Effect of prior hyperglycemia on IL-6 responses to exercise in children with type 1 diabetes

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Galassetti, P. R., K. Iwanaga, A. M. Pontello, F. P. Zaldivar, R. L. Flores, and J. K. Larson. Effect of prior hyperglycemia on IL-6 responses to exercise in children with type 1 diabetes. Am J Physiol Endocrinol Metab 290: E833–E839, 2006. First published December 6, 2005; doi:10.1152/ajpendo.00445.2005.—The proinflammatory cytokine interleukin-6 (IL-6) may modulate the onset and progression of complications of diabetes. As this cytokine increases after exercise, and many other exercise responses are altered by prior glycemic fluctuations, we hypothesized that prior hyperglycemia might exacerbate the IL-6 response to exercise. Twenty children with type 1 diabetes (12 boys/8 girls, age 12–15 yr) performed 29 exercise studies (30-min intermittent cycling at ~80% peak O2 uptake). Children were divided into four groups based on highest morning glycemic reading [blood glucose (BG) < 150, BG 151–200, BG 201–300, or BG > 300 mg/dl]. All blood exercises were performed in the late morning, after hyperglycemia had been corrected and steady-state conditions (plasma glucose <120 mg/dl, basal insulin infusion) had been maintained for ≥90 min. Blood samples for IL-6, growth factors, and counterregulatory hormones were drawn at pre-, end-, and 30 min postexercise time points. At all time points, circulating IL-6 was lowest in BG < 150 and progressively higher in the other three groups. The exercise-induced increment also followed a similar dose-response pattern (BG < 150, 0.6 ± 0.2 ng/ml; BG 151–200, 1.2 ± 0.8 ng/ml; BG 201–300, 2.1 ± 1.1 ng/ml; BG > 300, 3.2 ± 1.4 ng/ml). Other measured variables (growth hormone, IGF-I, glucagon, epinephrine, cortisol) were not influenced by prior hyperglycemia. Recent prior hyperglycemia markedly influenced baseline and exercise-induced levels of IL-6 in a group of peripubertal children with type 1 diabetes. While exercise is widely encouraged and indeed often considered part of diabetic management, our data underscore the necessity to completely understand all adaptive mechanisms associated with physical activity, particularly in the context of the developing diabetic child.

inflammatory cytokines; exercise adaptation; glycemia; insulin

THE PHYSIOLOGICAL RESPONSE to physical exercise includes secretion of pro- and anti-inflammatory cytokines, counterregulatory hormones, and growth factors (7, 26). All elements of this complex response pattern are relevant to children with type 1 diabetes (T1DM).

Circulating pro- and anti-inflammatory cytokines increase significantly in children after even moderate exercise (26); among these molecules, the proinflammatory interleukin-6 (IL-6) displays the greatest quantitative changes. Several studies have reported chronically elevated baseline levels of IL-6 in T1DM, at least early after diagnosis, and increased levels of IL-6 receptors (32), supporting the broadly accepted notion of diabetes as a chronic inflammatory disease (25). Indeed, most long-term tissue complications of the disease occur via inflammatory changes of endothelia surfaces (37). In addition to intrinsic increases related to diabetes per se, IL-6 has also been shown to acutely increase in response to hyperglycemia (14). While the role of IL-6 and other pro- and anti-inflammatory cytokines in the evolution of diabetes is still incompletely defined, the above evidence suggests that the simultaneous presence of diabetes, hyperglycemia, and intense exercise (all independently able to increase IL-6) may result in inappropriately elevated IL-6 concentrations, with potentially negative implications on the onset and progression of diabetic complications. It is also likely that hyperglycemia need not occur simultaneously with exercise to affect exercise-induced IL-6 secretion, as numerous exercise responses can be altered by prior, rather than concurrent, glycemic fluctuations (8, 16).

Counterregulatory responses (reduced insulin, increased glucagon, catecholamines, and cortisol) optimize availability of glucose and other energy substrates, preventing exercise-associated hypoglycemia (2), a well-known, and unfortunately frequent, phenomenon (12, 24). Growth factor responses to exercise are increasingly considered an independent growth stimulus that complements resting levels of the same hormones (5), as children tend to be physically active spontaneously and repeatedly, often with frequent and intense bursts (1); alterations in the growth hormone → insulin-like growth factor (GH → IGF-I) axis are known to occur in T1DM, with increased resting GH and reduced IGF-I (21). Both counterregulatory and growth factor responses to exercise may be acutely and reversibly blunted by prior hypoglycemia (8, 16), but it is unknown whether recent prior hyperglycemia may also alter these responses.

We therefore designed the present protocol with the aim to determine whether prior, early morning hyperglycemia may affect IL-6 and other adaptive responses to subsequent exercise, after normalization of blood glucose (BG). Twenty children with T1DM participated in a total of 29 exercise sessions [30-min intermittent cycling at ~80% peak O2 uptake (V˙O2)] that were performed ~5 h after highest morning glucose readings, ranging from 104 to 419 mg/dl.

METHODS

All protocols were approved by the University of California Irvine Institutional Review Board, and all subjects and their parents or guardians signed informed assent and consent forms. Studies were performed at the University of California Irvine General Clinical Research Center (GCRC).

Subjects. Twenty children (12 boys/8 girls) with T1DM were enrolled in the study; patient characteristics are shown in Table 1. Inclusion criteria were onset of disease >2 yr before enrollment, no...
medications other than insulin replacement, and absence of other chronic pathology. After a preliminary visit for assessment of fitness level, subjects participated in a standard 30-min exercise challenge during which a range of adaptive responses were assessed. As 9 of 20 subjects repeated the exercise challenge twice, a total of 29 studies were performed. Results from the 29 studies were then divided into four groups based on whether the highest V˙O₂ measurements on the morning of the exercise challenge was <150 mg/dl, between 151 and 200 mg/dl, between 201 and 300 mg/dl, or >300 mg/dl (BG <150, n = 7; BG 151–200, n = 7; BG 201–300, n = 8; and BG >300, n = 7, respectively). The reason why 9 of 20 subjects participated in repeat experiments was that, while subjects were given the option to participate in the study twice, some opted not to return for logistical reasons or had to postpone scheduling for several months. Therefore, recruitment continued until we achieved approximately seven usable experiments per hyperglycemic group. Furthermore, in two subjects, repeat visits were actually performed, but either glucose or IL-6 data were lost or unusable, and subjects could not be retested, having completed the number of visits allowed by our Internal Review Board. As per the distribution of repeat tests across groups, three times children fell in the same group (each couplet in a different group), and six times children fell in different groups, with no clear distribution pattern.

**Preliminary visit.** This visit was necessary to determine the work intensity at which each participant would exercise during the main study visit. Due to differences in body size and individual fitness, having all participants exercise at the same work intensity would result in very different individual effort. To standardize the exercise challenge, therefore, subjects were instead asked to exercise at the same percentage of their maximal aerobic capacity, which was assessed via a standard incremental exercise test on a stationary bike (an electronically braked cycle ergometer model Ergoline 800S, SensorMedics, Yorba Linda, CA). Subjects started pedaling with no resistance for ~2 min, and then the work rate was gradually increased by 10–20 W/min (based the subject’s age, sex, and body size) (6) so that the total exercise time was 12–14 min. Each subject exercised to the limit of his or her tolerance, and gas exchange was measured breath by breath with the use of a metabolic cart (SensorMedics), allowing determination of individual maximal aerobic capacity (peak V˙O₂) and anaerobic threshold (AT).

Peak V˙O₂, or the maximal rate of net V˙O₂ achievable during exercise, is the current gold standard measurement for the assessment of physical fitness, while the AT is the point beyond which muscular work cannot occur without supplementation with anaerobic mechanisms and normally occurs between 40 and 60% of peak V˙O₂. The chosen exercise levels for the main study, 80% of peak V˙O₂, was, therefore, roughly halfway between the AT and peak V˙O₂, a level of exertion able to fully activate most adaptive mechanisms in healthy individuals. Our study team has successfully utilized this technique on thousands of children over the last decade (36).

During the preliminary visit, a history and physical were also taken, and Tanner stage was assessed with a standard questionnaire (20, 29). The use of this validated questionnaire for the assessment of pubertal status presents the advantage, over direct physical examination, of easy administration and elimination of subjectivity, if analysis is performed by different team members. Our team has developed considerable experience in its use, as it is a standard tool in a broad, multicentric, school-based diabetes prevention study of which our institution is part.

**Main study visit.** At least 72 h after the preliminary visit, participants were admitted at the University of California Irvine GCRC at 7 AM. To reproduce a real-life scenario, participants had been asked to eat a light breakfast around 6 AM. Patients with TIDM using an insulin pump followed their usual regimen, while patients on multiple insulin injections (Glargine plus fast-acting insulin) had their last Glargine injection no later than the night before, and only injected the fast-acting component of their usual morning insulin administration. Upon admission, intravenous (IV) lines were placed in both arms for blood drawing and study infusions (saline in controls, insulin and 20% dextrose in patients).

In patients with TIDM, a continuous insulin infusion was immediately started with the target of maintaining BG between 90 and 110 mg/dl for at least 90 min before the start of exercise. Insulin infusion rate depended on patients’ insulin regimen and BG at the time of admission. If patients were hyperglycemic at admission, insulin was infused IV at a rate of 1.5 U/h for every 100 mg/dl above euglycemia, and gradually tapered down as BG approached euglycemia. Once euglycemia was achieved, or if the patient’s BG was already on target at admission, IV insulin infusion was continued at the minimum level allowing maintenance of euglycemia. For patients on insulin pumps, this roughly corresponded to their pump’s normal basal rate (between 0.9 and 1.4 U/h), while in patients on multiple insulin injections, in which the last Glargine injection had a residual effect estimated as equivalent to the infusion of 0.7–1.0 U/h, the additional IV infusion average was 0.35 ± 0.1 U/h.

The rationale for achieving stable euglycemia/insulinemia before exercise was the necessity to minimize the confounding effects of as many metabolic variables as possible. While the effect of differing prior hyperinsulinemia may indeed have lingered through exercise performance, this was likely minimized by achieving similar insulin infusion rates across groups 90 min before exercise and comparable plasma insulin concentrations during exercise. On the other hand, our design guaranteed identical glycemic levels during exercise, preventing confusion due to differing substrate availability and utilization, which would have seriously complicated data interpretation. Furthermore, our design allowed detection of the effect on subsequent IL-6 levels of prior hyperglycemia, a conceptually novel observation. An alternative design would have been to allow hyperglycemia to persist during exercise; this, however, would have simply confirmed known observations of the inflammatory effect of acute hyperglycemia and would have raised a series of ethical issues concerning prolonged exposure of children to hyperglycemia during physical exertion.

Once euglycemia with basal insulin infusion was achieved, the experimental clock was started (time t = 0 min); from this point forward, the insulin infusion rate was not modified until the end of the study, while small amounts of IV glucose were infused, if necessary.

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**Table 1. Subject demographics**

<table>
<thead>
<tr>
<th></th>
<th>&lt;150</th>
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<th>201–300</th>
<th>&gt;300</th>
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<td>M/3 F</td>
<td>M/4 F</td>
<td>M/1</td>
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<td>Height, cm</td>
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<td>166±4</td>
<td>167±4</td>
<td>163±4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>56±2</td>
<td>58±4</td>
<td>58±4</td>
<td>55±3</td>
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<tr>
<td>Tanner stage</td>
<td>3.5±0.2</td>
<td>3.6±0.3</td>
<td>3.4±0.6</td>
<td>3.1±0.4</td>
</tr>
<tr>
<td>Peak V˙O₂, ml/kg·min⁻¹</td>
<td>41±2</td>
<td>40±3</td>
<td>45±4</td>
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</tr>
</tbody>
</table>

Values are group means ± SE. V˙O₂, O₂ uptake; M, male; F, female.
to prevent hypoglycemia. After 90 min (steady-state period), exercise was started at \( t = 90 \) min and ended at \( t = 120 \) min, following exercise a 30-min recovery period ensued, and at \( t = 150 \) min the last blood sample was drawn and the study was concluded.

Immediately before exercise, basal blood samples were collected; patients then started the exercise protocol, consisting of ten 2-min bouts of constant work rate cycle ergometry with 1-min resting intervals. The work rate was calculated for each subject to be equivalent to 80% of peak VO\(_2\). This approach allowed us to ensure that the bouts of constant work rate cycle ergometry with 1-min resting blood sample was drawn and the study was concluded.

Baseline insulin levels were maintained via constant intravenous insulin infusion, even though it is heavy exercise, while allowing activation of intermittent protocol, we have found that children enjoy the constant exercise for more than several minutes at a time. With this type of intermittent protocol, we have found that children do not sustain the subject’s lactate threshold, which is that children often do not sustain constant exercise for more than several minutes at a time. In particular, we have been able to do studies comparing exercise responses in healthy children and in children with chronic diseases like cystic fibrosis (34). In addition, our studies comparing exercise responses in healthy children and in children with chronic diseases like cystic fibrosis (34). In addition, our studies comparing exercise responses in healthy children and in children with chronic diseases like cystic fibrosis (34). In addition, our studies comparing exercise responses in healthy children and in children with chronic diseases like cystic fibrosis (34). In addition, our studies comparing exercise responses in healthy children and in children with chronic diseases like cystic fibrosis (34).

**RESULTS**

All subjects tolerated the exercise protocol well and achieved or surpassed the expected levels of VO\(_2\) during the second half of the 30-min exercise time (Fig. 1 shows one representative subject, in which the VO\(_2\) during the last exercise bouts actually approached his predetermined peak VO\(_2\)).

**Plasma glucose and insulin, insulin infusion rate.** The mean highest morning plasma glucose reading was 127 ± 9 mg/dl in BG < 150, 174 ± 6 mg/dl in BG 151–200, 249 ± 13 mg/dl in BG 201–300, and 341 ± 14 mg/dl in BG > 300. By experimental time \( t = 0 \) min, all groups had similar plasma glucose (BG < 150, 101 ± 6 mg/dl; BG 151–200, 102 ± 10 mg/dl; BG 201–300, 112 ± 12 mg/dl; BG > 300, 110 ± 12 mg/dl) (Fig. 2). Plasma glucose levels remained similar across groups at the start of exercise, at end-exercise, and 30 min postexercise.

Similarly, exogenous insulin infusion rates, which were initially greater in the groups with highest initial plasma glucose, became similar across groups at \( t = 0 \) min (BG < 150, 18 ± 5 mU·kg\(^{-1}\)·h\(^{-1}\); BG 151–200, 14 ± 3 mU·kg\(^{-1}\)·h\(^{-1}\); BG 201–300, 19 ± 7 mU·kg\(^{-1}\)·h\(^{-1}\); BG > 300, 21 ± 4 mU·kg\(^{-1}\)·h\(^{-1}\)), and they were maintained unchanged at this level throughout the rest of the study. Consequently, plasma insulin concentrations were also similar across groups throughout exercise and recovery (Fig. 2).

**Circulating IL-6.** See Fig. 3. Immediately before starting exercise, circulating concentrations of IL-6 were lowest in the BG < 150 group (0.7 ± 0.1 ng/ml) and progressively greater in the other three groups (BG 151–200, 1.7 ± 0.5 ng/ml; BG 201–300, 2.4 ± 0.6 ng/ml, \( P < 0.02 \) vs. BG < 150; BG > 300, 3.5 ± 0.8 ng/ml, \( P < 0.005 \) vs. BG < 150). This trend was maintained at end exercise (BG < 150, 1.0 ± 0.1 ng/ml; BG 151–200, 1.7 ± 0.7 ng/ml; BG 201–300, 2.8 ± 0.7 ng/ml, \( P < 0.03 \) vs. BG < 150; BG > 300, 4.2 ± 1.3 ng/ml, \( P < 0.02 \) vs. BG < 150) and at 30 min postexercise (BG < 150, 1.3 ± 0.2 ng/ml; BG 151–200, 2.8 ± 1.2 ng/ml; BG 201–300, 4.5 ± 1.6 ng/ml, \( P < 0.05 \) vs. BG < 150; BG > 300, 6.7 ± 2.2 ng/ml, \( P < 0.02 \) vs. BG < 150). The exercise-induced IL-6 increments (30 min post value minus baseline value) were also proportional to the highest morning BG values (BG < 150, 0.6 ± 0.2 ng/ml; BG 151–200, 1.2 ± 0.8 ng/ml; BG 201–300, 2.1 ± 1.1 ng/ml; BG > 300, 3.2 ± 1.4 ng/ml, \( P < 0.05 \) vs. BG < 150), suggesting that the observed end- and postexercise data were not just the result of an initial shift in baseline values.
Growth factors and counterregulatory hormones. The dose-response effect between degree of prior hyperglycemia and adaptive exercise responses appeared to be restricted to IL-6, as the growth factors GH and IGF-I, and the counterregulatory hormones glucagon, cortisol, and epinephrine did not display any significant intergroup differences, as shown in Table 2.

DISCUSSION

The main finding of our study was that both baseline and exercise-induced concentrations of the proinflammatory cytokine IL-6 were influenced in a directly proportional, dose-dependent manner by prior hyperglycemia in peripubertal chil-

Fig. 2. Plasma glucose and insulin and insulin infusion rates in 29 exercise studies performed on 20 children with type 1 diabetes. Subjects are divided into 4 groups based on whether highest morning plasma glucose was <150, 151–200, 201–300, or >300 mg/dl. Data are group means ± SE of mean.

Fig. 3. Serum interleukin-6 (IL-6) from 29 exercise studies performed in 20 children with type 1 diabetes. Subjects are divided into 4 groups based on whether highest morning plasma glucose was <150, 151–200, 201–300, or >300 mg/dl. Data shown are from baseline (pre), end-exercise challenge (end), 30 min after exercise (30 post), and the pre-30 post increment. Data are group means ± SE of mean.
An important issue associated with our results is the origin of the reported circulating concentrations of IL-6. A considerable body of work has recently been published on exercise-induced IL-6 release, and consensus seems to point to the concept that, at least in healthy humans, the skeletal muscle is the main quantitative contributor to IL-6 concentrations following exercise (28), despite minor contributions by several other tissues, including the adipose tissue (35), kidney (3), and brain (27). Whether this general concept also holds in pathological states, however, and particularly in diabetes is still unclear. Interestingly, recent reports indicate that monocytes may play an important role in the process, as documented by the finding of elevated monocytic IL-6 secretion in both type 1 (23) and type 2 diabetic patients (10). Furthermore, exercise has been shown to upregulate both spontaneous and stimulated IL-6 expression in monocytes of healthy adult men (30), and IL-6 release was increased in monocytes from type 2 diabetic patients cultured in a hyperglycemic milieu (11). It would, therefore, appear that the combination of monocytic IL-6-producing stimuli (exercise and hyperglycemia) on the background of cells activated by the presence of specific condition (diabetes) may have contributed to the overall IL-6 response to exercise in our study.

It could be argued that the observed effects of prior hyperglycemia on subsequent IL-6 levels may actually reflect, at least in part, acute postprandial hyperglycemia and, therefore, represent the degree of insulin resistance in the subjects, rather than the severity of chronic hyperglycemia. However, the BG reading used for assignment to one of the experimental groups was based on the highest reading obtained at any time after children woke up that morning. They all tested their BG first thing in the morning, before breakfast, and they were in the laboratory within 1 h, from which point glucose was tested continuously. While in some of the children the highest morning BG was indeed recorded postprandially, in most of the children, particularly in the highest hyperglycemic groups, the highest morning BG was indeed recorded postprandially, in most of the children, particularly in the highest hyperglycemic groups, the earliest, prebreakfast value was actually the highest (this occurred in 5 of 7 children in the BG >300 group, and in 5 of 8 children in the BG 200–300 group). We, therefore, believe that the effect of postprandial insulin resistance had only a minor influence on the overall significance of our observations.

Table 2. Counterregulatory hormones and growth factors from 29 experiments in children with type 1 diabetes before, at the end, and 30 min after a cycling exercise challenge

<table>
<thead>
<tr>
<th>Glucagon, pg/ml</th>
<th>Pre</th>
<th>151–200</th>
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<tbody>
<tr>
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<td>56±7</td>
<td>48±4</td>
<td>61±5</td>
<td>76±12</td>
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<tr>
<td>End</td>
<td>55±3</td>
<td>57±5</td>
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<td>72±9</td>
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<tr>
<td>30 min Post</td>
<td>49±6</td>
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<tr>
<th>Cortisol, µg/dl</th>
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<tr>
<td>End</td>
<td>12±4</td>
<td>14±1</td>
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<td>13±3</td>
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<tr>
<td>30 min Post</td>
<td>8±3</td>
<td>10±1</td>
<td>13±1</td>
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<tr>
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<tr>
<td>End</td>
<td>9±2</td>
<td>12±5</td>
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<tr>
<td>30 min Post</td>
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<tr>
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<td>22±3</td>
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<tr>
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<td>8±1</td>
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<th>IGF-I, ng/ml</th>
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<td>1,059±201</td>
<td>506±62</td>
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<td>540±68</td>
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Values are group means ± SE. Data are grouped by highest morning blood glucose reading. Pre, before challenge; End, at the end of challenge; 30 min Post, 30 min after challenge.
In our study, the effect of prior hyperglycemia on pre- and postexercise IL-6 followed a clear dose-dependent pattern. This is compatible with several previous reports of adaptive responses to stress that were blunted in a dose-response manner by a prior stimulus of increasing intensity. Davis et al. (9) reported that, following a hypoglycemic period of depths between 70 and 50 mg/dl, widespread blunting of metabolic and counterregulatory responses to a subsequent episode of hypoglycemia occurred. More pertinent to the present study, Galassetti et al. (19) observed that prior hypoglycemia of increasing depth resulted in progressively greater blunting on adaptive responses to next-day euglycemic exercise in adult T1DM patients. In neither of the above studies was IL-6 measured, nor was the effect of differing hyperglycemic levels tested.

To maximize applicability to everyday diabetes management, our experimental design was conceived trying to reproduce real-life conditions. The target setting was a day in which a sports match or a hike was scheduled for the late morning, and the diabetic child woke up with BG concentrations anywhere between euglycemia and serious hyperglycemia. This, unfortunately, despite considerable advances in glycemic control, is still a very common occurrence in families with diabetic members. Consequently, in our study, we did not predetermine the levels of early morning hyperglycemia, but incorporated in the experiment naturally occurring glycemic values that were gradually corrected with insulin infusions similar to the subjects’ regular insulin regimen. To prevent confusion in data interpretation, however, after BG was normalized in all participants, at least 90 min at euglycemia with basal rates of insulin infusion had to elapse before exercise was started. It could be argued that, despite BG normalization at the time of exercise, children with the highest earlier BG concentrations had been exposed to greater insulin infusion rates, which may have influenced the observed effects on exercise-induced IL-6 concentrations. Indeed, strong associations have been detected between hyperinsulinemia and IL-6 (15), particularly in insulin-resistant states (33). At least two lines of evidence, however, indicate that, in our experimental setting, hyperinsulinemia is unlikely to be a contributory factor to the IL-6 response. First, recently published data report that, while very elevated inflammatory cytokine levels (including IL-6) were present in T1DM patients during hyperglycemic crises, these were promptly corrected by insulin-induced correction of hyperglycemia, prompting the authors to suggest an anti-inflammatory effect of insulin in this setting (31). Furthermore, closer analysis of our data indicates that the area under the curve of insulin infusion is similar between the two lowest and the two highest glycemic groups (Fig. 4), despite marked differences in the IL-6 response.

Unlike IL-6, the exercise response of measured counterregulatory hormones and growth factors did not differ among groups with increasing prior hyperglycemia. This lack of difference did not come as a surprise, as while several of these variables had been previously observed to change in response to prior glycemic fluctuations, this mostly occurred as blunted exercise responses following hypoglycemia (8, 16, 18), rather than hyperglycemia. The combination of hyperglycemia and hyperinsulinemia, on the other hand, can indeed depress glucagon secretion, but this effect has not been reported to last long after euglycemia/euinsulinemia has been restored.

In conclusion, the experiments presented here show that, in a group of peripubertal children with T1DM, real-life morning hyperglycemia induced a dose-dependent increase in both resting IL-6 and in the IL-6 response to subsequent intense exercise. If confirmed in larger populations, these findings may be relevant to diabetes management, in light of the role of IL-6 as an inflammatory mediator involved in multiple pathogenetic mechanisms leading to the onset and progression of diabetic complications. While exercise is increasingly encouraged as a component of healthy living and indeed prescribed as a diabetes management tool, our data indicate that, to maximize all potential beneficial effects of exercise, it is crucial to first gain a complete understanding of all exercise-related adaptive mechanisms.

ACKNOWLEDGMENTS

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GRANTS

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