Physical Activity at Altitude: Challenges for People With Diabetes

A Review

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REVIEW ARTICLE

BACKGROUND

A growing number of subjects with diabetes take part in physical activities at altitude such as skiing, climbing, and trekking. Exercise under conditions of hypobaric hypoxia poses some unique challenges on subjects with diabetes, and the presence of diabetes can complicate safe and successful participation in mountain activities. Among others, altitude can alter glucoregulation. Furthermore, cold temperatures and altitude can complicate accurate reading of glucose monitoring equipment and storage of insulin. These factors potentially lead to dangerous hyperglycemia or hypoglycemia. Over the last years, more information has become available on this subject.

PURPOSE

To provide an up-to-date overview of the pathophysiological changes during physical activity at altitude and the potential problems related to diabetes, including the use of (continuous) blood glucose monitors and insulin pumps. To propose practical recommendations for preparations and travel to altitude for subjects with diabetes.

DATA SOURCES AND SYNTHESIS

We researched PubMed, medical textbooks, and related Internet sites, and extracted human studies and data based on relevance for diabetes, exercise, and altitude.

LIMITATIONS

Given the paucity of controlled trials regarding diabetes and altitude, we composed a narrative review and filled in areas lacking diabetes-specific studies with data obtained from nondiabetic subjects.

CONCLUSIONS

Subjects with diabetes can take part in activities at high, and even extreme, altitude. However, careful assessment of diabetes-related complications, optimal preparation, and adequate knowledge of glycemic regulation at altitude and altitude-related complications is needed.

An increasing number of subjects with diabetes reside at high altitude for short periods of time, partly for work, but mainly for recreational purposes such as skiing, trekking, and climbing. Exercise under conditions of hypobaric hypoxia poses some unique challenges for subjects with diabetes and could potentially lead to dangerous situations such as unexpected hypoglycemia and hyperglycemia, inaccurate

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reading of blood glucose monitors (BGMs), and the freezing of insulin. New study results have become available in recent years. Here, we review and update the information regarding subjects with either type 1 or type 2 diabetes who intend to take part in activities such as high-altitude trekking (i.e., walking and hiking for several hours a day above 1,500 m altitude). The goal of the present review is to describe the physiological changes occurring at altitude and to identify potential problems when unacclimatized subjects with either type 1 or type 2 diabetes travel to or spend time at altitude for physical activities. Furthermore, we compose practical recommendations in preparation for being at altitude and when at altitude with diabetes (Table 1).

ALTITUDE

The following definitions are used to define different altitudes (1) (Fig. 1):

- High altitude: 1,500–3,500 m (5,000–11,500 feet),
- Very high altitude: 3,500–5,500 m (11,500–18,000 feet),
- Extreme altitude: above 5,500 m (18,000 feet).

With increasing altitude, the partial pressure of inspired oxygen (PiO_2) decreases because of a progressive decline in barometric pressure (hypobaric condition). Barometric pressure at sea level is ~760 mmHg (containing 20.9% oxygen) corresponding to a PiO_2 of 160 mmHg (2). At 8,848 m, the altitude at the summit of Mount Everest, the barometric pressure is ~253 mmHg and the PiO_2 is ~42 mmHg, which results in almost immediate unconsciousness in unacclimatized subjects (3).

PHYSIOLOGICAL CHANGES OCCURRING AT ALTITUDE AND SPECIFIC ISSUES IN SUBJECTS WITH DIABETES

Ventilatory Effects

When going to altitude, respiratory rate increases due to hypoxia, which will also result in a decrease in P_{ACO_2}. Temporarily, this hypocapnia lowers the ventilatory drive, but this effect disappears with acclimatization. The decline in P_{ACO_2} results in respiratory alkalosis, followed by renal compensatory loss of bicarbonate during the first days to weeks at altitude, partly restoring blood pH to sea-level values (4). Alkalemia increases the affinity of hemoglobin for oxygen, which is beneficial regarding the lower ambient oxygen pressure at altitude.

Diabetes, in particular type 2 diabetes, seems to be associated with a modest decrease in lung transfer capacity for carbon monoxide, lower ventilatory responses to hypoxia, and a mild restrictive lung function impairment, but the clinical implications are unclear (5,6). One might suspect that these subtle impairments result in lower arterial oxygen content and limitations in exercise capacity at altitude, but this is unknown. We found similar arterial O_2 saturation, as determined by pulse oximetry, in 12 nonsmoking subjects with uncomplicated type 2 diabetes compared with nondiabetic control subjects at 876, 3,200, and 4,167 m (97.4 ± 1.8% vs. 97.6 ± 0.8%; 92.9 ± 2.4% vs. 94.0 ± 2.7%; 91.5 ± 2.4% vs. 90.3 ± 3.2% hemoglobin oxygen saturation, respectively; unpublished data).

Altogether, we think that the condition of subjects with complication-free diabetes who have good glycemic control does not differ from that of nondiabetic subjects at high altitude with respect to ventilation and ventilatory adaptations. Whether clinically relevant respiratory impairments become apparent at very high or extreme altitude remains to be investigated.

Renal Effects

Luks et al. (7) advise subjects with chronic kidney disease to continue with sea-level medication therapy as usual at high altitude and to adjust diuretic therapy according to weight changes to anticipate fluid retention or dehydration. Given the fact that proteinuria may increase at altitude, it seems advisable also to continue therapy with ACE inhibitors or angiotensin receptor blockers in subjects with diabetes (7). Acetazolamide therapy for the prophylaxis of acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) (see below) can be used in patients with chronic kidney disease, provided that the patient does not have pre-existing metabolic acidosis and has an estimated glomerular filtration rate of >50 mL/min. Further advice regarding the use of medication at altitude has been reviewed in detail elsewhere (7–9).

Subjects with type 2 diabetes living at an altitude of 1,727 m have higher 24-h urinary protein excretion and serum creatinine levels, and decreased estimated glomerular filtration rate compared with matched subjects at sea level (10). Whether diabetic nephropathy complicates altitude acclimatization is unknown. Neither is it known whether diabetic nephropathy worsens during travel to, or prolonged stay at, altitude. In the context of the information provided above, this could theoretically be expected.

Cardiovascular Effects and Exercise Capacity

Acute altitude exposure increases heart rate (and thereby cardiac output), as a

Table 1—Attention points for physically active subjects with diabetes at altitude

Predeparture
Inform and instruct fellow travelers and expedition leaders of your diabetes and its treatment, including emergency medical treatment (e.g., glucagon injection)
Obtain information about local medical aid and (diabetic) resources
Consult your physician when planning high-altitude travel (including an ophthalmologist in case of travel at very high and extreme altitudes)
Make yourself familiar with diabetes management in the environment (cold, terrain) and with the intensity of exercise anticipated at altitude
Obtain adequate clothing for all conditions and test it before departure
Take spare supplies including short-acting insulin (Fig. 3).
At altitude
Stay in close contact with fellow hikers/travelers
Anticipate frequent blood glucose monitoring and correct glucose accordingly
Insulin requirements and oral antihyperglycemic dosages may be decreased because of exercise and appetite loss
Insulin doses may be increased, especially in case of high-altitude illnesses, rapid ascents, and higher (extreme) altitudes
Prevent BGMs, pumps, catheters, and insulin from freezing
Take adequate fluids and nutrition high in carbohydrates in case of prolonged exercise at altitude

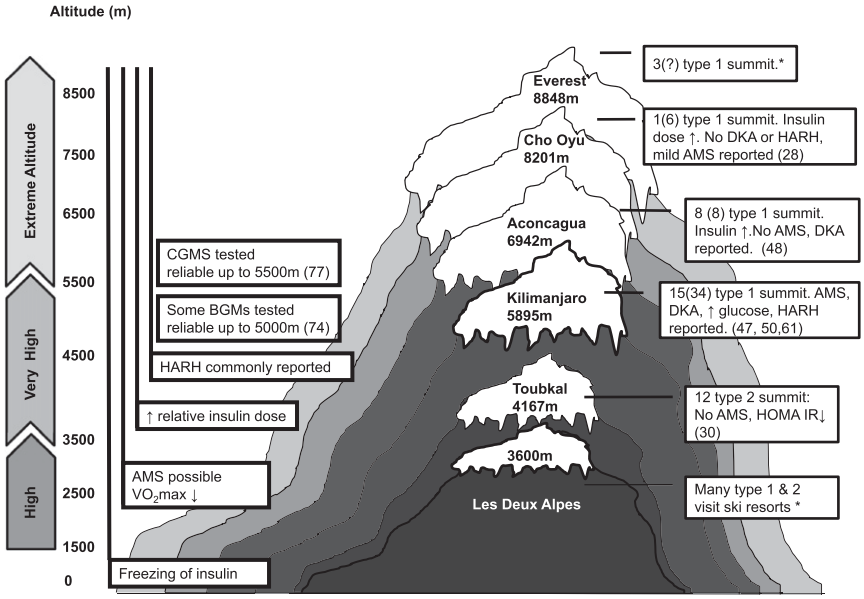

Figure 1—Summary of findings in studies involving subjects at high altitudes. *Left*: Arrows indicating different altitude zones and technical and physiological findings with implications for the subject with diabetes. *Right*: Outcomes and summit success rates (number of climbers successfully summiting [total climbers]) of reported diabetes studies in the medical literature. DKA, diabetic ketoacidosis. *Not studied.

consequence of cardiac β-adrenergic receptor stimulation by the sympathetic nervous system and by epinephrine release in response to hypoxia (11). During the process of acclimatization, the initial increase in heart rate decreases, probably because of decreased cardiac responsiveness to β-adrenergic stimulation (12) and increased vagal tone (13,14). As stroke volume is decreased after prolonged altitude exposure because of a decrease in plasma volume, heart rate remains increased to maintain cardiac output at altitude (15,16). Even after acclimatization, maximum heart rate, maximum cardiac output, and maximum exercise capacity remain suppressed (17,18).

$V_{O_{2max}}$ is reduced by 1% with every 100 m in elevation above 2,500 m (19). At altitude, $V_{O_{2max}}$ is lower and is reached at lower workloads; exercise feels more strenuous (20). However, the corresponding energy expenditure for a given workload is equal (21).

Mean arterial blood pressure at altitude often increases over the first days to weeks because of increased sympathetic tone (22). Acclimatization results in a reduction in plasma volume, cardiac output, and epinephrine levels, resulting in normalization of, or even a decrease in, blood pressure (23). Pulmonary vasoconstriction in response to hypobaric hypoxia leads to an elevated pulmonary artery pressure. Pulmonary hypertension is common during exposure to altitude and is most pronounced during exercise (23).

In patients with diabetes, ischemic heart disease and diabetic cardiac autonomic neuropathy may limit adaptive responses to altitude (24). One retrospective study (25) reported that in the Austrian Alps male hikers with diabetes had a 7.4 times higher risk for sudden cardiac death compared with nondiabetic subjects. Data suggest that subjects with coronary artery disease without diabetes can go to altitudes up to, and possibly over, 3,500 m, provided that their condition is stable, and they have preserved left ventricular function and normal exercise capacity (26,27). It is advised that therapy with medication for coronary artery disease (including β-blockers) be continued as prescribed at sea level and that blood pressure be monitored regularly (9). If cardiac autonomic neuropathy includes symptoms such as resting tachycardia and exercise intolerance (24), we discourage these subjects to go to very high or extreme altitudes where maximal heart rate and exercise capacity are further reduced (19).

There have been no specific studies regarding the effect of altitude exposure on exercise capacity in patients with diabetes. Relying on derivative measures, Pavan et al. (28) found no difference in heart rate and blood pressure responses to altitudes of 0, 3,700, and 5,800 m between subjects with complication-free, well-controlled type 1 diabetes and nondiabetic subjects. In agreement, we found no differences in blood pressure and echocardiographic parameters at sea level and at an altitude of 4,000 m between similar groups with and without type 1 diabetes (29).

Data on cardiovascular responses at altitude in subjects with type 2 diabetes are scarce and partly contradictory. We found no differences in systolic (3.7 ± 11.3 mmHg) and diastolic (1.5 ± 7.0 mmHg) blood pressure at an altitude of 3,200 m versus that at sea level in 13 trained subjects with uncomplicated type 2 diabetes who successfully hiked to 4,167 m (30). Others have reported (31) a slight decrease in blood pressure in 22 subjects with metabolic syndrome sojourning to an altitude of 1,700 m. At high altitude, regular monitoring of blood pressure is strongly recommended for subjects with hypertension. Antihypertensive medication should be continued at altitude, and adjustments to therapy should be made only in those individuals who have persistent and marked elevations or drops in blood pressure (9).

The American Diabetes Association and the American College of Sports

Medicine advise previously sedentary subjects with type 2 diabetes to undergo exercise stress testing when the intended exercise intensity exceeds that of brisk walking (32), which is obviously the case during hiking at altitude. Together, the available data suggest that subjects with well-controlled diabetes, both type 1 and type 2 diabetes, can successfully take part in trekking at high altitude (and possibly even very high to extreme altitude), provided that they are physically fit and free from microvascular and macrovascular complications.

Cerebrovascular Effects

The effect of altitude on the coagulation system is subject to debate (33,34). Although plausible, there is no direct evidence that antiplatelet aggregation and/or anticoagulant therapy are risk factors for high-altitude retinal hemorrhage (HARH) or hemorrhagic stroke. At sea level, the incidence of cardiovascular disease, including stroke, in patients with diabetes (especially type 2 diabetes) is increased compared with subjects without diabetes (35). At altitude, the incidence of stroke seems to be increased. This increase is associated with prolonged stay at very high and extreme altitudes. Polycythemia, in the context of increased erythrocyte mass due to stimulated erythropoietin production, is an important risk factor for stroke (36,37). Theoretically, the increased risk of dehydration and vascular disorders in patients with diabetes superimposed on the effects of altitude (hypoxia, increased viscosity, and hypocapnia causing cerebral vasoconstriction) may render patients with type 2 diabetes particularly at risk for stroke at very high and extreme altitudes. Still, this needs to be confirmed by future studies.

Sympathoadrenergic Effects

Altitude exposure elicits an increase in sympathoadrenergic activity, which is highly relevant for glucose regulation in subjects with diabetes (see below) (38). At rest, acute exposure to altitude causes a rise in epinephrine with higher concentrations of epinephrine at higher altitudes. This initial increase in epinephrine levels is partially restored to nearly sea-level concentrations after 1–2 weeks and rises again with a further rise in elevation (39). Norepinephrine concentrations are elevated at altitude, reflecting a persistent increase in sympathetic nervous system activity, even during and after prolonged altitude exposure (40).

Under conditions of acute hypoxia, the epinephrine response to exercise is more profound than under normoxic (sea-level) conditions. Again, this epinephrine response returns to sea-level concentrations after acclimatization, while norepinephrine concentrations remain increased during exercise at altitude (38). However, if the workload is adjusted to the corresponding relative workload at altitude (i.e., a similar percentage of $V\dot{O}_{2max}$), norepinephrine concentrations at altitude are similar to sea-level values (11).

Glucoregulatory Effects

Glucose regulation is clearly affected by altitude exposure in subjects with and without diabetes (41). A number of studies have been conducted to unravel the complex mechanisms in glucoregulation under conditions of acute and prolonged hypoxia at rest and during exercise, and are discussed below.

Acute Hypoxia

In a case of acute hypoxia, a state of relative hyperglycemia, as reflected by plasma glucose and insulin concentrations (at 3,500 and 5,080 m) (39), and a decrease in insulin-stimulated glucose uptake is induced as demonstrated by findings from hyperinsulinemic euglycemic clamping (at 4,559 m) (41).

Labeled glucose tracer studies (42,43) show an increase in glucose rate of appearance and disappearance, and leg glucose uptake at 4,300 m upon acute altitude exposure. Both β-blockage and submaximal exercise augment these effects. The increased turnover of glucose under β-blockade suggests that epinephrine is not solely responsible for the increments in glucose appearance, but that epinephrine may be involved in the initially decreased insulin-stimulated glucose uptake in skeletal muscle and increased muscle glycogenolysis (Fig. 2) (42). Central sympathetic inhibition by clonidine attenuates the initial insulin resistance (IR) induced by acute altitude exposure, as shown in a clamp study (44). This suggests an important role for the sympathetic nervous system in patients with hypoxia-induced IR.

Acclimatization

After prolonged altitude exposure (i.e., acclimatization), fasting glucose concentrations seem to decrease, while the concentration of insulin is unchanged and the glucose rate of appearance remains increased (43) This suggests a transition from an initial decrease to a subsequent increase in glucose disposal during a prolonged (weeks) stay at altitude. Glucose concentrations increase again when one ascends to higher elevations. Hereafter, normalization of glucose concentrations occurs again, and these changes in glucose concentrations are paralleled by similar changes in epinephrine concentrations (42). Cortisol concentrations seem to follow this same pattern, while growth hormone concentrations seem to be increased only after a prolonged stay at very high or extreme altitudes (39,45).

Exercise

Acute altitude exposure exaggerates the increases in epinephrine levels, glucose rate of appearance, and glucose disappearance in response to submaximal exercise. The plasma glucose concentrations in response to exercise are similar at sea level and during acute altitude exposure (42,43).

With acclimatization, the appearance and disappearance rates of glucose increase further. Glucose concentrations at rest and during exercise drop compared with sea-level concentrations (43), suggesting increased glucose disappearance or decreased glucose production. Increased glucose disappearance may be explained by the fact that both exercise and hypoxia facilitate insulin-independent glucose uptake into skeletal muscle (46). Possibly, this contributes to the creation of a new equilibrium with lower fasting glucose concentrations seen after acclimatization compared with those at sea level.

In summary, in nondiabetic subjects, altitude exposure seems to induce a state of temporary IR paralleled by sympathoadrenergic activation. With acclimatization, IR seems to wane and a state of increased dependency on glucose (increased glucose production and disposal) appears, resulting in lower fasting blood glucose concentrations (Fig. 2).

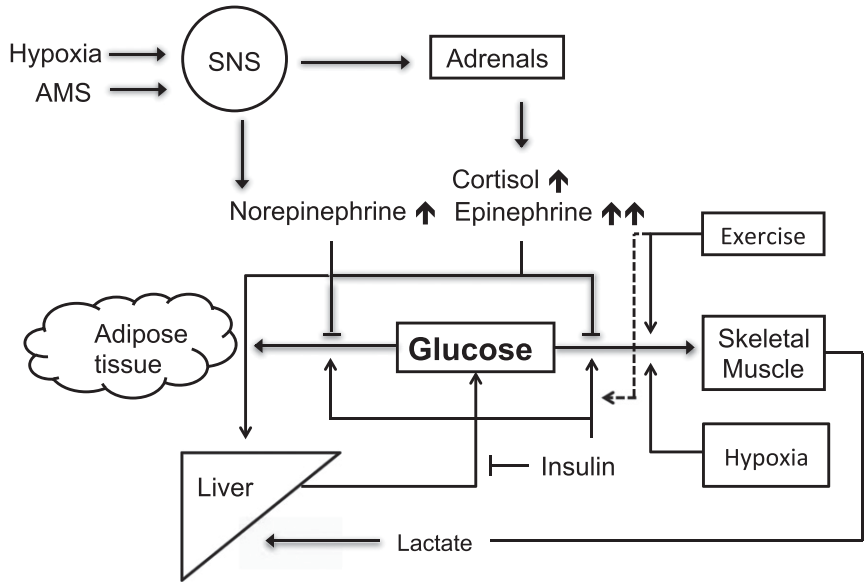

Figure 2—Concept of glucoregulation at altitude. Acute hypoxia stimulates (as indicated by arrows) the production of epinephrine, norepinephrine, and cortisol. This inhibits (indicated by T-shaped lines) insulin-stimulated skeletal muscle glucose uptake, stimulates muscle (and liver) glycogenolysis, and increases lactate production, resulting in increased glucose production by the liver. Exercise and hypoxia may partly compensate this relative hyperglycemia by stimulating insulin-independent skeletal muscle glucose uptake and insulin-dependent glucose uptake (the insulin-sensitizing effect of exercise is indicated by the dashed line). After acclimatization, the counter-regulatory actions of epinephrine (and cortisol) decrease, while glucose uptake is still enhanced by hypoxia and exercise. Possibly, this overcomes the remaining increment in norepinephrine levels that may play a partial role in (hepatic) glucose production and inhibition of insulin action. The presence of AMS causes increased activity of the sympathetic nervous system (SNS), contributing to glucose counter-regulation (see text for details).

Glucoregulatory Effects in Subjects With Diabetes

Type 1 Diabetes. Relative to those at sea level, most previous studies (47–49) in subjects with type 1 diabetes have reported reductions in insulin doses at lower altitudes and in increments in doses at higher altitudes (>3,700–5,000 m) (Fig. 1). Very high or extreme altitude seems to be associated with increased insulin requirements and worsening of HbA_{1c} levels, despite exercise (28). In most studies, carbohydrate intake was not monitored. A case report (49) observed hyperglycemia despite increased exercise with unchanged food intake and insulin dosing at 4,000 m. One study (50) that reported a 49% reduction in insulin requirements during the ascent of Mount Kilimanjaro also noted that ketonuria developed in 4 of 15 subjects with diabetes, of whom 2 had ketoacidosis. This suggests a relative underdosage of insulin; the insulin dosage was reduced, but the requirements may have been equal to or even increased relative to those at sea level.

Hypoxia and AMS stimulate sympathoadrenergic activity (51), which may partly explain the loss of glycemic control. We have reported (47) a positive correlation between increased insulin requirements and AMS symptom scores. More studies are needed to document the changes in sympathetic nervous system activity and glucose counter-regulatory hormones in response to altitude exposure in subjects with diabetes.

Cold may also play a role in increased insulin requirements, because it may decrease the potency and absorption of insulin from subcutaneous injection sites. As relative exercise intensity, and thereby catecholamine responses, increase with (acute) altitude exposure, glucose concentrations may be higher at higher altitudes.

A number of changes associated with altitude may increase the risk of hypoglycemia; the facilitated glucose uptake in skeletal muscle as a result of hypoxia and exercise; increased glucose disposal with acclimatization; appetite suppression, which is common at altitude; and difficulties in distinguishing symptoms of hypoglycemia from AMS (50). Most subjects with diabetes who exercise preferentially adjust insulin requirements to avoid hypoglycemia, thus instead seeing hyperglycemia as a result.

In summary, in subjects with type 1 diabetes it appears that because of the lower exercise intensity relative to hypoxia, the lower concentrations of glucose counter-regulatory hormones, and the low incidence of AMS, blood glucose concentrations decrease at lower altitudes in response to exercise. However, it is unknown whether the glucose-lowering effect at lower altitudes is greater than the glucose-lowering effect of exercise at sea level. The opposite occurs at very high to extreme altitudes, resulting in hyperglycemia despite exercise and possible anorexia. These mechanisms explain the observed differences in insulin need at different altitudes (44).

Type 2 Diabetes. A number of studies have investigated glucose and insulin sensitivity in response to exercise under hypoxic conditions in subjects with type 2 diabetes. Mackenzie et al. (52) showed that 1 h of exercise while breathing 14.8% O_2 (corresponding to an altitude of ±2,800 m) increased glucose disposal, and decreased blood glucose levels and HOMA-IR to a greater extent than normoxic exercise in subjects with uncomplicated type 2 diabetes. After acclimatization, we found lower fasting insulin concentrations, while fasting glucose concentrations and food intake did not differ from sea-level values in 12 subjects with uncomplicated type 2 diabetes hiking up to an altitude of 4,167

m. Also, we did not observe changes in the number of (mild) hypoglycemic episodes, whereas the number of hyperglycemic episodes initially increased at high altitude compared with the number at sea level. There were no differences in glycemia between subjects using insulin, metformin, sulfonylurea derivatives, dipeptidyl peptidase-4 inhibitors, or thiazolidinedione, although the number of subjects using these drugs was small (30). Schobersberger et al. (31) found reductions in glucose concentrations and HOMA-IR after oral glucose loading, following 3 weeks of exercise at an altitude of 1,700 m in subjects with metabolic syndrome, four of whom had type 2 diabetes. These findings indicate increased insulin sensitivity at high to very high altitude and a possible additive effect of hypoxia and exercise in subjects with type 2 diabetes.

In summary, in subjects with type 2 diabetes altitude does not seem to cause major glycemic changes and possibly even contributes to improved insulin sensitivity. However, data are very limited and comprise studies conducted only at relatively low (sometimes simulated and acute) elevations (1,700–4,000 m). We advise the continuation of therapy with anti-hyperglycemic medication at altitude. One should anticipate possible hyperglycemia during the first days at higher altitudes, especially following a rapid ascent. Short-acting insulin to correct hyperglycemia should be carried. After acclimatization, reductions in dosages of insulin and sulfonylurea derivatives may be necessary especially during prolonged submaximal exercise.

Effect on Body Mass and Fluid Balances

A commonly reported finding at altitude is appetite loss, which perhaps is associated with changes in hormones affecting satiety, resulting in decreased food intake (53,54). Together with increased energy needs, this often results in a caloric imbalance and weight loss. Furthermore, renal excretion of body water and insensible fluid losses, due to the increase in ventilatory rate and perspiration during exercise, can contribute to weight loss at altitude (55).

Theoretically, especially in subjects with type 1 diabetes, fluid loss and a tendency toward hyperglycemia at altitude may increase the risk of dehydration and the development of diabetic ketoacidosis. One case of an experienced diabetic climber with severe dehydration in the absence of ketoacidosis managed by saline solution infusion (28), and two cases of diabetic ketoacidosis on descent from Mount Kilimanjaro (50) have been reported. The latter two cases were probably induced by a reduction in insulin doses and continued exercise while ketonuria was present, but dehydration may have played a role.

Adequate fluid intake to balance fluid losses at altitude is paramount for successful travel at altitude because dehydration at altitude is a common finding. Fluid intake and hydration status can be based on urine quantity (equal to or, initially, even more than at sea level) and color (light yellow urine indicating proper fluid status; dark urine indicating dehydration) (56). However, in subjects with glucosuria, urine quantity, and color cannot be used to judge fluid status. Because early fluid retention due to decreased renal excretion of body water is associated with the development of AMS, overhydration should be avoided (57).

ACUTE MOUNTAIN ILLNESSES

Acute mountain illnesses comprise a spectrum of conditions ranging from a mild, self-limiting disease (AMS) to potentially lethal conditions, such as high-altitude pulmonary edema (HAPE) and HACE. See Table 2.

AMS is uncommon at altitudes below 2,500 m. The exact pathophysiology of AMS is unknown (58). Its symptoms can present within hours of (often acute) altitude exposure. Physical fitness does not protect against AMS, and individuals of both sexes and all ages are affected. HACE refers to a condition in which the patient with AMS deteriorates due to cerebral edema and increased intracranial pressure. The conditions of subjects with HAPE can deteriorate quickly as signs of pulmonary edema develop. The pathogenesis of HAPE comprises hypoxic pulmonary vasoconstriction, increased pulmonary capillary pressure, and increased capillary endothelial permeability resulting in edema (59).

HARH is frequently found in subjects experiencing AMS and climbers going to extreme altitude for the first time (60).

ACUTE MOUNTAIN ILLNESSES IN SUBJECTS WITH DIABETES

Preventive measures, treatment, and diabetes-specific points of attention are listed in Table 2. The incidence of AMS in subjects with type 1 diabetes does not differ from that of nondiabetic subjects, and, in reported studies, the use of acetazolamide was similar in both groups (47,50,61). Acetazolamide should be used with caution as it may lead to increased diuresis and acidosis (62). Theoretically, this may precipitate the development of diabetic ketoacidosis, although this has not been shown in humans. In fact, the International Mountaineering and Climbing Federation advises against the use of acetazolamide in subjects with type 1 diabetes (63). The alternative prophylactic drug for AMS, dexamethasone, is unattractive because it causes hyperglycemia (64). We have found a total of eight reported or cited cases of diabetic ketoacidosis at altitude, three of which were lethal (65), and one occurred in a subject with undiagnosed type 2 diabetes and HAPE (66). One fatal case of HACE in a subject with type 1 diabetes was reported (67), and one case of AMS in a subject with metabolic syndrome was reported (68). Type 2 diabetes is associated with obesity and a lower ventilatory response to hypoxia (6), both of which are risk factors for the development of AMS (69,70). Subjects with type 2 diabetes may, therefore, be at higher risk for the development of AMS. We found, however, no differences in AMS symptoms in subjects with type 2 diabetes compared with nondiabetic subjects at altitudes up to 4,167 m (30). HACE has not been reported in subjects with type 2 diabetes. Acetazolamide can be used in subjects with type 2 diabetes, taking into account the restrictions mentioned earlier. The risk of the development of ketoacidosis is probably low in subjects with type 2 diabetes who are receiving therapy with oral anti-hyperglycemic drugs, but the risk of the development of ketoacidosis in subjects with insulin-deficient type 2 diabetes probably approaches that in subjects with type 1 diabetes.

SPECIFIC CONDITIONS

High-Altitude Retinal Hemorrhage

Previous studies have found no retinal hemorrhages in six subjects with uncomplicated type 1 diabetes who had good glycemic control at altitudes

Table 2—High-altitude illnesses: preventive measures, treatment options, and specific attention points in subjects with diabetes

Illnesses	Symptoms	Prevention	Treatment	Relevance for diabetes
AMS	Headache; nausea, vomiting; dizziness, fatigue, insomnia	Slow ascent; acetazolamide, 125 mg b.i.d.; dexamethasone, 4 mg b.i.d.	Descent; acetazolamide, 250 mg b.i.d.; dexamethasone, 8 mg b.i.d (82)	Acetazolamide may increase risk of ketoacidosis (?) (50,63); dexamethasone induces hyperglycemia (64)
HAPE	Inappropriate dyspnea, orthopnea, pink frothy sputum, drowsiness	Nifedipine; salmeterol, 125 μg b.i.d. inhalations (83,84); tadalafil, 10 mg b.i.d.	As in AMS + oxygen, nifedipine (82)	
HACE	Ataxia, confusion, altered consciousness, coma, death	As in AMS	As in AMS + supplemental oxygen and hyperbaric therapy (Gamow bag) (82)	See AMS
HARH	Often asymptomatic; highest risk: often with AMS, first ascent, extreme altitude	Slow ascent	No specific treatment; most cases resolve spontaneously	Possibly increased risk when background retinopathy; Proliferative retinopathy? Do not go to high altitude (60,71)

Note: These conditions may develop rapidly and are potentially life-threatening. When in doubt, descend and call for assistance.

ranging from 5,800 to 8,201 m (28), and two cases of asymptomatic HARH in a group of 15 subjects with type 1 diabetes after summiting Mount Kilimanjaro (50). One subject in these two cases had a pre-existing background of retinopathy; hemorrhages resolved within 3 months. Leal et al. (71) investigated seven subjects with well-controlled type 1 diabetes by nonmydriatic retinography before and 2 weeks after an average stay of ±30 days at altitudes above 5,000 m (three subjects reached 7,134 m) and found one case of HARH. Thus, it is advised that any patient with diabetes should undergo an ophthalmological examination by a skilled specialist before and after visits to very high and extreme altitudes.

Neuropathy

Cold perception may be impaired in subjects with diabetes, even if signs of peripheral sensory neuropathy are absent (72). This can lead to serious cold injuries under extreme conditions at altitude. Daily inspection of extremities exposed to cold; and maintenance of adequate nutrition, hydration, footwear (good fit, nonsweating socks with good insulation), and handwear (mittens instead of gloves; consider chemical hand warmers), and layered clothing comprise basic precautions for preventing injuries due to cold.

BLOOD GLUCOSE MONITORING

The performance of hand-held BGMs can be affected by environmental conditions at altitude. Most studies (73,74) have reported overestimation of true blood glucose concentrations and possibly better performance of glucose dehydrogenase–based, as opposed to glucose oxidase–based, blood glucose monitoring at altitude. Of all interfering factors, cold may be more problematic than hypoxia in the determination of accurate blood glucose measurements at altitude (73,75) because modern BGMs do not show large deviations from true blood glucose levels when kept above the freezing point (74,76). Keeping test strips, batteries, and BGMs above the freezing point is of major importance. This can be done by wearing them in pouches close to bare skin and inside all layers of clothing. The regular assessment of BGM accuracy with glucose control solutions is recommended (Fig. 3).

Continuous glucose monitoring (CGM) may limit the necessity for frequent capillary blood glucose measurements, and built-in alarms for changing glucose levels are a practical advantage. An early study (77) on the accuracy and reliability of a CGM system at altitude is promising, but further studies are warranted. Some CGMs are susceptible to interference caused by local tissue hypoxia, temperature, and chemicals such as, among others, acetaminophen (78,79).

INSULIN STORAGE AND INSULIN DELIVERY

At altitude, both freezing and prolonged exposure to sunlight or high temperature (>30°C) can lead to the loss of potency of insulin or the freezing of insulin (80) (Fig. 3). Freezing can be prevented by keeping insulin close to the skin (47,67).

Modern insulin pumps have built-in pressure equilibration mechanisms, but some pumps have been reported to deliver excess insulin due to acute or subacute pressure changes during air flight (81). However, excess insulin delivery was limited and predictable. It is unknown whether this phenomenon could have clinical implications during gradual ascents such as those during hiking at altitude. Part of the contradictory results of this aspect of using insulin pumps might be due to the inadvertent presence of small air bubbles in the insulin vials: the expansion of bubbles might influence insulin delivery. Care must be taken to remove such air bubbles as much as possible before starting to use the vials in a pump or for injections.

SAFETY MEASURES

Trekking at altitude is often associated with conditions of low levels of hygiene and scarcity of (adequate) medical care. Therefore, basic therapeutic supplies should be carried. Medical emergencies often require expensive helicopter assistance, and not only altitude but many other factors hamper a successful helicopter rescue. Adequate insurance coverage should be arranged before departure. It is of vital importance to notify travel companions and guides of the hiker's diabetes and to teach them how to recognize (severe) hypoglycemia and hyperglycemia. Travel companions

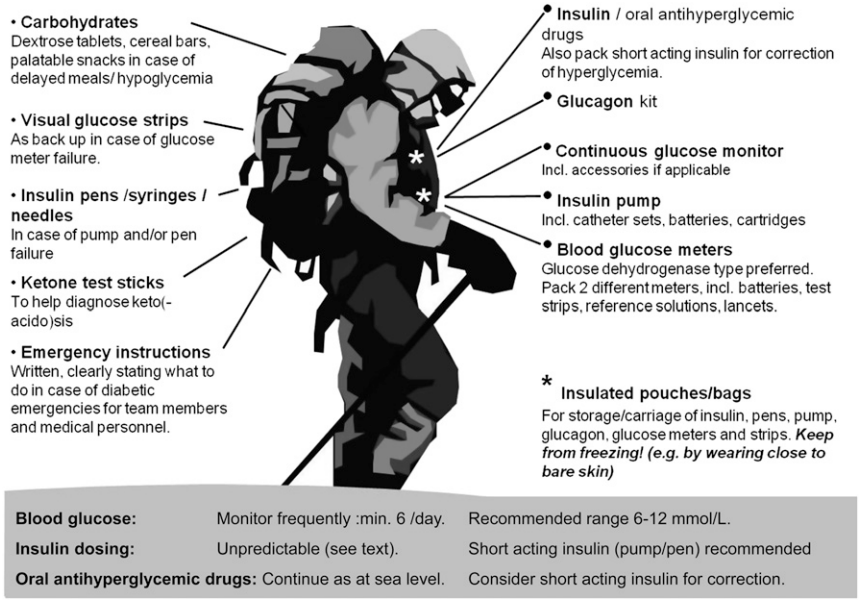

Figure 3—Diabetes travel supplies and recommendations for activities at altitude of multiple days' duration. All items should be taken in sufficient quantities (triple the normal amount), easily accessible, and in separate rucksacks (e.g., subject and fellow traveler). A third pack should be stored at a timely reachable place (e.g., hotel, base camp). min. 6/day, minimum of six times per day; incl., including.

should be able to measure blood glucose levels and should be instructed on how to administer glucose or to inject insulin and glucagon. Furthermore, carrying an emergency medical kit with instructions in a common, easily accessible place is of vital importance (Fig. 3).

CONCLUSIONS AND RECOMMENDATIONS

Subjects with diabetes should not be discouraged from taking part in activities at altitude. Most likely, active and sensible subjects with well-controlled, uncomplicated diabetes will not experience major problems at high altitude, or even very high altitudes, provided that they take sufficient time to acclimatize. However, factors including diabetes complications and comorbidities, and exposure to very high and extreme altitudes or extreme conditions (especially cold exposure) can complicate successful travel at altitude and demand careful preparation and planning of diabetes management. It is important for the treating physician to check for contraindications to travel at altitude, to promote adequate self-management skills and understanding of diabetes regulation, and to compose an individualized plan that limits risks and includes treatment adjustments. Recommendations for travel at altitude for subjects with diabetes and their treating physicians are listed in Fig. 3 and Table 1.

Clearly, the presence of diabetes can increase the potential dangers of travel at extreme altitudes. Still, even the highest mountains in the world can be conquered by subjects with diabetes, as evidenced by several subjects with diabetes successfully summiting Mount Everest. Despite the potential difficulties, the accomplishment of summiting a mountain, finishing a hiking trail, or just enjoying a skiing holiday will definitely boost a sense of achievement and well-being in the individual with diabetes.

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