Increased Insulin Requirements During Exercise at Very High Altitude in Type 1 Diabetes

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OBJECTIVE—Safe, very high altitude trekking in subjects with type 1 diabetes requires understanding of glucose regulation at high altitude. We investigated insulin requirements, energy expenditure, and glucose levels at very high altitude in relation to acute mountain sickness (AMS) symptoms in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Eight individuals with complication-free type 1 diabetes took part in a 14-day expedition to Mount Meru (4,562 m) and Mount Kilimanjaro (5,895 m) in Tanzania. Daily insulin doses, glucose levels, energy expenditure, and AMS symptoms were determined. Also, energy expenditure and AMS symptoms were compared with a healthy control group.

RESULTS—We found a positive relation between AMS symptoms and insulin requirements ($r = 0.78$; $P = 0.041$) and AMS symptoms and glucose levels ($r = 0.86$; $P = 0.014$) for Mount Kilimanjaro. Compared with sea level, insulin doses tended to decrease by 14.2% (19.7) (median [interquartile range]) ($P = 0.41$), whereas glucose levels remained stable up to 5,000 m altitude. However, at altitudes >5,000 m, insulin dose was unchanged (36.8 ± 17 vs. 37.6 ± 19.1 international units [mean ± SD] $P = 0.75$), but glucose levels (7.5 ± 0.6 vs. 9.5 ± 0.8 mmol/L [mean ± SD] $P = 0.067$) and AMS scores (1.3 ± 1.6 vs. 4.4 ± 4 points [mean ± SD] $P = 0.091$) tended to increase. Energy expenditure and AMS symptoms were comparable in both groups ($P = 0.84$).

CONCLUSIONS—Our data indicate that in complication-free individuals with type 1 diabetes, insulin requirements tend to increase during altitudes above 5,000 m despite high energy expenditure. This change may be explained, at least partly, by AMS.

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An increasing number of people with type 1 diabetes participate in extreme physical activity, such as very high altitude trekking, defined as trekking at altitudes between 3,500 and 5,500 m (11,500–18,000 ft) (1). Very high altitude trekking poses specific demands on individuals with type 1 diabetes, because many physiologic processes, including glucose metabolism, energy expenditure, and insulin requirements, differ at altitude compared with sea level (2).

In individuals without diabetes, exercise at altitude initially elicits an increase in both glucose and insulin. However, after 3 weeks at 4,300 m, resting glucose levels and glucose levels during exercise decrease compared with sea level values, whereas insulin levels return to and remain at sea level values. This suggests decreased glucose mobilization or increased insulin sensitivity as a result of acclimatization to high altitude (3,4).

In individuals with type 1 diabetes, the increase in glucose uptake by skeletal muscle in response to aerobic exercise at sea level is comparable to that in subjects without diabetes (5). However, because individuals with type 1 diabetes, by definition, lack the ability to automatically adjust insulin levels and have defective counterregulatory mechanisms (6), the initial response to exercise at high altitude will be different from that of healthy individuals.

Furthermore, all individuals at very high altitude are at risk for developing acute mountain sickness (AMS), which, in its early stages, is characterized by headache, depressed appetite, gastrointestinal symptoms, fatigue, and sleeping problems. AMS is accompanied by increased sympathetic activity and an increase in plasma catecholamines that could result in a deterioration of glycemic control (7).

It is difficult to predict individual insulin requirements and glucose profiles in response to exercise at very high altitude in individuals with type 1 diabetes. In addition, AMS may deteriorate glycemic control. These factors could therefore compromise safe trekking at very high altitude.

To our knowledge, no study has yet assessed a possible relationship between the occurrence of AMS and hyperglycemia in type 1 diabetes. Furthermore, whether insulin requirements increase or decrease in response to very high altitude in type 1 diabetes remains subject to debate (8–10).

Therefore, in this study, we determined daily insulin doses and glucose levels in subjects with type 1 diabetes at very high altitude. Furthermore, we compared daily energy expenditure and AMS symptoms in subjects with type 1 diabetes with those of a healthy control group.

RESEARCH DESIGN AND METHODS

Subjects

Eight patients with complication-free type 1 diabetes were recruited by advertisement and selected to take part in the

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"*Bas van de Goor Foundation Kilimanjaro Challenge*" (11). Nonmedical criteria for selection were personal motivation and willingness to function in a team.

Medical exclusion criteria were the presence of complications (retinopathy, neuropathy, nephropathy), uncontrolled hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg), severe hypoglycemia unawareness, cardiac disease (abnormal electrocardiogram, implantable cardioverter defibrillator or pacemaker, cardiomyopathy, coronary or clinically relevant valvular disease), peripheral arterial insufficiency, and smoking or use of illicit drugs.

The control group consisted of nine individuals without diabetes (four MDs, one clinical chemist, one laboratory technician, one echocardiographer, and two research assistants), and all were subjected to the same criteria and training program as the type 1 diabetes group.

Before the expedition, all participants underwent a physical examination, maximal exertion cycle ergometer testing, electrocardiography, echocardiography, and laboratory testing, and were given general training advice. The research protocol was approved by the local ethics committee of the Isala Clinics, Zwolle, the Netherlands, and all subjects gave written informed consent.

Itinerary

After arrival in Arusha, Tanzania (altitude 1,254 m), a 3-day ascent of Mount Meru (altitude 4,568 m) was made to facilitate acclimatization to altitude. Subsequently, all subjects remained at 1,254 m altitude for 1 day and continued for the 7-day ascent of Mount Kilimanjaro (altitude 5,895 m), taking the Machame route (12).

Measurements

Daily insulin dosages were recorded from subcutaneous insulin pumps (MiniMed Paradigm MMT 770, Medtronic Inc., Minneapolis, MN [$n = 6$] and Accu Chek Spirit, Roche Diagnostics, Basel, Switzerland [$n = 1$]) and manual recording by one subject using a four times daily insulin injection regimen. All subjects with diabetes regulated their own glucose levels and, in principle, determined their own insulin doses. Daily glucose levels were recorded by the diabetes group using a continuous glucose monitoring (CGM) system (MiniMed Paradigm Real Time, Medtronic Inc.) and handheld blood glucose meters (BGMs) (Accu Chek Compact Plus, Roche Diagnostics). The BGMs used were successfully tested for accuracy at very high altitude (5,000 m) as previously reported (13) and tested regularly at different altitudes using standard reference glucose solutions (NOVA Biomedical, Waltham, MA). Per subject, per day, a total of 17 h 42 min ± 1 h 12 min data of CGM were available for analysis (mean ± SD). CGM calibrations with handheld BGMs were performed four (six) times daily (median [interquartile range, IQR]).

Energy expenditure was monitored in all subjects using a right upper armband estimating energy expenditure from various physiologic and movement parameters monitored (SenseWear Pro Armband, Bodymedia, Pittsburgh, PA).

AMS score was recorded daily in all subjects according to the Lake Louise Score. This score is composed of five items graded from 0 (not present) to 3 (severe): headache, gastrointestinal symptoms, dizziness or light headedness, difficulty sleeping, and fatigue or weakness. A diagnosis of AMS is based on the presence of headache, at least one other symptom, and a total score of ≥4 (14).

Statistical analysis

Differences between two means were tested by Student *t* tests for data with normal distribution. Mean glucose was calculated by area under the curve analysis from CGM data. Also, the time subjects spent in hyper- and hypoglycemia, defined as episodes with glucose levels >10 mmol/L and <3.5 mmol/L, respectively, was calculated by CGM data analysis. Correlations were calculated using Spearman ρ analyses for data that were not normally distributed. For comparisons between groups in time, mixed repeated-measures ANOVA was used for data that were normally distributed.

The SPSS personal software package (version 16.0; SPSS Inc., Chicago, IL) was used for statistical analysis. A P value of < 0.05 was considered statistically significant. Data are presented as means ± SD unless stated otherwise.

RESULTS

Subjects

Baseline characteristics of all tested subjects are listed in Table 1. Apart from younger age and HbA_{1c} levels, participants with diabetes were comparable to the control group.

During the ascent of Mount Meru, two subjects of the diabetes group did not reach the summit because of viral gastroenteritis in one and AMS in the other. One subject reached camp two at 3,580 m altitude, and one subject returned to camp one at 2,514 m altitude. These subjects were still included in the analysis, because both eventually reached the summit of Mount Kilimanjaro.

During the climb of Mount Kilimanjaro, all participants with type 1 diabetes reached the summit without major problems. One subject from the nondiabetes group stayed at base camp because of knee problems, after successfully summiting mount Meru. The altitude profile of the expedition is presented in Fig. 1 (*shaded area*).

Insulin doses

Daily insulin doses are depicted in Fig. 1 (*top*). During the ascents of both mount Meru and mount Kilimanjaro, mean insulin dose decreased nonsignificantly with a subsequent return to baseline values on resting days ($P = 0.84$). Although there was substantial interindividual variation, the insulin dose was reduced, albeit not significantly: −14.2 ± 19.2% (median ± IQR) ($P = 0.41$) (Fig. 2). When analyzed over the whole expedition period, insulin dose tended to be lower at higher altitudes ($r = -0.51$, $P = 0.054$).

Table 1—*Baseline characteristics of study participants*

	Type 1 diabetes	Control participants
N (male/female)	8 (5/3)	9 (4/5)
Age (years)	31.6 ± 5.3	42.1 ± 9.9*
HbA_{1c} (%)	6.8 ± 0.6	5.2 ± 0.4*
Diabetes duration (years)	10.4 ± 8.1	n.a.
Blood pressure (mmHg)	117/69 ± 5.9/3.3	118/75 ± 11.9/9.2
BMI (kg/m^2)	23.9 ± 1.9	23.7 ± 1.8
Acetazolamide use (yes/no)	6/2	7/2

Data are presented ± SD. n.a., not applicable. *$P < 0.05$.

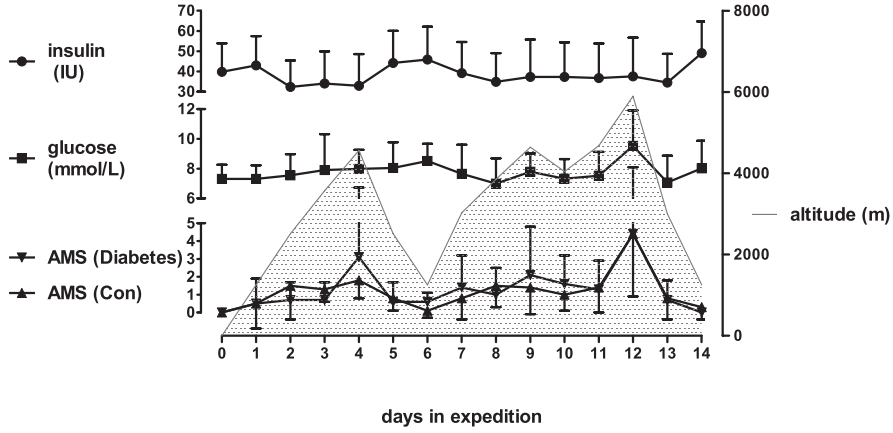

Figure 1—*Mean insulin dosage* (black circles; top)*, mean glucose from CGM* (black squares; middle)*, and mean AMS score per day* (black triangles*: downward: diabetes group, upward: control group;* bottom) *during the expedition; left Y axis. Altitude profile of expedition* (gray line, shaded area)*; right y-axis. Note: Altitude presented on expedition days is the highest altitude reached that specific day. AMS scores comprise seven subjects with type 1 diabetes. Data are presented as means ± SD.*

Glucose

Mean daily glucose measured by CGM is depicted in Fig. 1 (*middle*). Glucose levels tended to increase, compared with baseline (1,254 m), during the ascent of Mount Meru ($P = 0.086$) but remained elevated even after the descent to 1,254 m ($P = 0.002$; day 1 vs. day 6). During the ascent of Mount Kilimanjaro, glucose levels initially decreased nonsignificantly ($P = 0.079$). However, glucose levels increased steeply to their highest level on the summit day (day 1 vs. day 12, $P = 0.020$). We found no relation between glucose levels and altitude ($r = 0.12$, $P = 0.67$).

Time per day in hyperglycemia tended to increase on Mount Meru compared with baseline values (212 ± 228 min [sea level] vs. 284 ± 405 min [day 3], $P = 0.076$), subsequently decreased nonsignificantly on Mount Kilimanjaro (127 ± 168 min [day 11], $P = 0.47$), but peaked significantly on the summit day (500 ± 568 min [sea level vs. day 12], $P = 0.041$, Friedman analysis, median ± IQR). Time per day in hypoglycemia did not differ between sea level and any altitude (11 ± 31 vs. 0 ± 54 min [median ± IQR], $P = 0.9$, Friedman analysis). None of the subjects required help of a second party for hypoglycemic episodes.

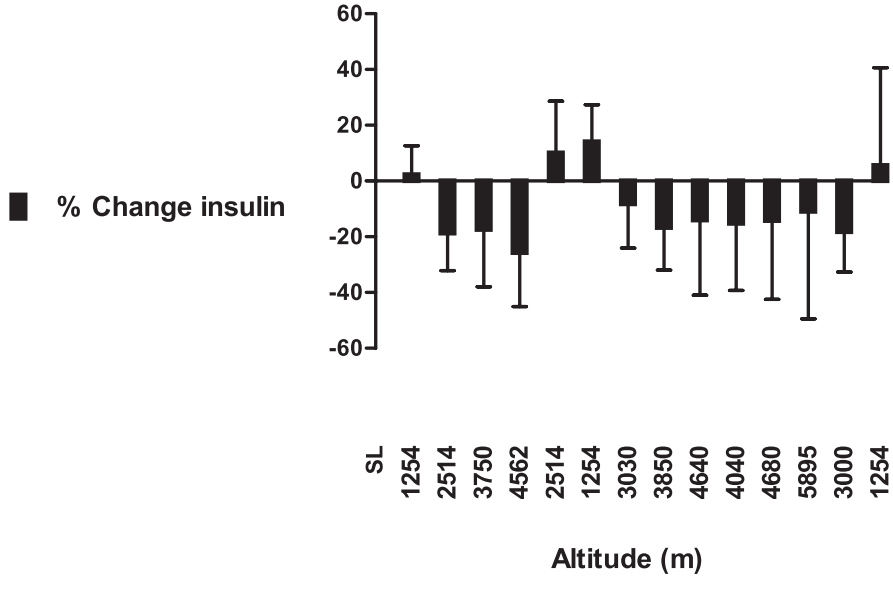

Figure 2—*Relative change in daily insulin dose compared with sea level doses during the expedition (mean ± SD; %).*

Acute mountain sickness

As expected, mean AMS scores increased in parallel with altitude in both groups (sea level vs. 4,562 m [$P = 0.015$] and sea level vs. 5,895 m [$P = 0.019$]) and were strongly correlated; $r = 0.92$ ($P = 0.0001$) (Fig. 1, *bottom*). There were no significant differences in AMS scores between the diabetes group and the control group ($P = 0.79$).

When analyzing both ascents separately for possible effects of acclimatization, there was a strong relation between AMS and glucose levels for Mount Kilimanjaro ($r = 0.86$; $P = 0.014$). Also, for Mount Kilimanjaro, we found a positive relation between insulin doses and AMS scores ($r = 0.78$; $P = 0.041$). However, there was no relation between AMS and glucose levels over the whole expedition period ($r = 0.15$; $P = 0.60$).

Energy expenditure

Energy expenditure increased significantly at altitude, 3,012 ± 578 (day 6) vs. 5,044 ± 937 (day 12) cal/day (mean ± SD) ($P = 0.0001$), and followed the same trend as the altitude profile (Fig. 3). Energy expenditure was comparable between the diabetes group and the control group ($P = 0.57$).

CONCLUSIONS—This study investigated the relationships among daily insulin doses, glucose profiles, and AMS symptoms in response to exercise at very high altitude in subjects with complication-free type 1 diabetes. As anticipated, insulin doses initially tended to decrease while glucose levels remained fairly stable at altitude. However, during the final ascent (day 12), glucose levels increased sharply in parallel to an increase in AMS scores but insulin doses did not change. Taken together, these results are in accordance with an increased insulin requirement when extreme altitudes (>5,000 m) are reached (day 12). On the final ascent, the increments in AMS symptoms and mean glucose are borderline significant. However, the significant increase in time in hyperglycemia and the positive relations between AMS and mean glucose levels, and AMS and insulin doses, support the notion of increased insulin requirements at extreme altitude, possibly related to AMS.

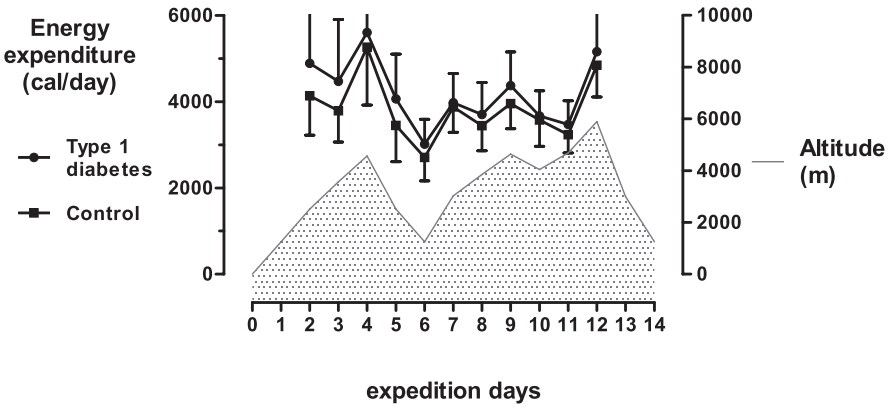

Figure 3—*Energy expenditure per day of the type 1 diabetes group* (black circles) *and the control group* (black squares) *(left y-axis) during the expedition in relation to the altitude profile* (gray line, shaded area; *right y-axis). Day 6 is a day of rest in between ascents.*

The increased glucose levels (day 12) cannot be attributed to an increased carbohydrate intake, because higher anorexia scores on the Lake Louise Questionnaire suggested markedly reduced caloric intake at altitudes >4,500 m (data not shown). In addition, reduced exercise-stimulated glucose uptake is unlikely because energy expenditure increased in response to exercise at altitude. The fact that increments in glucose, together with unchanged insulin doses, were accompanied by parallel increments in AMS scores suggests a shared causative factor.

Even after partial restoration of glucoregulatory hormone levels because of acclimatization, ascent to higher altitudes will elicit increments in gluco-counterregulatory hormones (3). Furthermore, AMS in itself is related to increments of counter regulatory hormones (7). Therefore, it seems likely that after an initial acclimatization to altitudes of up to ± 4,500 m, increments in AMS and altitude on day 12, again, induced a state of insulin resistance by increments in counterregulatory hormones.

Previous expeditions with individuals with type 1 diabetes have shown diverging results (8–10). Moore et al. (10) have reported decrements in insulin doses on Mount Kilimanjaro of up to 50%. This expedition had a very low summit success rate and was complicated by cases with keto-acidosis. This suggests insulin underdosing. In our study, insulin dose was initially decreased by approximately 15–20% (Fig. 2). However, it is likely that above a critical altitude of approximately 5,000 m this decreased insulin dose becomes inadequate as glucose levels increase. A critical altitude of approximately 5,000 m might also explain why for Mount Meru we did not find a relation between AMS and glucose levels.

Admettla et al. (9) found increased insulin requirements at altitudes above 5,000 m when adjusting for carbohydrate intake in a group of type 1 diabetic climbers on Mount Aconcagua (6,962 m). Pavan et al. (8) reported increased insulin requirements in eight climbers with type 1 diabetes on Mount Cho Oyu (8,201 m) and increased HbA_{1c} levels in type 1 diabetic subjects and healthy controls after this 39-day expedition. Thus, most reported studies seem to be in line with the concept that at extreme (>5,500 m) and even very high (3,500–5,000 m) altitudes, glucose levels and insulin requirements increase despite the high energy expenditure and lower carbohydrate intake.

Our study has clinical implications. At very high altitude, we would recommend climbers with type 1 diabetes to maintain or only slightly decrease insulin doses despite strenuous exercise and reduced caloric intake. Also, if more symptoms of AMS occur, one should expect to see an increase in insulin requirements.

Although the use of acetazolamide is not recommended in patients with type 1 diabetes because of the perceived risk for keto-acidosis (9), six of eight subjects with diabetes in our study used the drug without any complications.

This study has limitations. First, we did not monitor caloric intake because we were not informed in advance what type of food would be provided. Also, it was difficult to estimate carbohydrate contents of local foods. However, higher anorexia scores on the Lake Louise Questionnaire suggests markedly reduced caloric intake at altitudes >4,500 m. Furthermore, because of ethical and financial constraints, it was not feasible to use CGM devices to measure glucose continuously in the control group. Insulin requirements can hardly be determined in subjects without diabetes while exercising at very high altitude. Therefore, it was not possible to compare between groups for insulin requirements and glucose levels.

Second, acetazolamide, which was used by ±75% of all subjects in both groups, could have influenced AMS scores and insulin doses at very high altitude. Acetazolamide helps to prevent AMS and thus could attenuate counterregulatory hormonal responses associated with high altitude and AMS. As far as we know, this has not been investigated in humans, so the degree of interference remains speculative. Because of the small number of subjects who did not use acetazolamide (Table 1), we could not statistically analyze whether acetazolamide use influenced insulin requirements or not. However, we could not discover any consistent pattern between acetazolamide users and nonusers regarding insulin requirements. Finally, we were unable to measure counterregulatory hormone levels because of local limitations of blood sampling, handling, and storage.

One strength of our study is the use of continuous measurement of energy expenditure and glucose monitoring at very high and extreme altitudes, which provides detailed information on glucose trends and exercise intensity. Furthermore, CGM proved to function well at very high altitudes and provides the subjects with diabetes with instant access of actual glucose levels and trends.

In summary, in individuals with type 1 diabetes, insulin requirements tend to increase during very high altitude trekking despite high energy expenditure and reduced caloric intake. This change may be explained, at least partly, by AMS. The role of AMS and counterregulatory hormones warrants further investigation.

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P.d.M. wrote study protocol, researched data, and wrote the article. S.T.d.V. researched data, reviewed the article, and contributed to design/data collection. E.J.P.d.K. and R.O.B.G. contributed to and reviewed and edited the article and contributed to study design. C.J.T. contributed to and reviewed and edited the article. H.J.G.B. reviewed and edited the article and contributed to study design.

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