Hyperglycemia is a risk factor for cardiovascular complications in metabolic syndrome (Literature review).

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Abstract:

In the presented literature review, the authors consider the role of hyperglycemia that develops in patients with diabetes mellitus, which is a trigger for the development of complications of diabetes mellitus, leads to a deterioration in the quality of life of patients, reduces their ability to work and shortens life expectancy.

Keywords: hyperglycemia, metabolic syndrome, cardiovascular disease

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Cardiovascular disease develops in patients with diabetes mellitus, even with adequate glycemic control. Intensive control with metformin helps reduce complications of diabetes, including cardiovascular disease, suggesting that increased insulin sensitivity, rather than plasma glucose levels, plays an important role in improving diabetes outcomes. Therefore, insulin resistance, as measured by glucose tolerance tests, is a better predictor of future cardiovascular events than fasting glucose in non-diabetics. Insulin resistance precedes the clinical onset of type 2 diabetes by decades and impairs the metabolic control of type 1 diabetes. Literature data from various studies, meta-analyses and systematic reviews provide strong evidence that insulin resistance itself is a cardiovascular risk factor in various patient groups, including the general population and patients with diabetes. Some measures of insulin resistance are consistently associated with an increased incidence of cardiovascular disease, independent of other risk factors and diabetic status. The clinical manifestations of insulin resistance (metabolic syndrome or any of its components, including obesity, hyperinsulinemia, hypertension, and dyslipemia) are also associated with cardiovascular disease.

Melo M, Gavina C, Silva-Nunes J, (2021) estimate the risk of cardiovascular events associated with hyperglycemia, and its ability to increase even below the threshold for diabetes, although this association is stronger for microvascular complications. Paradoxically, the therapeutic strategies used for intensive glycemic control have not been shown to be effective in preventing serious adverse cardiovascular events compared with less stringent strategies, as shown by the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial) in 2008. There was a significant increase in mortality in the ACCORD study, which led to termination of the study, butapparently , this is due to significant glycemic variability, as those who experienced mortality did not have a significant decrease in HbA1c levels despite forced treatment. titration of their therapy. These studies used hypoglycemic drugs available at the time, including drugs from pharmacological classes classically associated with a significant risk of hypoglycemia, for treatment. In light of the findings of the new studies on cardiovascular outcomes (CVOT), the evaluation of the ACCORD and ADVANCE trials should be reassessed. Perhaps attention should not only be focused on achieving the lowest glycemic levels, but also on the mechanisms by which glycemic reduction and associated metabolic benefits are achieved.

Husain M, Birkenfeld AL, Donsmark M. (2019) Although the majority of diabetes-related deaths in the ACCORD and ADVANCE trials were attributable to cardiovascular disease, and the association of glycemic levels with MACE was only marginal, it is interesting to see why in previous studies of diabetic drugs, the focus was on lowering glucose levels rather than on cardiovascular outcomes. Despite the positive results of the use of metformin in the United Kingdom Prospective Diabetes Study, it was a meta-analysis of rosiglitazone trials showing an increase in MI and a numerical increase in all-cause mortality that alarmed regulators and, since 2008, prompted safety trials assessing cardiovascular outcomes for new hypoglycemic drugs.

For this purpose, the study "Effect and action of liraglutide in diabetes: assessment of cardiovascular outcomes" (LEADER) was conducted. Authors [Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. 2016] performed a multicenter, double-blind, placebo-controlled study designed to evaluate the long-term cardiovascular effects of once-daily subcutaneous liraglutide. outcomes and other clinically important events in patients with type 2 diabetes who were at high risk for cardiovascular disease (CVD). This was a post-approval study designed primarily to test non-inferiority, so the non-inferiority upper limit of the 95% confidence interval (CI) for MACE (primary outcome) was set at 1.3. Two groups of patients were considered for inclusion in the study: a) patients ≥ 50 years of age with eCVD [defined as: prior MI; previous stroke or transient ischemic attack; previous revascularization of the coronary, carotid or peripheral arteries; > 50% stenosis of the coronary, carotid, or lower extremity arteries; a history of symptomatic coronary artery disease confirmed by a positive exercise test or any cardiac imaging, or unstable angina with electrocardiogram (ECG) changes; asymptomatic cardiac ischemia confirmed by positive nuclear imaging, stress testing, or dobutamine stress echocardiography; chronic HF [New York Heart Association (NYHA) class II or III] or chronic renal failure [defined as an estimated glomerular filtration rate (eGFR) less than 60 ml per minute per 1.73 m2] and b) patients aged ≥ 60 years with at least one high CV risk factor (presence of microalbuminuria or proteinuria; left ventricular hypertension and hypertrophy on ECG or imaging; left ventricular systolic or diastolic dysfunction on imaging; ankle-brachial index <0.9).). A total of 9340 patients were included, 81.3% of whom had CV risk at baseline and were followed up for a median of 3.8 years. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are hypoglycemic drugs used in the treatment of T2DM that have a low risk of hypoglycemia and cause weight loss. CVOTs with GLP-1 RA included a variable number of patients with established cardiovascular disease (eCVD) or at high risk for cardiovascular events with different inclusion criteria. These differences make it impossible to compare between trials and may have influenced the test results. For this reason, the scientists considered it appropriate to review the various CVOTs performed with GLP-1 RA and conduct a comparative analysis between them, highlighting different study designs for each.

In the article by the authors Hernandez AV, Roman Y, Cuello-García CA. (2018) demonstrated the possibility of sliding-scale DM insulin therapy for hospitalized adults with non-critical diabetes mellitus. There are several treatment options for people with diabetes admitted to the hospital who have both low glucose levels (hypoglycemia) and high glucose levels (hyperglycemia), which can increase the risk of death and complications such as infections and longer hospital stays, and therefore should be avoided. The most common treatment for hospitalized people with diabetes is sliding scale insulin therapy. The term "sliding scale" refers to an increase in pre-meal insulin dose based on pre-meal blood sugar levels. For example, if a person has a blood glucose level between 140 mg/dL and 180 mg/dL, the usual dose of short-acting insulin might be 4 units of insulin, and if the blood glucose level is

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between 181 mg/dL and 220 mg/dL. dl, it could be 6 units of insulin. This type of hard insulin delivery usually fixes the amount of carbohydrates to be eaten at each meal, but does notenhances insulin delivery in a physiological manner. Therefore, it is doubtful whether good glycemic control (satisfactory blood glucose levels) can be achieved with sliding scale insulin in hospitalized diabetic patients and whether this approach leads to better results in the long term. Other insulin strategies exist, such as baseline (basal) insulin doses combined with flexible pre-meal insulin (bolus insulin) depending on what and how much the person wants to eat. Sliding scale insulin means adhering strictly to a regular meal and physical activity schedule, and people must follow the prescribed diet. The Intensive Insulin Therapy (basal bolus strategy) allows you to flexibly administer insulin doses based on physical activity, stress, and eating habits. and in the hospital setting requires well-trained medical personnel. Sliding scale insulin is still widely used and it remains unclear which insulin strategy is best suited to treat hospitalized diabetics. The main comparison was between sliding scale insulin and basal bolus insulin therapy with the following results. Of the four studies that reported deaths, one of 268 participants in the SSI group died compared to two of 334 participants in the basal-bolus group. Episodes of severe hypoglycemia, defined as blood glucose levels below 40 mg/dL, occurred in 5 people per 1000 people in the sliding scale insulin groups compared to 24 per 1000 people in the basal bolus insulin groups. These data are uncertain as further analyzes showed no positive or negative effect when comparing both insulin strategies. The length of stay in the hospital was 0.5 days longer in the sliding scale insulin groups than in the basal-bolus insulin groups, and again, further analyzes showed that this information is questionable. Results for adverse events other than episodes of hypoglycemia, such as postoperative infections, did not indicate advantages or disadvantages of either strategy. Mean blood glucose during hospital stay was 14.8 mg/dl higher in the sliding scale groups compared to the basal bolus groups. The researchers are uncertain about these data because the analyzes showed no positive or negative effect when comparing both insulin strategies.

Of interest is the article by American scientists Wallace AS, Wang D, Shin JI.2020, which provides screening and diagnosis of prediabetes and diabetes in children and adolescents in the United States. Beginning in 2018, the American Diabetes Association expanded generic screening for type 2 diabetes in asymptomatic youth aged 10 years and older to include all overweight youth with one or more of these risk factors. The consequences of this change are not characterized; it is not known how many children and adolescents in the US are eligible for screening under these new guidelines. The authors conducted a cross-sectional analysis of 14,119 young people aged 10 to 19 in NHANES 1999–2016. Approximately a quarter of American children and adolescents, 10.6 million in 2016, were overweight or obese and had at least one risk factor for diabetes, making them eligible for diabetes screening under the 2018 criteria. In comparison, <10% of children and adolescents in the US, 3.6 million in 2016, would be eligible for screening through the 2018 criteria. Undiagnosed diabetes was unusual, regardless of screening eligibility (2018 criteria) or the definition of diabetes used. Unconfirmed cases of undiagnosed diabetes defined by HbA1c alone ≥6.5% occurred in 0.3% (95% confidence interval [CI]: 0.1%–0.5%) of eligible youth and < 0.1% in youth not eligible for screening. The prevalence of undiagnosed diabetes using a single elevated PPG level, an increase on any test, or a clinical confirmatory finding (both tests are elevated) in the screening-eligible population, and the prevalence on all determinations in the ineligible population were too low to estimate with precision. Diagnosed diabetes occurred in 0.5% (95% CI: 0.4%–0.7%) of youth (0.2 million), corresponding to >85% of total confirmed cases of diabetes. A quarter of US youth are eligible for screening for diabetes and prediabetes; however, few will test positive, especially for

diabetes. Most cases of diabetes in US youth are diagnosed. Regardless of meeting screening criteria, scientists have found that HbA1c is a specific and useful anti-freeze test for identifying high-risk youth who may benefit from lifestyle interventions to preventeffects of diabetes and cardiovascular risk in adulthood.

Inzucchi SE. (2018) According to recent studies and recommendations of professional endocrinological communities, among the variety of antidiabetic drugs in the presence of ASCVD, priority is given to drugs from the groups of sodium-glucose cotransporter type 2 inhibitors (SGLT-2) and glucagon-like peptide-1 receptor agonists - GLP-1 (liraglutide, dulaglutide, semaglutide). Since 2008, according to the decision of the US Food and Drug Administration (FDA), when conducting clinical trials of new drugs, their cardiovascular safety is mandatory. Studies conducted for these drugs have proven not only their safety, but also the presence of many positive aspects. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, LEADER, SUSTAIN-6, REWIND studies on the cardiovascular safety of empagliflozin, canagliflozin and dapagliflozin, liraglutide, semaglutide, dulaglutide, respectively, demonstrated various positive cardiovascular effects and confirmed a reduction in cardiovascular mortality, as well as a reduction in the incidence of non-fatal strokes and heart attacks. Cardioprotective effects when taking SGLT-2 inhibitors are due to secondary mechanisms, which are based on natriuresis and osmotic diuresis. An important consequence of these processes is a decrease in the volume of circulating fluid and blood pressure, both systolic and diastolic. Also, SGLT-2 inhibitors have a nephroprotective effect, which makes it possible to eliminate another factor in the development of ASCVD - CKD. For liraglutide and semaglutide, nephroprotective properties have also been proven. The mechanisms by which GLP-1 receptor agonists reduce cardiovascular risk are not yet fully understood. However, they are known to reduce oxidative stress, affect endothelial dysfunction, and have antiatherosclerotic and antihypertensive effects. The authors of the studies recommended drugs of these classes as primary prevention in the presence of cardiovascular risk factors. It is strongly not recommended to use glibenclamide (a drug from the sulfonylurea group) in the presence of ASCVD, due to the high risk of developing hypoglycemic reactions.

The effect of glycemia on CVD risk in type 1 diabetes is reviewed in Bebu I, Braffett BH, Orchard TJ, 2021. The authors assessed whether and to what extent established cardiovascular disease (CVD) risk factors mitigate (increase/reduce) the impact of hyperglycemia on CVD outcomes in a long-term follow-up type 1 diabetes (DM1) cohort (N = 1441). the subsequent risk of serious adverse cardiovascular events (MACE: fatal or non-fatal myocardial infarction or stroke) and any cardiovascular disease (MACE plus confirmed angina, silent MI, revascularization, or congestive heart failure) was assessed separately using terms of the interaction between HbA1c and others risk factors in Cox's proportional hazard models. During a mean follow-up period of 29 years, 120 cases of MACE and 239 cases of cardiovascular disease were reported. Increased heart rate, elevated triglycerides, calcium channel blockers, and the presence of neuropathy individually increase ($p < 0.01$) the effect of glycemia on any CVD. Higher pulse and triglyceride levels, albumin excretion rate, hypertension, and no family history of type 2 diabetes increased ($p < 0.01$) the effect of glycemia on MACE. This moderation analysis identifies subgroups at increased risk for CVD that may particularly benefit from earlier and/or more intense glycemic control. Interventions that treat modifiable mitigating factors can independently reduce the risk of cardiovascular disease, as well as reduce the risk associated with higher HbA1c.

Japanese scientists Huang YY, Qin XK, Dai YY, (2022) propose a new drug Acetobacteraceti rich in chromium and zinc (A. aceti) and its ability to enhance the hypoglycemic effects of probiotics in the treatment of diabetes. A. aceti

was cultured in a liquid medium containing chromium trichloride and zinc chloride, both at a concentration of 64 mg/ml, at an initial concentration of the bacterial solution of 1 × 10 4cfu/ml. After induction with a bacterial solution for 48 h, the nutrient medium was changed and the induction was repeated once. The levels of chromium and zinc in bacteria were determined using inductively coupled plasma mass spectrometry, and the content of NADH and glucose dehydrogenase was determined using the NAD/NADH kit and the glucose dehydrogenase kit, respectively. Streptozotocinwas used to create a mouse model to evaluate the hypoglycemic effects of the proposed chromium-zinc rich A. aceti. A tenfold therapeutic dose was administered to assess biosafety. The effect on islet cells of MIN6 was also evaluated in vitro. The levels of chromium metal, zinc metal, coenzyme NADH and glucose dehydrogenase in A. aceti obtained by this method were 28.58–34.34 mg/kg, 5.35–7.52 mg/kg, 5.13–7.26 μM and 446.812–567.138 units. /g, respectively. The use of these bacteria resulted in a better hypoglycemic effect than metformin, promoting repair of pancreatic islet tissues and cells in vivo and facilitating the growth of MIN6 pancreatic islet cells and increasing insulin secretion in vitro. A tenfold therapeutic dose of the drug was non-toxic to mice. The authors state that chromium trichloride and zinc chloride can be used to induce production of chromium-zinc rich A. aceti, which can then contribute to the hypoglycemic effect characteristic of normal A. aceti. The bacteria biotransform chromium and zinc in a way that may improve their safety in the treatment of diabetes.

Mozaffarian D. (2016) the author presents his position to prevent the development and progression of all macrovascular complications of DM, it is important to modify lifestyle, achieve glycemic control goals, control blood lipids, and control blood pressure. Lifestyle modification. Lifestyle modification includes adherence to dietary recommendations, increased physical activity, weight loss, smoking cessation. Healthy dietary advice should be given individually according to calorie needs, personal and cultural eating habits, type of diabetes, medications prescribed, and comorbidities. In the presence of excess body weight, hypocaloric nutrition is considered. Recommendations also include monitoring carbohydrate intake, eating fruits, legumes, vegetables, whole grains, and dairy products, and replacing saturated and trans fats with healthy fats (eg, monounsaturated and polyunsaturated fatty acids). The content of dietary fiber should be at least 30-40 g per day. In the absence of sufficient effect from lifestyle interventions, drug therapy or bariatric surgery may be considered. Regular physical activity reduces cardiovascular and overall mortality in patientsThe effect of glycemia on CVD risk in type 1 diabetes is reviewed in Bebu I, Braffett BH, Orchard TJ, 2021. The authors assessed whether and to what extent established cardiovascular disease (CVD) risk factors mitigate (increase/reduce) the impact of hyperglycemia on CVD outcomes in a long-term follow-up type 1 diabetes (DM1) cohort (N = 1441). the subsequent risk of serious adverse cardiovascular events (MACE: fatal or non-fatal myocardial infarction or stroke) and any cardiovascular disease (MACE plus confirmed angina, silent MI, revascularization, or congestive heart failure) was assessed separately using terms of the interaction between HbA1c and others risk factors in Cox's proportional hazard models. During a mean follow-up period of 29 years, 120 cases of MACE and 239 cases of cardiovascular disease were reported. Increased heart rate, elevated triglycerides, calcium channel blockers, and the presence of neuropathy individually increase ($p < 0.01$) the effect of glycemia on any CVD. Higher pulse and triglyceride levels, albumin excretion rate, hypertension, and no family history of type 2 diabetes increased ($p < 0.01$) the effect of glycemia on MACE. This moderation analysis identifies subgroups at increased risk for CVD that may particularly benefit from earlier and/or more intense glycemic control. Interventions that treat modifiable mitigating factors can independently

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An important condition for the successful achievement of treatment of patients with glycemia is adherence to the prescribed therapy. In the European study EUROHEART found that out of 2183 patients with type 2 diabetes with coronary artery disease, only 60% were prescribed a combination of all four cardioprotective drugs. Target BP<140/90 mmHg Art. was achieved in only 54%, the target LDL cholesterol <1.8 mmol/l in 28%, and only 53% achieved a decrease in HbA1c to 7.0% [Gyberg V, De Bacquer D, De Backer G et al. 2015]

Barsukov I.A., Demina A.A. (2018) also consider it extremely important to control the level of glycemia by the patients themselves, training in the use of new, improved glucometers, as well

as systems for continuous monitoring of glycemia. Considering that the choice of therapy and, consequently, the level of compensation of carbohydrate metabolism depends on the accuracy of the measurement, it is extremely important that the glucometer used by the patient meets all the necessary standards. The most promising method of treatment is insulin therapy with an insulin pump, the effectiveness of which has been repeatedly confirmed in clinical trials. Insulin pump therapy is the method of choice both for groups of patients with DM who need strict glycemic control (pregnant women and those planning pregnancy, who are on program hemodialysis, who have low sensitivity to hypoglycemic reactions, etc.), and for young patients who adhere to an active lifestyle. life and adjust insulin therapy according to their needs. Obviously, insulin pump therapy in patients with an active lifestyle has significant advantages over the multiple injection regimen and allows you to more accurately adjust the amount of insulin entering the body, thereby achieving better compensation for carbohydrate metabolism.

Podzolkova V. A., Vitebskaya A. V. (2019) consider the treatment of hyperglycemia in children and adolescents during pulse therapy with glucocorticosteroids. HA pulse therapy is the treatment of choice for conditions requiring rapid immunosuppressive and anti-inflammatory effects. The advantageous feature of PT is a rather low frequency of side effects. Studies investigating the short-term and long-term complications of PT have shown good tolerability compared to long-term oral GCs. Daily fluctuations in glycemia against the background of GC PT were studied in 12 patients (11 girls and 1 boy) aged (Me [min-max]) 13.4 years (9.4-17.6), with an SDS body mass index of 0.69 (2.99; -1.21). Mean values of fasting venous blood glucose were 4.6 mmol/l (3.9-5.8), HvA1c 5.3% (4.6-5.9). The average total dose of methylprednisolone during PT was 27 mg/kg (21-35 mg/kg), the drug was administered intravenously with a solution of 0.9% NaCl once a day for 3 days. In the period between injections, other drugs from the GC group were not prescribed. Using a glucometer, glycemiawas monitored after 2, 4, 7, 10, 21, 24, 28, 31, 34, 45, 48, 52, 55, 58, 69, 72 hours after the first administration of the drug, repeated infusions were carried out after 24 and 48 hours respectively. The data obtained indicate that the rise in the level of glucose in capillary blood begins 4 hours after the introduction of GC, reaching maximum values after 7 hours. On the first day of PT, the maximum glucose level was 11.1 mmol/l (15.4-9.6), on the second and third days 9.6 mmol/l (12.1-8.6) and 9.0 mmol/l l (12.1-7.7), respectively. All patients showed normalization of glycemia before repeated administration of HA 21 hours after the previous infusion, however, at the end of the first day, the glucose level, on average, was slightly higher (5.9 mmol/l) than on subsequent days (5.2 and 5 .0 mmol/l). After the end of PT, in all patients, capillary blood glucose values returned to normal after 69 hours from the first administration of methylprednisolone. The maximum indicators of glycemia are recorded on the first day from the onset of PT, normalize independently and do not require medical correction.

Thus, the sources considered in the literature review show the whole variety of risk factors for cardiovascular diseases that threaten to significantly increase the global burden of cardiovascular diseases and mortality. The risk of death from cardiovascular disease is significantly higher in individuals with early glucose intolerance than in those with normal glucose levels, and pathological changes in vascular function begin many years before the diagnosis of overt type 2 diabetes mellitus. Different categories of hyperglycemia are particularly detrimental to vascular function and impaired glucose tolerance, but not impaired fasting glycemia, and may be an independent risk factor for cardiovascular disease throughout development glucose intolerance.

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