Association of Hypoglycemia and Cardiac Ischemia

A study based on continuous monitoring

Cyrus Desouza, md[1]
Holger Salazar, md[2]
Benjamin Cheong, md[2]
Joseph Murgo, md[2]
Vivian Fonseca, md[1]

OBJECTIVE — In some studies intensive diabetes treatment in patients with type 2 diabetes may be associated with increased cardiovascular events. It is not clear whether these events are related to hypoglycemic episodes. To determine whether episodes of hypoglycemia were more likely to be associated with cardiac ischemia than normoglycemia or hyperglycemia, we carried out a study in 21 patients with coronary artery disease (CAD) and type 2 diabetes treated with insulin who had good glycemic control.

RESEARCH DESIGN AND METHODS — We carried out 72-h continuous glucose monitoring along with simultaneous cardiac Holter monitoring for ischemia. Patients also recorded symptoms of cardiac ischemia (chest pain) and symptoms of hypoglycemia.

RESULTS — Satisfactory continuous glucose monitoring system recordings were obtained in 19 patients. We recorded 54 episodes of hypoglycemia (blood glucose <70 mg/dl; 26 of these were symptomatic) and 59 episodes of hyperglycemia (blood glucose >200 mg/dl; none symptomatic). Of the 54 episodes of hypoglycemia, 10 were associated with symptoms of chest pain, during 4 of which electrocardiographic abnormalities were documented. In contrast, only 1 episode of chest pain occurred during 59 episodes of hyperglycemia. No chest pain or electrocardiographic abnormalities occurred when the blood glucose was within the normal range. The difference between the frequency of ischemia during hypoglycemia and the frequency during both hyperglycemia and normoglycemia was statistically significant ($P < 0.01$). There were 50 episodes during which the blood glucose changed by >100 mg over a 60-min period, and ischemic symptoms occurred during 9 of these episodes ($P < 0.01$ compared with stable normoglycemia or hyperglycemia).

CONCLUSIONS — Hypoglycemia is more likely to be associated with cardiac ischemia and symptoms than normoglycemia and hyperglycemia, and it is particularly common in patients who experience considerable swings in blood glucose. These data may be important in the institution of insulin treatment and attempting near-normal glycemia in patients with known CAD. Further research is needed to determine strategies to prevent ischemia associated with hypoglycemia.

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Diabetes is associated with an increased risk of development of coronary artery disease (CAD). Patients with CAD and diabetes have higher mortality and morbidity than patients without diabetes. Data from studies such as the U.K. Prospective Diabetes Study suggest that very good glycemic control is associated with fewer cardiovascular events (1). However, tight glycemic control may increase the risk of hypoglycemia. Increased cardiovascular events were noted in the Veterans Affairs Cooperative Study on Glycemic Control and Complications (VA CSDM), after the institution of tight glycemic control (2). It is possible that acute hypoglycemia may trigger ischemia and cardiovascular events. Hypoglycemia and rapid changes in blood glucose have been shown to increase counterregulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and thereby ischemia (3,4). Furthermore, in the presence of hypokalemia and raised serum catecholamines, often present during hypoglycemia, cardiac repolarization could be prolonged enough to induce cardiac arrythmias (5). Animal studies have documented the effect of hypoglycemia on myocardial ischemic injury (6). Although the literature is replete with anecdotal cases of hypoglycemia-triggered cardiac events, it has previously been difficult to document an association between hypoglycemia and cardiac ischemia in humans (7,8).

Several studies have documented electrocardiogram (ECG) changes, especially an increased QT interval and a proarrhythmic state in acutely induced hypoglycemia in both type 1 and type 2 diabetes (9). However, these were not in ambulatory patients with known CAD and were not specific for cardiac ischemia (10,11)

With the availability of a continuous glucose sensor, combined with continuous ECG monitoring, new technologies make it possible to examine relationships between hypoglycemia and cardiac ischemia (12,13). We therefore conducted this study to determine the feasibility of simultaneous monitoring of ECG and blood glucose and to determine whether an association exists between changes in the two parameters

From the [1]Department of Medicine, Section of Endocrinology, Tulane University Health Sciences Center, New Orleans, Louisiana; and the [2]Department of Medicine, Section of Cardiology, Tulane University Health Sciences Center, New Orleans, Louisiana.

Address correspondence and reprint requests to Vivian Fonseca, Professor of Medicine, Department of Medicine, Section of Endocrinology, 1430 Tulane Ave., SL 53, New Orleans, LA 70112-2699. E-mail: vfonseca@tulane.edu.

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Abbreviations: CAD, coronary artery disease; CGMS, continuous glucose monitoring system; ECG, electrocardiogram.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient characteristics and CGMS features*

Parameter	Value
Mean duration of known diabetes (years)	12.9 ± 5.6
Mean age at diagnosis of diabetes (years)	50.4 ± 7.1
Number of patients taking β-blockers	15
Number of patients with known neuropathy	10
Mean episodes of hypoglycemia per patient (mg/dl)	3.2 ± 1.6
Mean episodes of rapid glucose changes per patient (mg/dl)	3.8 ± 2.1
Mean duration of hypoglycemia per patient (h)	3.01 ± 0.5
Mean duration of hyperglycemia per patient (h)	6.44 ± 0.92
Mean duration of normoglycemia per patient (h)	61.72 ± 5.6
Mean depth of hypoglycemia per patient (mg/dl)	50.1 ± 7.6

Data are means ± SD.

RESEARCH DESIGN AND METHODS

Patient characteristics

A total of 21 patients were enrolled, and 19 completed the study. Two patients were not able to successfully use the continuous glucose monitoring system (CGMS). The study included patients with type 2 diabetes with a history of frequent hypoglycemia and an HbA_{1c} of <8%. Patients had CAD defined as a history of myocardial infarction, coronary bypass surgery, or angioplasty. The group consisted of 12 men and 7 women, with a mean age of 58 ± 16 years. The HbA_{1c} (means ± SE) was 7.1 ± 0.8%. Total cholesterol, LDL, HDL, and triglyceride levels were 160 ± 31, 95 ± 28, 36 ± 13, and 186 ± 95 mg/dl, respectively. Eight patients had coronary artery bypass grafts alone; six patients had percutaneous, transfemoral coronary angiography alone; and five patients had both procedures. The mean duration of known diabetes 12.9 ± 5.6 years, and the average age at diagnosis was 50.4 + 7.1 years. All patients were being treated with insulin, and six patients were treated with metformin in addition to insulin. Patients were taking either bedtime NPH (n = 5) or twice-daily NPH (n = 14) insulin. None of the patients adjusted their insulin doses based on glucose readings. A total of 15 patients were on β-blockers (Table 1).

Methods

An ECG (supine position) and cutaneous blood glucose were obtained at baseline. Patients were excluded if the baseline ECG had one of the following: voltage criteria for LVH with >0.1 mv of ST-segment depression, an abnormal baseline ST-segment depression of >0.1 mv, Wolff-Parkinson-White syndrome, and digoxin use with baseline abnormal repolarization in the ST-segment. A GE/Marquette Holter system was used to monitor for cardiac ischemia, and a CGMS (Minimed, CA) was placed on the patient simultaneously. Patients were instructed and trained on the use of the CGMS and Holter monitor for ~1 h. Patients were instructed to monitor their capillary blood glucoses at least four times a day and if they were aware of hypoglycemia. Continuous glucose and cardiac ischemia monitoring was performed over a period of 72 h. Patients were also asked to record symptoms of typical chest pain and hypoglycemia separately over the 72-h period. Patients were encouraged to maintain their usual daily activities at home during this monitoring period. Patients were also asked to record their meal and exercise timings.

At the end of the testing period of 72 h, the Holter monitor and CGMS were removed. Holter tracings and ECGs were read by a cardiologist, and glucose monitoring results were read by an endocrinologist, both blinded to each others results. The entire 72 h of the CGMS recording was used. Significant ischemic changes were defined as a transient horizontal or down-sloping ST-depression ≥0.1 mv, measured 80 ms after the J point, lasting for at least 1 min. ST-segment elevations were evaluated similarly, except in leads with pathological Q waves (14). Blood glucose values of <70 mg/dl were considered to be hypoglycemia, and >200 mg/dl was considered to be hyperglycemia. Insulin secretion decreases as plasma glucose levels fall within the physiological range, and counterregulatory hormone secretion increases as plasma glucose levels fall just below the physiological range at substantially higher glucose levels than those required to produce symptoms and impair cognitive function (15–18). Thus, it is appropriate to define "hypoglycemia" as a blood glucose level <70 mg/dl in a study such as this one. Changes in blood glucose >100 mg/dl within a 60-min period were also noted.

Statistical analysis

Hypoglycemic and hyperglycemic episodes were compared with episodes of cardiac ischemia or ECG abnormalities. Hypoglycemic and hyperglycemic episodes occurring within the preceding 30 min of an ischemic event were noted. Symptoms of typical chest pain were similarly compared with both blood glucose levels and ECG abnormalities. Rapid changes in blood glucose were also compared with ECG changes. Statistical analysis was performed using the Yates-corrected χ^2 test.

RESULTS — A total of 54 episodes of hypoglycemia (CGMS glucose <70 mg/dl) were recorded. Patients reported

Table 2—*CGMS and Holter monitoring abnormalities*

	Total episodes	Episodes with chest pain/angina	Episodes with ECG abnormalities
Hypoglycemia	54	10*	6*
Symptomatic	26	10*	4*
Asymptomatic	28	—	2
Normoglycemia without rapid changes	N/A	0	0
Hyperglycemia	59	1	0
Rapid changes in glucose (>100 mg · dl^{-1} · h^{-1})	50	9*	2

*$P < 0.01$ vs. episodes during hyperglycemia and normoglycemia.

symptoms of hypoglycemia in 26 of the 54 episodes. Patients also reported chest pain in 10 of 54 hypoglycemic episodes. Of these 10 chest pain episodes, 4 were associated with significant ECG abnormalities (Table 2). Hyperglycemia (CGMS glucose >200 mg/dl) occurred a total of 59 times. Of these 59 episodes, only one patient reported chest pain, and there were no ECG abnormalities.

There were 50 episodes during which the CGMS glucose changed rapidly, i.e., by >100 mg/dl over a 60-min period. All of these episodes were associated with a rapid fall in glucose concentrations, rather than a rapid rise. Of these 50 episodes, patients reported chest pain in 9 episodes, 2 of which were associated with ECG abnormalities. There were no episodes of chest pain or ECG changes during normoglycemia. There were 28 episodes of recorded asymptomatic hypoglycemia, of which 2 episodes showed ECG abnormalities (Table 2).

The difference between the frequency of ischemia during hypoglycemia and the frequency during both hyperglycemia and normoglycemia was statistically significant ($P < 0.01$). The difference between the frequency of ischemic episodes with rapid glucose changes (>100 $mg \cdot dl^{-1} \cdot h^{-1}$) and with both hyperglycemia and normoglycemia was also statistically significant ($P < 0.01$).

The mean number of episodes of hypoglycemia was 3.2 + 1.6, and the mean number of episodes of rapid changes was 3.8 + 2.1. The average time spent in hypoglycemia was 3.01 + 0.5 h, the time in hyperglycemia was 6.44 + 0.92 h, and the time in normoglycemia was 61.72 + 5.6 h (Table 1). Only two episodes of hypoglycemia were related to exercise, and neither were associated with chest pain or ischemia on the Holter monitor.

CONCLUSIONS — Out-of-hospital ambulatory Holter monitoring of ST-segment abnormalities in patients with CAD has shown that most ischemic events occur during activities of daily living (12). Patients with CAD and diabetes have more episodes of silent ischemia than patients without diabetes (19). Although angina is usually recognized as the cardinal symptom of underlying CAD, silent ischemia is actually the most common manifestation of myocardial ischemia (20,21). The presence of silent ischemia is predictive of future cardiac events and cardiovascular mortality (22). Several studies have shown that hypoglycemia predisposes to cardiac arrhythmias, although these findings were not specific for ischemia (10,11). These studies were not performed in patients with known CAD. Koh et al. (23) have shown that in patients with CAD who did not have diabetes, typical ECG changes of ischemia were present during hypoglycemia. Animal and some human studies have showed that hypoglycemia may increase the size of the infarct in myocardial infarction (6–8). Elderly patients are especially vulnerable to the cardiac effects of hypoglycemia.

There is scant evidence to either support or negate the relationship between cardiac ischemia and hypoglycemia. This may be due to the past lack of availability of adequate technology. Our results show that some patients with diabetes have definite ECG abnormalities during hypoglycemia suggestive of cardiac ischemia. Some of these patients had typical chest pain, whereas some were asymptomatic. It is estimated that ~30% of patients with CAD will have silent ischemia by Holter monitoring (24). However, Holter monitoring is not particularly sensitive for cardiac ischemia and may therefore underestimate the prevalence of cardiac ischemia during hypoglycemia (25,26).

Rapid drops in glucose levels, even when within the normal range, were associated with increased episodes of chest pain and ECG abnormalities. Catecholamine release and increased myocardial work and oxygen consumption has been shown to occur with hypoglycemia and rapid falls in blood glucose (6,27). However, the degree of catecholamine response is related to the nadir plasma glucose concentration. Therefore, the relevance of the association of chest pain with rapid decrements in subcutaneous glucose is unclear (28).

Many of the episodes of hypoglycemia were asymptomatic, suggesting hypoglycemia unawareness in these patients. Several studies have documented impaired counterregulatory hormone release associated with hypoglycemia unawareness (17). In a study in patients with type 1 diabetes without CAD, Young et al. (29) demonstrated that myocardial adaptation to hypoglycemia is impaired during hypoglycemia. Their hypothesis was that the lack of adequate catecholamine release leads to a decrease in the normal augmentation of myocardial function during hypoglycemia. However, several studies have shown that the catecholamine response in type 2 diabetes is adequate (30,31). Other possible mechanisms include abnormal intracellular metabolism or abnormal endothelial responses to stress in patients such as ours who have type 2 diabetes and established coronary disease. Many of our patients were on β-blockers, which may mask the catecholamine-induced symptoms. Because many patients with type 2 diabetes and coexistent CAD may be on β-blockers and may not recognize hypoglycemia, studies in such a patient population are important. β-Blockers may also decrease the number of ischemic events than would normally be present during hypoglycemic episodes. The time spent in hypoglycemia was far shorter than that spent in hyperglycemia or normoglycemia. Despite this, the number of ischemic events occurred almost exclusively during this short time period.

In six of the episodes with chest pain and glucose concentrations <70 mg/dl, there were no ECG changes, a finding compatible with other studies in patients with known CAD. In a study of 63 patients with documented CAD, only 33% of the reported anginal chest pain was associated with ischemic ST depression (32). Myocardial ischemia can occur without ST-segment shift, as documented by evidence of left ventricular abnormalities. In 119 patients who underwent exercise echocardiography, 74% of them developed angina during exercise, but only 53% developed ST-segment depression (33).

Further studies are needed to understand the mechanisms involved so that strategies can be developed to minimize such events, thus rendering intensive insulin therapy safer in such patients.

The CGMS has limitations, particularly because it measures interstitial fluid rather than blood glucose. Nevertheless, studies suggest that the CGMS is able to accurately track acute changes in plasma glucose when calibrated across a range of plasma glucose and insulin levels (34). However, this accuracy diminishes toward the 40-mg/dl glucose level and may give false readings below this level (35).

We conclude that hypoglycemia is more likely to be associated with cardiac ischemia than are hyperglycemia and nor-

moglycemia. These data may be important in the institution of insulin treatment and attempting near-normal glucose levels in patients with known CAD. However, this association does not prove a causal relationship between hypoglycemia and myocardial ischemia in patients with type 2 diabetes and CAD. Further research involving larger numbers of subjects is needed to determine strategies to prevent ischemia associated with hypoglycemia.

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