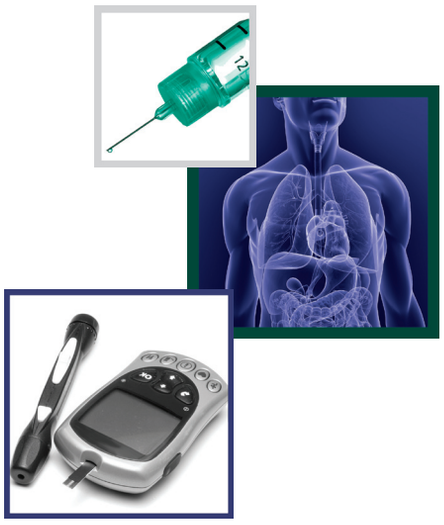
REVIEW



Hypoglycemia, diabetes and atherosclerosis: is there a link?

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Practice Points

- Some risk and predisposing factors to hypoglycemia in patients with Type 1 diabetes/Type 2 diabetes:
  - Insulin- or insulin secretagogue-based therapies, and insulin therapy aimed at near normoglycemia
  - Long duration of insulin therapy/long duration of the disease
  - Recent and past history of hypoglycemia (nonsevere and severe) and hypoglycemia unawareness
  - Older age
  - Impaired renal and liver function
  - Mental illnesses and cognitive dysfunction including dementia
  - Lower HbA1c and aggressive glycemic therapy
  - Exercise, alcohol and high risk for missed meals
- Summary of responses to hypoglycemia
  - Sympathoadrenal activation and counter-regulatory hormone release:
    - Hemodynamic and vascular changes
      - Increase in heart rate, systolic blood pressure, cardiac output and myocardial contractility
      - Decrease in diastolic blood and central pressure
      - Changes in ECG: ST depression and QT enlargement
      - Redistribution of regional blood flow
    - Blood cells
      - Increase in circulating erythrocytes
      - Increase in circulating lymphocytes
      - Increase in circulating platelets and platelet aggregation
    - Coagulation
      - Increase in von Willebrand factor
      - Accelerated thrombin generation
      - Increase in fibrinogen
    - Inflammation/endothelial function
      - Increase in C-reactive protein
      - Increase in endothelin and VEGF
      - Rise in IL-6, IL-1β, IL-8 and TNF-α
      - Rise in ICAM and VCAM

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SUMMARY Cardiovascular disease represents a major cause of morbidity and mortality in subjects with diabetes mellitus. Hypoglycemia associated with glucose-lowering therapy causes recurrent morbidity and represents a significant barrier to successful treatment of the disease. The response to hypoglycemia includes direct and indirect changes mainly related to the activation of the sympathoadrenal axis, which produces significant changes in the cardiovascular system. The latest results derived from several recent large randomized clinical trials have raised the major point that severe hypoglycemia may increase the risk of a poor outcome in patients with Type 2 diabetes. The concept that hypoglycemia could be a potential aggravating factor for atherosclerotic processes is discussed in this article.

Patients with diabetes have a shorter life expectancy when compared with individuals without the disease and this excess mortality is largely attributable to accelerated atherosclerotic processes. Cardiovascular disease (CVD) represents the major cause of morbidity and mortality in subjects with both Type 2 (T2D) and Type 1 diabetes mellitus (T1D) [1–3]. CVD is responsible for approximately 70% of all mortality among patients with diabetes and is also a major contributor to diabetes-related healthcare costs. The majority of data concerning CVD epidemiology, pathophysiology, treatment efficacy and its link to diabetes comes from research performed mostly in T2D. T1D is comparatively less frequent than T2D and usually affects younger populations. Even though many of the CVD risk factors recognized in T2D are not present in T1D subjects, the age-adjusted relative risk for CVD in T1D is even higher than in T2D and may be increased by a factor of 8–10 [1].

Hypoglycemia associated with glucose-lowering therapy represents a significant barrier to successful treatment of all types of diabetes (Table 1). Iatrogenic hypoglycemia causes recurrent morbidity in most people with the disease [4]. Moreover, it is an obstacle to the maintenance of euglycemia over a lifetime and thus precludes euglycemia's long-term benefits [5]. In addition to this, severe hypoglycemia has recently been associated with an increased risk of a range of adverse cardiovascular outcomes [6].

Table 1. Severe hypoglycemia rate in some clinical trials (third-party assistance).

	n	Event rate
Type 2 diabetes		
ACCORD	861	3.1
ADVANCE	150	0.7
VADT	899	12
Type 1 diabetes		
DCCT	711	62

Values expressed as episodes per 100 patient-years (patients taking insulin and allocated in intensive management groups).
ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; DCCT: Diabetes Control and Complications Trial; VADT: Veterans Affairs Diabetes Trial.
Data taken from [6].

It is well known that hypoglycemia acutely provokes changes in hemodynamics, several hemorheological parameters and inflammatory markers [7]. The concept that hypoglycemia could be a potential aggravating factor for atherosclerotic processes is discussed in this article.

Hypoglycemia & diabetes: the magnitude of the problem

The case of T2D

Despite the heterogeneity in definition and criteria for hypoglycemia in different studies, there is no doubt that glucose management, particularly if intensive, is related to an increased risk of nonsevere and severe episodes of hypoglycemia in patients with T2D [8].

The estimation of mild episodes is especially difficult because although more common, they are frequently unreported. In some studies (retrospective and prospective) mild episodes of hypoglycemia occurred at a frequency of 16.3 events/patient/year with a prevalence of symptoms of hypoglycemia in 16% of patients treated with oral antidiabetic agents and 30% of those treated with insulin [9]. Data from UKPDS showed that the rates of severe hypoglycemia (episodes requiring third-party assistance) were 7, 10, 14 and 18 episodes per 1000 patient-years in the conventional, chlorpropamide, glibenclamide and insulin-treated groups, respectively [10]. We can consider that data on severe episodes of hypoglycemia are more reliable and less subjective than data on nonsevere episodes and that severe episodes are much more frequent in the case of insulin management of T2D. From the UK Hypoglycemia study group we know that in these patients with T2D who are insulin treated for less than 2 years, the rate for severe hypoglycemia is ten episodes per

100 patient-years and that this is much higher (70 episodes per 100 patient-years) in those receiving insulin for more than 5 years [11].

We have data on recent randomized clinical trials evaluating the effects of glycemic control on cardiovascular events. For example, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) studies (using various oral agents and/or insulin) the rates of severe hypoglycemia were 5–10% in the standard treatment arms and 16–21% (participants with ≥1 episodes during study) in the intensive treatment arm over the duration of the study [12,13]. Regarding only those subjects receiving insulin in the intensive arms of both studies, the rates expressed as episodes per 100 patient-years were 3.1 and 12 in the ACCORD and VADT trials, respectively.

■ Severe hypoglycemia & the risk of cardiovascular events & death in T2D

The latest results derived from several recent large randomized clinical trials performed in subjects with T2D aimed to evaluate the effect of improving glycemic control in CVD have raised the very important point that severe hypoglycemia may increase the risk of a poor outcome in patients with T2D assigned to an intensive glucose-lowering intervention. In fact, the ACCORD trial was halted due to a significant increase in death and cardiovascular mortality (22 and 35%, respectively) in the intensive treatment arm [14]. Whichever the arm allocated, intensive or conventional, those patients with severe hypoglycemia had a higher mortality risk than those without episodes. However, it should be underlined that in a *post-hoc* analysis, the relative risk of death associated with severe hypoglycemic episodes was higher in the standard arm (2.87) when compared with intensive strategy (1.28), despite a larger number of severe hypoglycemic episodes in the intensive group [14]. Additionally, data analysis from the same study suggested that the excess mortality in the intensive treatment group was not directly explained by the high rate of episodes of hypoglycemia. In the VADT trial, an increased incidence of severe hypoglycemia was also found in the group receiving intensive treatment of hyperglycemia, but at the end of the study there was no significant difference in CVD events between standard and intensive treatment arms [13]. Considering HbA_{1c} goals at the beginning of both studies (more rigorous in VADT) and differences achieved at the end of both trials (-1.16 and -1.01 for VADT and ACCORD, respectively), more intensive glycemic control regimen could be the explanation for differences in rates of severe hypoglycemia (16 and 21% of participants with ≥1 episodes during study; ACCORD and VADT, respectively). In addition to this, participant characteristics at baseline (age, disease duration, HbA_{1c} and history of macrovascular disease) could also be related to the higher rate of episodes of severe hypoglycemia observed in the VADT trial.

Recent data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study indicates that severe hypoglycemia was associated with increased risks of microvascular and macrovascular events and death (from both CVD and non-CVD causes) [15]. However, this association was markedly attenuated after adjustment for different confounding factors.

■ The case of T1D

Intensive insulin therapy significantly reduces the risk of complications in subjects with T1D and represents the standard treatment from the onset of the disease. However, this therapy is associated with a higher risk of nonsevere and severe hypoglycemic episodes [16]. This adverse event is an obstacle to the maintenance of euglycemia over a lifetime. In patients with T1D under strict and intensive glucose management exposed to repeated episodes of hypoglycemia, threshold of normal response to low glucose values are shifted to lower blood glucose levels. The concept of hypoglycemia-associated autonomic failure is related to defective glucose counter-regulation (reduced epinephrine responses to hypoglycemia) and hypoglycemia unawareness (reduced sympathoadrenal and the resulting neurogenic symptom responses to low glucose levels). This syndrome of hypoglycemia unawareness frequently occurs in T1D and the lack of warning symptoms predisposes patients to a vicious cycle of recurrent nonsevere and severe hypoglycemia [17,18]. Thus, it is essential that intensive insulin therapy for T1D is designed not only to maintain near-normoglycemia, but also to prevent and minimize the burden of hypoglycemia. Although such a goal is feasible, a consensus on which is the best rational plan of insulin therapy remains undecided [19].

Unquestionably, the rate of episodes of severe hypoglycemia is much higher in T1D than in T2D. In the Diabetes Control and Complications Trial (DCCT) those patients in the conventional group of treatment had 0.19 episodes per patient-year and those in the intensive group had 0.62 episodes per patient-year [16,20]. This means that patients with T1D had approximately 5- to 20-times more episodes than T2D patients allocated to intensive insulin groups in recent clinical trials (ACCORD and VADT).

■ Severe hypoglycemia & the risk of cardiovascular events & death in T1D

Despite the high number of severe hypoglycemic episodes in patients with T1D, they were not associated with increased adverse cardiovascular outcomes and mortality in clinical trials. It should be pointed out that clinical profile (e.g., age and presence of classical CVD risk factors) and vulnerability to CVD events risk and death is completely different in patients with T1D in comparison with T2D patients in order to be clinically evident during a trial.

Recently, the relationship between hypoglycemia and endothelial function and intima-media thickness in T1D was tested in T1D subjects with and without repeated hypoglycemia [21]. Those subjects without repeated episodes of hypoglycemia were used as an age/sex-matched control group. There were no major differences in the whole set of clinical and laboratory parameters between both groups of T1D patients. Regarding endothelial function, flow-mediated dilatation in response to ischemia was significantly reduced in comparison with a control group of patients without repeated episodes of hypoglycemia. Moreover, intima-media thickness (carotid and femoral) values were significantly higher in subjects suffering from repeated hypoglycemia. The multivariate regression analysis confirmed the association of repeated hypoglycemia and carotid intima-media thickness composite independent of the other considered CVD risk factors: age, gender, disease duration, BMI, systolic blood pressure, HbA_{1c}, glucose variability and cLDL. Although preliminary, these results suggest that repeated hypoglycemia should be considered a new potential risk factor. The exposure to a risk factor throughout a young person's lifespan could promote the accumulation of subclinical atherosclerosis, which may be translated into CVD events, but not until much later in life.

■ Which mechanisms can potentially link hypoglycemia, atherosclerosis & vascular disease?

As previously mentioned, anecdotal reports, and epidemiological, observational and randomized clinical trials have raised the possibility that hypoglycemia is related to a worse prognosis in terms of CVD and mortality. Although it seems that this association is because hypoglycemia is a marker of a high risk for adverse clinical outcomes and there is no current evidence of causality, the total absence of a direct causal link is far from proven.

Possible explanations for the putative relationships between hypoglycemia and CVD are related to the fact that the response to hypoglycemia includes direct and indirect changes, mainly related to the activation of the sympathoadrenal axis (increase in adrenalin and noradrenalin) and counter-regulatory hormonal secretion (glucagon and hypothalamo–pituitary–adrenal axis), which produces significant changes in the cardiovascular system [22]. Normal hemodynamic response to hypoglycemia includes an increase in heart rate, an increase in systolic and a small decrease in diastolic blood pressure, which is due to the sympathetic neural activation.

Recently, Gill *et al.* reported QT prolongation and cardiac/rhythm disturbances in response to nocturnal hypoglycemia in ambulant patients with T1D, which may support the idea of an arrhythmic basis for 'death in bed syndrome' [23]. Moreover, Feldman-Billard *et al.* demonstrated a close temporal relationship between low values of glucose measurements and an increase in blood pressure by performing 24-h monitoring of subcutaneous glucose level using continuous glucose monitoring and simultaneous ambulatory blood pressure measurement in a group of patients with T1D and T2D [24]. The authors hypothesized that the deleterious effect of hypertension in the cardiovascular system could be amplified in patients with related severe and nonsevere hypoglycemic episodes, which are common in T1D and T2D patients receiving intensive insulin therapy.

During acute hypoglycemia there is a rapid proinflammatory, platelet aggregatory, antifibrinolytic and prothrombotic response, as well as disturbances in normal endothelial function [7,25,26]. The vast majority of these abnormalities are interdependent and are caused by the activation of the sympathoadrenal axis. If recurrent, hypoglycemic episodes may provoke changes

in hemostatic factors and viscosity; this might reduce perfusion in diabetic microangiopathy. In addition to this, repeated hypoglycemia throughout life could potentially aggravate atherosclerosis processes and increase the cardiovascular risk.

Recent studies have been specifically designed to address the effects of acute hypoglycemia and confirm its proinflammatory and prothrombotic effects [26,27]. Rodrigues *et al.* have recently published an article demonstrating that higher fibrinogen levels predict progression of coronary artery calcification in adults with T1D [28]. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study has also described elevated inflammatory markers even in young people with T1D and good metabolic control compared with controls, suggesting an explanation for accelerated atherosclerosis in T1D [29]. We also included the measurement of coagulation markers of endothelial damage and inflammation markers in our study that examined the differences in terms of the preclinical atherosclerosis profile of subjects with T1D with or without repeated episodes of hypoglycemia. In some, but not all, of the inflammatory markers included in the study (leucocytes and ICAM-1), we detected significantly higher values at baseline in subjects with repeated episodes of hypoglycemia. Accordingly, von Willebrand factor-related antigen and fibrinogen levels were significantly higher in subjects with a background of repeated hypoglycemia [21].

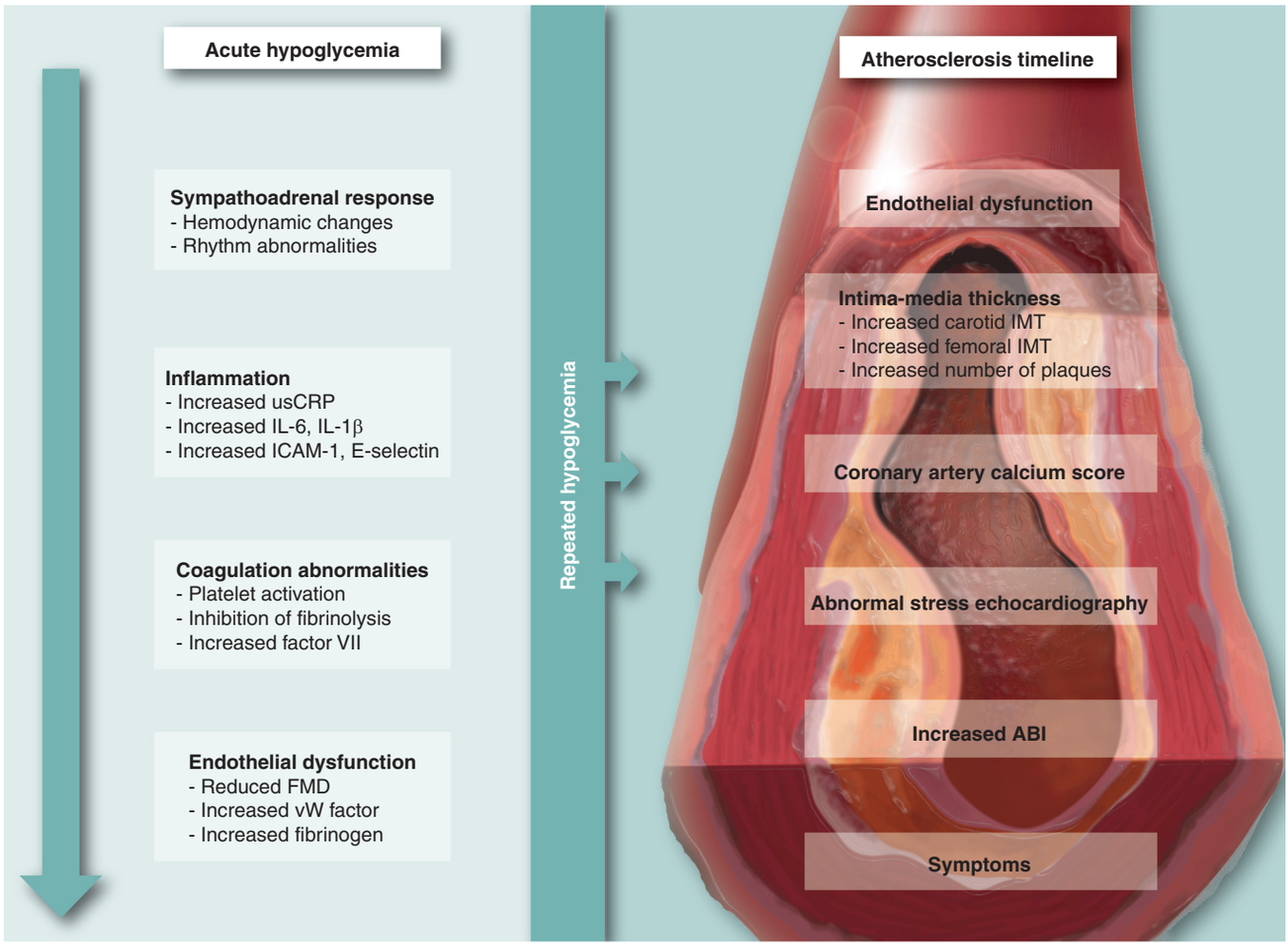

Figure 1. Potential link between hypoglycemia, diabetes and atherosclerosis. On the left side, rapid sympathoadrenal response, proinflammatory, pro-aggregation and coagulation abnormalities related to acute hypoglycemia. If repeated, hypoglycemic episodes may aggravate atherosclerosis processes increasing cardiovascular risk, particularly in vulnerable subjects.
ABI: Ankle brachial index; FMD: Flow-mediated dilatation; IMT: Intima-media thickness; usCRP: Ultra-sensitive C-reactive protein; vW factor: von Willebrand factor.

In the case of T2D, the potential proinflammatory and prothrombotic effects of hypoglycemia could be added to those promoted by chronic hyperglycemia, postprandial glucose excursions and other risk factors of metabolic origin clustered together in the metabolic syndrome (e.g., atherogenic dyslipidemia and elevated blood pressure).

Conclusion & future perspective

Current available information confirms that nonsevere and severe hypoglycemia is a far from uncommon adverse event in T1D and T2D, especially in patients undergoing an intensive management of glucose levels. In addition to recurrent short- and long-term morbidity, iatrogenic hypoglycemia could be considered a major barrier (particularly in T1D) to achieving near euglycemia over a lifetime of using intensive therapy and thus precludes normoglycemia's long-term benefits.

In the short term, the acute hemodynamic changes induced by hypoglycemia may precipitate and aggravate a vascular event during an acute episode. In the long term, especially if repeated, the abnormalities in coagulation, fibrinolysis and inflammation associated with hypoglycemia could be related, theoretically, to the induction and progression of atherosclerosis **(Figure 1)**.

An association between hypoglycemia and adverse clinical events, mainly cardiovascular, has been claimed in some studies. However, although direct causality cannot be completely excluded, at present, current data suggest that hypoglycemia could merely identify patients with a high vulnerable profile.

From the clinical practice perspective it seems essential not only to achieve good glycemic control in patients with diabetes, but also to avoid hypoglycemia. The optimal use of antihyperglycemic therapies, especially in patients fulfilling risk factors predisposing to hypoglycemia, remains a huge challenge for the future. From the clinical research point of view, specific trials that examine the pathophysiologycal mechanisms directly linking hypoglycemia and CVD are required.

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