformin therapy [40].

Beyond UKPDS, it is established without any doubt that outcomes in those whose blood pressure and glycemic control were near normal were better, and it proved evidence base for the use of metformin.

The first years, following study initiation, were crucial to outcome. The authors of UKPDS-PTM suggested that this was no memory effect which was used by DCCT trial. Here, this was a legacy effect most likely related to atherosclerosis [40].

Other trials of glycemic control in type 2 diabetes however showed different results: ACCORD Study patients had longer disease duration 0f 11 years when comparing with the UKPDS population. The intensive group targeted HbA1c concentrations toward 6 %. At one year, stable HbA1c levels of 6.4 % and 7.5 % were achieved in the intensive group and the standard group, respectively. However, 257 patients in the intensive group died, and 203 patients in the standard therapy group. Hypoglycemia rates were three times higher in the intensive therapy groups as compared to control groups. Therefore, the trial was closed after 3.5 years because of 25 % increase in all-cause mortality in the intensive control group [46].

The ADVANCE trial is a randomized controlled international study of 11,140 patients with type 2 diabetes with glycemic intervention, comparing strategy of intensive blood glucose control (gliclazide) to a target on HbA1c of 6.5 %. In the ADVANCE trial no increase in cardiovascular mortality occurred, and there

was a 12 % decrease in mortality among the intensively treated patients [47]. Subsequent analyses showed a 25 % relative reduction in all-cause mortality for every 1 % point reduction in HbA1c [47].

The VADT Study was a multicenter trial that investigated the effects of intensive control at HbA1c targets of 6 % or less compared with standard glycemic control (HbA1c 8–9 %) on cardiovascular outcomes among 1.791 patients with type 2 diabetes [48]. Intensive HbA1c lowering in VADT and in ACCORD as well resulted in increased cardiovascular death rates and all-cause mortality rates when compared with ADVANCE and UKPDS [40, 47].

On the other hand, the results from ADVANCE [47] and UKPDS-PTM Studies [48] have shown that the effect of intensive glucose control was associated with decreased risk of myocardial infarction and death from any-cause in addition to reduction in the risk of microvascular complications in type 2 diabetes.

As shown by UKPDS data, intensive control should be started as early as possible at the time of disease manifestation.

UKPDS data have shown a so called legacy effect in reduction of cardiovascular morbidity that persisted for 10 years and after the loss of differences in HbA1 c levels [40].

Possible mechanisms behind the observed effect could be, that changes in glycation may alter the electric charges of proteins thus contributing to alterations in their properties and/or functions. As many proteins are sensitive to glycation, this may contribute to functional and structural consequences in many organs in the long term [49].

The therapeutic efforts in type 2 diabetes should not be focused only on glycemic control. Type 2 diabetes cannot simply be treated as a disease of abnormal glucose metabolism. Trial data show that lipid abnormalities and blood pressure should be treated in parallel [50, 51].

Targets of glycemia are an HbA1c lower than 7.5 % and near to 6.5 %, if achieved slowly and without hypoglycemia. Early interventions are beneficial. Late interventions and tight glucose control require a careful approach by avoiding hypoglycemias. Table shows a meta-analysis of intensified vs. conventional control including the major trials conducted in patients with type 2 diabetes.

Hyperglycemia and CVD in type 1 diabetes

The increased risk of CAD in type 1 diabetes has been recognized since long time [52, 53]. It was suggested that the most likely factor that primarily accounts for this increased risk is hyperglycemia [54], but the epidemiologic association between glycemia and CAD was rather weak [55]. Since long time an increased occurrence of CHD in type 1 diabetes has been reported [56, 57].

Over the past years, a reduction was observed in the mortality due to CVD both in the diabetic and non-diabetic population, presumably of the progress in cardiovascular risk management and interventional cardiology [58]. In type 1 diabetes, a decrease in mortality and an improvement in life expectancy occurred during the last years [59, 60].

However, the increased risk of CHD for people with type 1 diabetes compared to people without diabetes remained obvious. Increased CVD mortality was related to increasing HbA1c levels [61]. The benefits of improved diabetes care did not result in lowering CVD mortality [62].

On the other hand, an early and intensive metabolic control has been shown to reduce micro- and macrovascular morbidity and mortality, favouring the «imprinting « theory of metabolic control.

Nevertheless, in type 1 diabetes we have to consider still other pathogenetic factors: an excess CAC in type 1 diabetes is providing support for accelerated atherosclerosis [63, 64]. Here, angiographic and autopsy studies have shown more extensive disease. Of note, changes in arterial compliance, endothelial dysfunction and changes in vasculature structure and function occur early in the course of type 1 diabetes [65–68]. Type 1 diabetes is associated with increased risk for CHD and that is already evident at young age.

Beside the impact of hyperglycemia, there is a wide range of modifiable risk factors and indicators, such as blood pressure, lipid abnormalities and smoking and specific factors as renal disease. In the EDIC — Study inflammation, depressive symptomatology and insulin resistance were considered as CAD predictors; however, not hyperglycemia [69]. Similar data were found by the EURODIAB Study [70], and the WESDR Study [71]. In all these studies HbA1c showed only weak associations with CAD in type 1 diabetes [72]. However, another risk factor, i.e. diabetic autonomic neuropathy, implicated an increased CAD risk in type 1 diabetes [72].

Concerning lipids, HDL-cholesterol levels are generally higher in type 1 diabetes, thus reflecting an altered HDL metabolisms by enhanced lipoprotein lipase and reduced hepatic lipase activity due to systemic insulin administration.

Atherosclerosis is increasingly considered as an inflammatory disease. The oxidative modification of LDL, activation of macrophages, and endothelial cells, impaired nitric oxide and resulting vascular cytotoxicity may be involved in the pathogenetic process [73]. Other factors, for example, adhesion molecules and cytokines have still not extensively been studied in the development of CAD in type 1 diabetes [74].

The DCCT data have shown a durable effect of initially intensive metabolic control despite a loss of glycemic separation later on in the disease progress, an effect of metabolic memory. A reduction of early-stage complications during the course of DCCT has been demonstrated as well as a substantial reduction in severe complications and in cardiovascular disease [62].

The phenomenon of a durable reduction of complications by prior intensive metabolic control was named «metabolic memory». The effect lasted at least 10 years [62]. Major beneficial effects of intensive control on advanced complications included retinopathy, nephropathy and autonomic neuropathy. Measurements of atherosclerosis included carotid intima thickness and coronary artery calcification. Fatal and nonfatal myocardial infarctions were reduced by intensive treatment with 58 % after a mean of 18 years of follow-up [75]. The EDIC observational follow up confirmed the durability of DCCT effects [76].

T a b l e

Meta-analysis of intensified vs. conventional glycemic control

Trials	Annualeventrate (%)			
	Intensified	Conventional	(%)	Hazard ratio (95 %CI)
Major cardiovascular event				
ACCORD	352(2.11)	371(2.29)	–1.01	0.90 (0.78–1.04)
ADVANCE	557(2.15)	590(2.28)	–0.72	0.94 (0.84–1.06)
UKPDS	169(1.30)	87(1.60)	–0.66	0.80 (0.62–1.04)
VADT	116(2.68)	128(2.98)	–1.16	0.90 (0.70–1.16)
Overall	**1194**	**1176**	**–0.88**	**0.91 (0.84–0.99) (Q=1.32; P=0.72; I^2=0)**
Myocardialinfarction				
ACCORD	198 (1.18)	245 (1.51)	–1.01	0.77 (0.64–0.93)
ADVANCE	310 (1.18)	337 (1.28)	–0.72	0.92 (0.79–1.07)
UKPDS	150 (1.20)	76 (1.40)	–0.66	0.81 (0.62–1.07)
VADT	72 (1.65)	87 (1.99)	–1.16	0.83 (0.61–1.13)
Overall	**730**	**745**	**–0.88**	**0.85 (0.76–0.94) (Q=2.25; P=0.52; I^2=0)**
Cardiovasculardeath				
ACCORD	135 (0.79)	94 (0.56)	–1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	–0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	–0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	–1.16	1.32 (0.81–2.14)
Overall	**497**	**441**	**–0.88**	**1.10 (0.84–1.42) (Q=8.61; P=0.04; I^2=65.1 %)**
All-causemortality				
ACCORD	257 (1.41)	203 (1.14)	–1.01	1.22(1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	–0.72	0.93(0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	–0.66	0.96(0.70–1.33)
VADT	102 (2.22)	95 (2.06)	–1.16	1.07(0.81–1.42)
Overall	**980**	**884**	**–0.88**	**1.04(0.90–1.20) (Q=5.71; P=0.13; I^2=47.5 %)**

Adapted from reference [80]: Turnbull et al. Diabetologia. — 2003. — Vol. 52. — P. 2288–2298.

Abbreviations: ACCORD — Action to Control Cardiovascular Risk in Diabetes; ADVANCE — Action in Diabetes and Vascular Disease Preterax and Diamicron controlled evaluation; UKPDS — United Kingdom Prospective Diabetes Study; VADT — Veterans Affairs Diabetes Trial; HbA1c — glycated hemoglobin.

Hazard ratios < 1.0 are favouring intensified glycemic control. Hazard ratios >1.0 are favouring conventional glycemic control.

It was convincingly demonstrated, that the glucose hypothesis was correct. Blood glucose control aimed to achieve glycemia close to non-diabetic levels as safely as possible, reduced microvascular and macrovascular complications. This suggests that long-lived proteins might account for this effect [62].

Introduction of these findings into clinical care has improved the long-term health of patients with type 1 diabetes [62]. A strong relation of glycemia with CAD was not seen in other studies [69–71]. However, the DCCT patients had shorter diabetes duration, and obese hypertensive and hypercholesterolemic patients were excluded. Consequently, sufficiently low HbA1c levels of 7.4 % were achieved [62].

Conclusions

This survey shows that early intensive metabolic control near to the normal level initiated in type 1 diabetes patients with short diabetes duration and without microangiopathic complications resulted in significantly reduced micro- and macrovascular morbidity. It caused long-lasting effect (memory effects) and resulted even in decreasing CAD morbidity and mortality [77, 78].

The Guidelines of the DDG in considering the results of the above mentioned studies suggest:

Type 1 diabetes

In patients with type 1 diabetes HbA1c concentrations <7.5 % are aimed. Guidelines recommend individually targeted HbA1c levels in order to avoid hypoglycemias and recommend blood glucose self control at least 4times daily, i.e. before meals and at bedtime [79, 80].

Type 2 diabetes

(1) For type 2 diabetes HbA 1c levels are aimed at 6.5 % to 7.5 % by taking into account individually targeted HbA1c concentrations [79], even though, meta-analysis of four large randomized controlled trials of intensive vs. conventional glycemic control in type 2 diabetes have shown an only modest but still significant cardiovascular benefit in intensively treated patients (Table). The effect of intensive glucose control resulted in a 15 % reduction risk (RR) of myocardial infarction [81].

The benefits of intensified blood glucose control in reducing cardiovascular disease should not be overestimated by giving records in terms of relative risk reduction (RR). They should rather be given in terms of absolute risk reduction or the corresponding NNT, i.e. the number of individuals who would require 5 years of treatment to prevent one event would be 44 with cholesterol lowering, 34 with blood pressure lowering and 119 with intensive blood glucose lowering [81].

(2) Intensive glucose control has to be started as early as possible (legacy effect), and hypoglycemia should be avoided [40].

(3) Hyperglycemia has shown to be a weaker cardiovascular risk factor than increased cholesterol or hypertension [81].

(4) Reducing the cardiovascular risk by decreasing elevated cholesterol levels and hypertension has shown to be more effective than intensive blood glucose control.

Common features

Comparing both types of diabetes the survey has shown type 1 and type 2 diabetes are different entities. Major epidemiological trials provided evidence that hyperglycemia causes the microangiopathic complications both in type 1 and type 2 diabetes, and intensified glycemic control decreases significantly the microangiopathic complications.

A special role both in type 1 and type 2 diabetes plays an increased cardiovascular morbidity and mortality. Patients of both types have an increased prevalence of cardiovascular complications. These complications appear earlier than in the non-diabetic population, the clinical course is accelerated and there are no sex differences.

When comparing both types of diabetes, the major epidemiological trials have brought the evidence that intensified glycemic control equally resulted in longlasting effects, thus reducing significantly cardiovascular morbidity and mortality in both types of diabetes. In both types of diabetes treatment has to be initiated early in the clinical course of the disease, and hypoglycemias have to be avoided.

Nevertheless, we have to consider that in both types of diabetes beneficial effects of intensified glycemic control in reducing the cardiovascular morbidity and mortality are considerably lower than those of reducing the classic cardiovascular risk factors.

References

1 *Green A.* Relative mortality of type 1 (insulin dependent) diabetes mellitus in Denmark: 1933–1981 // Diabetologia. — 1985. — Vol. 28. — P. 339–342.

2 *Panzram G. et al.* Mortality and Survival in type 2 (non-insulin-dependent) diabetes mellitus // Diabetologia. — 1987. — Vol. 30. — P. 123–131.

3 *Zimmet P.Z.* The growing pandemic of type 2 diabetes: a crucial need for prevention and improved detection // Medicographia. — 2011. — Vol. 33. — P. 15–21.

4 International Diabetes Federation. Diabetes and Cardiovascular Disease. Time to Act Brussels, Belgium // International Diabetes Federation. — 2001.

5 *Maahs D.M. et al.* Epidemiology of type 1 diabetes // Endocrinol. Metab. Clin. North Am. — 2010. — Vol. 39, No. 3. — P. 481–497.

6 *Cockram C.S., Tong P.C.Y.* The burden type 2 diabetes: an epidemiological approach // Medicograhia. — 2004. — Vol. 26. — P. 11–20.

7 *Holman R.R. et al.* 10-year follow-up of intensive glucose control in type 2 diabetes // N. Engl. J. Med. — 2008. — Vol. 359. — P. 1577–1589.

8 *Nathan D.M. et al.* Diabetes Control and Complications Trial / Epidemiology of Diabetes. Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive treatment and cardiovascular disease in patients with type 1 diabetes // N. Engl. J. Med. — 2005. — Vol. 353. — P. 2643–2653.

9 *Preis S.R. et al.* Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study,1950–2005 // Circulation. — 2009. — Vol. 119. — P. 1728–1735.

10 *Damssgaard E.M. et al.* Overmortality as related to age and gender in patients with established non-insulin-dependent diabetes mellitus // J. Diabetic Complications. — 1997. — Vol. 11. — P. 77–82.

11 *Zander E., Kerner W.* Cardiovascular risk factors in type 1 and type 2 diabetes: Common conventional and diabetes related variables? // Vascular Involvement in Diabetes, Clinical, Experimental and Beyond / Ed. by D. Cheta. — Editura Academiei Romana Bucurestiand Karger, 2005. — P. 263–271.

12 *Fuller J.H. et al.* Diabetes mortality: new light on an underestimated public health problem // Diabetologia. — 1983. — Vol. 24. — P. 336–341.

13 *Reindel et al.* Metabolisches Syndrom bei Patienten mit Diabetes mellitus Typ 1 // Herz. — 2004. — Vol. 29. — P. 463–469.

14 *Zander E. et al.* Das kardiovaskuläre Risiko des Typ-1-Diabetes: Koronare Herzkrankheit und peripherearterielle Durchblutun gsstörungen // Diabetes und Stoffwechselstörungen. — 2005. — Vol. 14. — P. 119–126.

15 *Schnell O. et al.* Type 1 diabetes and cardiovascular disease // Cardiovascular Diabetology. — 2013. — Vol. 12. — P. 156 / [ER]. Access mode: http://www.cardiodiab.com/content/12/1/156.

16 *Matthews D.R.* Key landmark studies in the clinical management of type 2 diabetes: evolution or revolution? // Medicographia. — 2011. — Vol. 33. — P. 22–27.

17 *Jarrett R.J.* Risk factors for coronary heart disease in diabetes mellitus // Diabetes. — 1992. — Vol. 41 (Suppl. 2). — P. 1–3.

18 *Brownlee M.* The pathobiology of diabetic complications // Diabetes. — 2005. — Vol. 54. — P. 1615–1625.

19 *Heilig C.W. et al.* Overexpression of glucose transporters in rat mesangial cells cultured in a normal glucose milieu mimics the diabetic phenotype // J. Clin. Invest. — 1995. — Vol. 96. — P. 1802–1814.

20 *Lee A.Y. et al.* Contributions of polyol pathway to oxidative stress in diabetic cataract // FASEB J. — 1999. — Vol. 13. — P. 20–30.

21 *Giardino J. et al.* Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity: a model for intracellular glycosylation in diabetes // J. Clin. Invest. — 1994. — Vol. 94. — P. 110–117.

22 *Charconis A.S. et al.* Laminin alterations after in vitro nonenzymatic glycosylation // Diabetes. — 1990. — Vol. 39. — P. 807–814.

23 *Li Y.M.* Molecular identity and cellular distribution of advanced glycation endproduct receptors: relationship of p60 to OST 48 and p90 to 8 OK-H membrane proteins // Proc. Nat. Acad. Sci. USA. — 1996. — Vol. 93. — P. 11047–11052.

24 *Koya D. et al.* Protein kinase C activation and the development of diabetic complications // Diabetes. — 1998. — Vol. 47. — P. 859–866.

25 *Du X.L. et al.* Hyperglycemia-induced mitochondrial superoxide over-production activates the hexosamine pathway and induces plasminogen activator-inhibitor-1 expression by increasing Sp1 glycosylation // Proc. Nat. Acad. Sci. USA. — 2000. — Vol. 97. — P. 12220–12226.

26 *Frederici M. et al.* Insulin-dependent activation of nitric oxide synthese impaired by O-linked glycosylation modification of signalizing proteins in human coronary endothelial cells // Circulation. — 2002. — Vol. 106. — P. 466–472.

27 *Mogensen C.E.* Diabetes mellitus: a look at the past, a glimpse to the future // Medicographia. — 2011. — Vol. 33, No. 1. — P. 9–14.

28 *Keen H.* Reducing the burden: the diabetes debate // Diabet. Metab. Rev. — 1997. — Vol. 13. — P. 119–123.

29 *Tuomilehto J. et al.* Prevention of type 2 diabetes by changes in life style among subjects with impaired glucose tolerance // N. Engl. J. Med. — 2001. — Vol. 344. — P. 1343–1350.

30 *Haffner S.M. et al.* Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction // Eng. J. Med. — 1998. — Vol. 339. — P. 229–234.

31 *Stamler J. et al.* Multiple Risk Factor Intervention Trial Group. Diabetes, other risk factors and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial // Diabetes Care. — 1993. — Vol. 16. — P. 434–444.

32 *Schernthaner G.* Microalbuminuria in non-insulin-dependent diabetes mellitus // Microalbuminuria. A marker for organ damage / Ed. by Mogensen. — Oxford, UK: Science Press, 1993. — P. 29–43.

33 *Wei M. et al.* Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality // Diabetes Care. — 1998. — Vol. 21. — P. 1167–1172.

34 *Knöbl P. et al.* Hemostatic abnormalities persist despite glycemic improvement by insulin therapy in lean type 2 diabetic patients // Thromb Hemostat. — 1994. — Vol. 71. — P. 692–697.

35 *Steinberg H.O. et al.* Obesity, insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance // J. Clin. Invest. — 1996. — Vol. 97. — P. 2601–2610.

36 *Engström G. et al.* Diabetes and mortality and incidence of myocardial infarction and stroke // Diabetes. — 2003. — Vol. 52. — P. 442–447.

37 *Fuller J.H. et al. and the WHO Multinational Study Group.* Risk factors for cardiovascular mortality and morbidity: The WHO multinational study of vascular disease in diabetes // Diabetologia. — 2001. — Vol. 44 (Supl. 1). — P. S54–S64.

38 *Hadden D.R. et al.* Macrovascular disease and hyperglycemia: 10 year survival analysis in type 2 diabetes mellitus: The Bedford Diet Study // Diabete Med. — 1997. — Vol. 14. — P. 663–672.

39 *Jarrett R.J. et al.* The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetes and normoglycemic controls and risk indices for coronary heart disease in borderline diabetes // Diabetologia. — 1982. — Vol. 22. — P. 79–84.

40 *Holman R.R. et al.* 10-year follow up of intensive glucose control in type 2 diabetes // N. Engl. J. Med. — 2008. — Vol. 359. — P. 1577–1589.

41 *UK Prospective Study Group*. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) // Lancet. — 1998. — Vol. 352. — P. 837–853.

42 *UK Prospective Diabetes Study Group*. Effect of intensive blood – glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) // Lancet. — 1998. — Vol. 352. — P. 854–865.

43 Implications of the United Kingdom Prospective Diabetes Study. American Diabetes Association // Diabetes Care. — 1998. — Vol. 21. — P. 2180–2184.

44 *UK Prospective Diabetes Study Group.* Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38) // BMJ. — 1998. — Vol. 317. — P. 703–713.

45 *UK Prospective Diabetes Study Group.* Efficacy of atenolol and captopril in reducing risk of both macrovascular and microvascular complications in type 2 diabetes (UKPDS 39) // BMJ. — 1998. — Vol. 317. — P. 713–720.

46 Action to Control Cardiovascular Risk in Diabetes Study Group / *Gerstein H.C. et al.* Effects of intensive glucose lowering in type 2 diabetes // N. Engl. J. Med. — 2008. — Vol. 358, No. 24. — P. 2545–2559.

47 *Zoungas S.* Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: new results from the ADVANCE trial / Diabetes Care. — 2009. — Vol. 342. — P. 2968–2974.

48 *Duckworth W. et al.* Glucose control and vascular complications in veterans with type 2 diabetes // N. Engl. J. Med. — 2009. — Vol. 360. — P. 129–139.

49 UKPDS group Effects of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) // Lancet. — 1998. — Vol. 352. — P. 854–865.

50 *Adler et al.* Associations of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36) prospective observational study // BMJ. — 2000. — Vol. 321. — P. 412–419.

51 *Gaede P. et al.* Effect of a multifactorial intervention on mortality in type 2 diabetes // N. Engl. J. Med. — 2008. — Vol. 358. — P. 580–591.

52 *Krolewski A.S. et al.* Magnitude and determinants of coronary artery disease in juvenile, insulin-dependent diabetes mellitus // Am. J. Cardiol. — 1987. — Vol. 59. — P. 750–755.

53 *Deckert T. et al.* Prognosis of diabetes with diabetes onset before the age of thirty-one. A survival causes of death and complications // Diabetologia. — 1998. — Vol. 14. — P. 363–370.

54 *Schnell O., Standl E.* Diabetes and cardiovascular disease. Current status of trials // Clin. Res. Cardiol. Suppl. — 2010. — Vol. 5. — P. 27–34.

55 *Orchard T.J. et al.* Type 1 diabetes and coronary artery disease // Diabetes Care. — 2006. — Vol. 29. — P. 2528–2538.

56 *Deckert T. et al.* Prognosis of diabetics with diabetes onset before the Age of thirty-one. Factors influencing prognosis // Diabetologia. — 1978. — Vol. 14. — P. 371–377.

57 *Christlieb A.R. et al.* Hypertension, the major risk factor in juvenile-onset insulin-dependent diabetics // Diabetes. — 1981. — Vol. 30 (Suppl. 2). — P. 90–96.

58 *Juutilainen V.A. et al.* Similarity of the impact of type 1 diabetes and type 2 diabetes on cardiovascular mortality in middle-aged subjects // Diabetes Care. — 2008. — Vol. 31. — P. 714–719.

59 *Nishimura R. et al.* Mortality trends in type 1 diabetes. The Allegheny County (Pennsylvania) Registry 1965–1999 // Diabetes Care. — 2001. — Vol. 24. — P. 823–827.

60 *Miller R.G.* Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications Study Cohort // Diabetes. — 2012. — Vol. 61. — P. 2987–2992.

61 *Koivisto V.A. et al.* Cardiovascular disease and its risk factors in IDDM in Europe. EURODIAB IDDM Complications Study Group // Diabetes Care. — 1996. — Vol. 19. — P. 689–697.

62 *Nathan D.M. et al., the DCCT Group.* Intensive therapy and carotid intima-media thickness in type 1 diabetes mellitus // N. Engl. J. Med. — 2003. — Vol. 348. — P. 2294–2303.

63 *Colhoun H.M. et al.* The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification// J. Am. Coll. Cardiol. — 2000. — Vol. 36. — P. 2160–2167.

64 *Olsen et al.* Coronary calcium in adults with type 1 diabetes // Diabetes. — 2000. — Vol. 49. — P. 1571–1578.

65 *Crall P.V.* The extramural and intramural coronary arteries in juvenile diabetes mellitus: analysis of nine necropsy patients aged 19 to 38 years with onset of diabetes before the age of 15 years // Am. J. Med. — 1978. — Vol. 64. — P. 221–230.

66 *Pajunen P. et al.* Angiographic severity and extent of coronary artery disease in patients with type 1 diabetes mellitus // Am. J. Cardiol. — 2000. — Vol. 86. — P. 1080–1085.

67 *Larsen J. et al.* Silent atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control // Diabetes. — 2002. — Vol. 51. — P. 2637–2641.

68 *Jarvisalo M.J. et al.* Endothelian dysfunctional increased arterial intima-media thickness in children with type 1 diabetes // Circulation. — 2004. — Vol. 109. — P. 1750–1755.

69 *Forrest K.Y. et al.* Are predictors of coronary heart disease and lower extremity arterial disease in type 1 diabetes the same? A prospectivestudy // Atheroscleroseis. — 2009. — Vol. 148. — P. 159–169.

70 *Soedemah-Muthu S.S. et al.* The EURODIAB Prospective Complications Study Group: Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the Europe Prospective Complications Study // Diabetes Care. — 2004. — Vol. 27. — P. 530–537.

71 *Klein B.E.K. et al.* Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy // Arch. Intern. Med. — 2004. — Vol. 164. — P. 1917–1924.

72 *Ewing D.J. et al.* Mortality in diabetic autonomic neuropathy // Lancet. — 1976. — P. 601–603.

73 *Ross R.* Atherosclerosis: an inflammatory disease // N. Engl. J. Med. — 1999. — Vol. 340. — P. 115–126.

74 *Bevilacqua M.P.* Endothelial-leucocyte adhesion molecules // Annu Rev Immunol. — 1993. — Vol. 11. — P. 767–804.

75 *Nathan D.M. et al.* Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetic treatment and cardiovascular disease in patients with type 1 diabetes // N. Engl. J. Med. — 2005. — Vol. 353. — P. 2643–2653.

76 *Nathan D.M., for the DCCT/EDIC Research Group.* The Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Study at 30 years. Overview // Diabetes Care. — 2014. — Vol. 37. — P. 9–16.

77 *Orchard T.J. et al.* Type 1 diabetes and coronary artery disease // Diabetes Care. — 2006. — Vol. 29, No. 11. — P. 2528–2538.

78 *Lehto S. et al.* Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy // Atheroscler. Thromb. Vasc. Biol. — 1999. —Vol. 19. — P. 1014–1019. [ER]. Access mode: www. versorgungsleitlinien.de // Nationale Versorgungsleitlinie Therapie des Typ-2-Diabetes, 1. Auflage, Version 4, September 2013, geändert November 2014.

79 *Böhm B.O. et al.* Therapie des Typ 1 Diabetes // Diabetologie. — 2012. — Vol. 7. — P. 33–83.

80 *Turnbull F.M. et al.* Intensive glucose control and macrovascular outcomes in type 2 diabetes // Diabetologia. — 2009. — Vol. 52. — P. 2288–2298.

81 *Yudkin J.S. et al.* Intensified glucose lowering in type 2 diabetes time for reappraisal // Diabetologia. — 2010. — Vol. 53. — P. 2079–2085.

Е. Цандер, К.-Д.Конерт, Ч. Аллвардт, И. Райндел, И.Шмидт, В. Кернер, В. Мотц

1- және 2-типті диабет кезіндегі жүрек-қан тамырлар ауруларының гипергликемиясы және даму қауіпі

Мақалада диабетпен ауыратын адамдар үшін ең елеулі және тұрақты қауіп ретінде атеросклероз және ЖҚТ аурулардың саны жоғарылауы және соның салдарынан өліммен аяқталу болып табылады. Жұмыстың мақсаты — 1- және 2-типті диабет кезінде гипергликемияның, жүрек-қан тамырлар ауруларының дамуы мен өлім көрсеткішіндегі рөлін зерттеу. 2-типті диабет кезіндегі ADVANCE және UKPDS зерттеулері ЖҚТ ауруларының дамуы мен капиллярлардың зақымдануына байланысты болған аурудың азаюымен қатар, олардың өлім көрсеткішінің азаюына алып келетінін көрсетті. Мақсат — HbA1 дәрежесін 7,5 %-дан төмен, 6,5 %-ға дейін төмендету мен гипогликемияны болдырмау. Нәтижелер 1-типті диабетпен ауыратындардың ерте басталған метаболитті қадағалау арқасында микрогангиопатияның, нефропатияның және микро- және макроваскулярлы қабынулардың санының азайғанын көрсетті. HbA1 дәрежесінің 7.5 % -ға тең болуы ұсынылды. Алайда нәтижелер көрсеткіші бойынша гиперхолестеринемия немесе гипертонияға қарағанда гипергликемия ЖҚТ аурулары ішінде ең әлсіз фактор болып табылады.

Е. Цандер, К.-Д.Конерт, Ч. Аллвардт, И. Райндел, И.Шмидт, В. Кернер, В. Мотц

Гипергликемия и риск развития сердечно-сосудистых заболеваний при диабете 1 и 2 типов

В статье отмечено, что наиболее серьезной и постоянной угрозой здоровью больных диабетом лиц остаются атеросклероз и повышенный риск развития сердечно-сосудистых заболеваний (ССЗ), наблюдается высокая смертность от них. Цель работы — исследовать роль гипергликемии в развитии ССЗ и смертности от этих заболеваний при диабете 1 и 2 типов. Исследования ADVANCE и UKPDS при диабете 2 типа показали, что интенсивный контроль за глюкозой приводил к снижению риска развития ССЗ и смертности от других причин в сочетании с уменьшением заболеваний, связанных с

поражением капилляров: наблюдалось снижение уровня HbA1c до 6,5 % и предотвращение гипогликемий. Результаты показали наличие снижения числа микроангиопатий, нефропатий и числа микро- и макроваскулярных расстройств у больных диабетом 1 типа при рано начатом метаболическом контроле. Рекомендуемый уровень HbA1c — 7,5 %. Между тем результаты показывают, что гипергликемия является более слабым фактором риска развития ССЗ, чем гиперхолестеринемия или гипертония.