Acetone Metabolism in Humans During Diabetic Ketoacidosis

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SUMMARY

Plasma acetone turnover rates were measured with the primed continuous infusion of 2-[^{14}C]acetone in patients with moderate to severe diabetic ketoacidosis. Plasma acetone turnover rates ranged from 1.52 to 15.9 μmol · kg^{-1} · min^{-1} (108–1038 μmol · 1.73 m^{-2} · min^{-1}) and were directly related to the plasma acetone concentrations that ranged from 0.47 to 7.61 mM. The average acetone turnover rate was 6.45 μmol · kg^{-1} · min^{-1} (533 μmol · 1.73 m^{-2} · min^{-1}), a value twice that obtained in a similar group of diabetic ketoacidotic patients via the single-injection technique of 2-[^{14}C]acetone administration.

Degradation of urine glucose revealed that ^{14}C from administered 2-[^{14}C]acetone was principally located in carbons 1, 2, 5, and 6 of the glucose molecule in five of six patients. This distribution is similar to that expected from 2-[^{14}C]pyruvate, suggesting that acetone was converted to glucose through pyruvate. In one patient, label was located predominantly in glucose carbons 3 and 4, indicating that acetone metabolism may be different in some patients.

Acetol (1-hydroxyacetone) and 1,2-propanediol (PPD), two possible metabolites of acetone, were detected in plasma of the patients. The concentrations of Acetol ranged from 0 to 0.48 mM and of PPD ranged from 0 to 0.53 mM. The concentrations of each metabolite were directly related to the plasma acetone concentrations.

During the continuous infusion of 2-[^{14}C]acetone, the specific activities of plasma glucose and PPD rose continuously but did not reach constant values. Estimates of the minimal percent plasma glucose and PPD derived from plasma acetone averaged 2.1 and 74%, respectively. DIABETES 1986; 35:668–74.

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Acetone is one of the intriguing substrates rediscovered this decade. Whereas the physiologic and pathologic roles of acetoacetate (AcAc) and β-hydroxybutyrate (β-OHB) in fuel homeostasis have been extensively studied, the metabolism of acetone remains somewhat obscure. However, acetone can be excreted in breath and urine and undergoes in vivo metabolism.[1–3] Sakami and Rudney[1] summarized the results of numerous in vitro label-chase studies in animal systems and suggested two major pathways for acetone metabolism. One pathway involves acetone cleavage into acetate and formate, and the other pathway involves acetone conversion into pyruvate.

We reported the appearance of label derived from infused 2-[^{14}C]acetone in plasma glucose, lipid, and protein and in expired CO_2 from obese humans during starvation studies[2] and from diabetic patients during diabetic ketoacidosis.[3] Most of the infused 2-[^{14}C]acetone was directly or indirectly metabolized to $^{14}CO_2$ and H_2O. After a small pulse dose of 2-[^{14}C]acetone, radioactivity was detected in plasma glucose in nine of nine fasting subjects[2] and in three of nine diabetic ketoacidotic patients.[3] These limited data suggested the possibility of gluconeogenesis from fatty acid–derived acetone. Coleman[4] subsequently reported the conversion of 2-[^{14}C]acetone to lactate by mitochondria-free homogenates from mice starved for 3 days. Thereafter, Casazza et al.[5] reported that isolated rat liver microsomes convert acetone into acetol, which fluxes into pyruvaldehyde and PPD.

In our previous studies of patients during diabetic ketoacidosis (DKA) we gave small quantities of 2-[^{14}C]acetone by the single (pulse)-injection technique. This method may have prohibited detection of radioactivity in plasma glucose in all of the patients studied. In addition, the single-injection technique may have resulted in inadequate mixing of the labeled acetone in the body pools of acetone and may have been responsible for our failure to show a linear relationship between plasma acetone concentrations and acetone turnover

TABLE 1
Clinical characteristics

Patient	Sex	Age (yr)	Height (cm)	Weight (kg)	Body surface area (m^2)	Ideal body weight (%)	Duration of diabetes	Therapy before hospitalization (daily U insulin)	Time without insulin	Concomitant disease
1	M	23	170	94.0	2.05	148.3	1 mo			Obesity
2	M	34	188	117.9	2.42	145.8	7 mo	65 N	1 day	Transvestite on estrogen therapy
3	M	44		72.6			22 yr	15 R, 15 N		Bilateral above-knee amputations
4	M	53	169	72.6	1.83	114.8	7 yr	15 R, 20 N	4 mo	
5	M	56	192	77.0	2.04	94.0				Hypertensive cardiovascular disease
6	F	43	179	107.9	2.26	161.8	11 yr	50 R, 20 N		Obesity
7	F	50	165	88.7	1.96	165.1	32 yr	50 R, 50 N		Obesity, viral upper respiratory infection
Mean ± SEM		43 ± 4	177 ± 4	90.1 ± 6.7	2.09 ± 0.09	138.3 ± 11.5				
Range		23–56	165–192	72.6–117.9	1.83–2.42	94.0–165.1				

rates.[3] In the current studies, larger quantities of 2-[^{14}C]acetone were administered by the primed continuous-infusion technique to obtain constant plasma acetone specific activity (sp act). This method allowed us to *1*) reassess the relationship between plasma acetone concentration and turnover rate; *2*) examine the relationships among plasma acetone, glucose, and PPD, a novel gluconeogenic metabolite of acetone; and *3*) to demonstrate a net gain of glucose from acetone.

MATERIALS AND METHODS

Patients. The clinical characteristics of the seven patients studied are shown in Table 1, and their laboratory data are shown in Table 2. Patients 1 and 5 received no diabetic therapy prior to developing DKA, and patients 2 and 4, respectively, omitted their insulin injections 1 day and 4 mo before they developed DKA. In addition, patient 2 was a transvestite who took oral estrogen. Many years before admission, patient 3 had bilateral traumatic above-the-knee amputations (Table 1). All patients had hyperglycemia, hyperketonemia, and metabolic acidosis and fulfilled the criteria for establishing the diagnosis of moderate to severe DKA. Wide ranges of blood glucose and ketone body concentrations and metabolic acidosis were intentionally sought to examine the differences among patients with varying degrees of DKA (Table 2). After the diagnosis was established, clinical stability assessed, and informed voluntary consent obtained, the patients were admitted to the Temple University Hospital General Clinical Research Center for study and therapy. The protocol for investigating acetone metabolism during DKA was approved by the Research Institutional Review Board at Temple University Hospital and School of Medicine.

Experimental design, chemical analysis. An intravenous infusion of 0.9 or 0.45% saline was given throughout the study period. Patients in moderate to severe DKA can usually be maintained in near steady-state conditions for several hours by partial rehydration with intravenous saline. Partial rehydration with saline may reduce plasma glucose concentration,[6,7] but it generally has minimal or no effect on plasma AcAc, β-OHB, and acetone concentrations and on arterial pH.[7] The patients' clinical conditions and blood chemistries were closely monitored throughout the studies. No complications were encountered, and therapy for DKA was given after the investigative studies were completed. All patients recovered fully from their ketoacidotic episodes.

Plasma acetone turnover rates were measured in the seven patients with 2-[^{14}C]acetone (Amersham, Arlington Heights, IL). It was dissolved in ice-cold isotonic saline and sterilized by passage through a 0.22-μm Swinnex filter unit (Millipore, Bedford, MA). This primary 2-[^{14}C]acetone solution contained 25 μCi/ml.

The patients were studied in the supine position in a bed in a special room equipped with an efficient ventilation system to exhaust $^{14}CO_2$ and [^{14}C]acetone. Intravenous catheters were placed in peripheral veins of each forearm for administration of the 2-[^{14}C]acetone and for collection of blood samples.

Immediately before use, the primary 2-[^{14}C]acetone solution was diluted with ice-cold isotonic saline in a glass syringe. The 2-[^{14}C]acetone was administered by primed con-

TABLE 2
Clinical laboratory data

Patient	pH	PCO_2 (mmHg)	HCO_3^- (mM)	Glucose (mg/dl)	Na^+ (meq/L)	K^+ (meq/L)	Cl^- (meq/L)
1	7.27	26	11.6	307	134	3.6	101
2	7.25	18	7.6	341	131	4.0	95
3	7.30	38	18.1	241	134	4.6	104
4	7.30	23	10.8	454	140	4.4	105
5	7.33	13	6.9	603	133	4.4	95
6	7.31	23	11.3	592	128	5.4	103
7		26	21.0	353	135	4.4	97
Mean ± SEM	7.29 ± 0.01	24 ± 3	12.5 ± 2.0	413 ± 53	134 ± 1	4.4 ± 0.2	100 ± 2
Range	7.25–7.33	13–18	6.9–21.0	241–603	128–140	3.6–5.4	95–105

tinuous infusion for 6 h by means of an infusion pump. The priming dose (μCi) to infusion rate (μCi/min) ratio was 200:1.

Throughout the infusion period, blood samples were collected at hourly intervals, and plasma was immediately obtained by centrifugation at 4°C. In all studies, the total quantity of 2-[^{14}C]acetone administered was 150–175 μCi (5.7–6.7 μmol) in 150–175 ml isotonic saline. Before the tracer administration, patients voided, and urine was collected throughout and at the end of the infusion period.

The sp act and concentrations of acetone and glucose were determined in plasma and urine by previously described methods.[2,3] With our method,[2] plasma made to contain 2.15 μmol/ml and 2150 dpm/ml acetone was analyzed 10 times. The mean acetone concentration was 2.06 μmol/ml (range, 1.96–2.20), and the mean radioactivity was 2096 dpm/ml (range, 1999–2200). Acetol and PPD concentrations and PPD sp act were determined in ultrafiltrates prepared by passing plasma through membranes with a nominal molecular weight cutoff of 10,000 (Millipore). Acetol and PPD concentrations were measured with a gas chromatograph equipped with a flame ionization detector and a 91-cm × 2-mm glass column packed with 80/100 Carbopack C/0.8% THEED (Supelco, Bellefonte, PA). The injection port, column, and detector temperatures were 150, 125, and 150°C, respectively. Nitrogen was the carrier gas at a flow rate of 40 ml/min. Three-microliter aliquots of the ultrafiltrate were injected onto the column. Acetol and PPD concentrations were determined by peak area analysis by means of an integrator system (Hewlett-Packard Model 3380A integrator recorder) attached to the gas chromatograph (Hewlett-Packard Model 5730A).

For radiochemical analysis, [^{14}C]PPD was isolated from ultrafiltrates by partition chromatography with Celite 535 (Johns-Manville, Denver, CO) as described by Neish.[8] Briefly, 0.5 ml ultrafiltrate was applied to a 100 × 11-mm column of acid-washed Celite, and 50 ml ethyl acetate was passed through the column at a rate of 15 ml/min with nitrogen gas pressure. PPD was then eluted from the column with 40 ml benzene:*n*-butanol (3:1). Four columns, equivalent to 2 ml ultrafiltrate, were run for each sample to obtain sufficient radioactive material for counting purposes. The benzene:*n*-butanol eluates were combined and flash evaporated to concentrate the [^{14}C]PPD in 2–5 ml of water; aliquots of the concentrate were counted in ACS II (Amersham). Standards prepared with chromatographically pure 1-[^{14}C]PPD (ICN Biomedicals, Irvine, CA) were routinely run with each set of samples. Recovery of radioactivity was 85–95%. The PPD isolated with this method was free from other potentially important plasma constituents such as acetone, acetol, pyruvate, lactate, glycerol, AcAc, β-OHB, and glucose.

Published methods were used to isolate and degrade glucose to determine the distribution of radioactivity in the carbon atoms of the molecule.[9–11] For these studies, glucose was isolated from the urine of the diabetic patients. Briefly, an aliquot of urine containing 15–20 mg glucose was reduced in volume to ~2.0 ml by heat and a stream of nitrogen. The concentrated urine was applied to a column of MB-3 resin and glucose eluted with water. Glucose was quantitatively converted to lactate with sarcoma 37 ascites tumor cells,[9] and the lactate was oxidized with ceric sulfate[10] to yield glucose carbons 1, 2, 5, and 6 as acetaldehyde and carbons 3 and 4 as CO_2.[11] The acetaldehyde was trapped and counted as the acetaldehyde-dimedone complex[11] and CO_2 trapped and counted in hyamine.

Calculations. In these studies, plasma acetone concentrations and sp act were constant by the 4th h of the infusion period. During the plateau period, the SEMs expressed as a percent of the mean for plasma acetone concentrations and sp act were 5.00% (range, 1.91–9.90) and 2.25% (range, 0.37–9.64), respectively. Under these steady-state conditions, plasma acetone turnover rate was calculated by dividing the infusion rate of the 2-[^{14}C]acetone (dpm/min) by the plasma acetone sp act (dpm/μmol). During the plateau period, the concentrations of AcAc and β-OHB were also constant. The SEMs expressed as a percent of the mean for plasma AcAc and β-OHB concentrations were 3.69% (range, 1.38–8.47) and 3.82% (range, 0.90–10.43), respectively. The sp act of plasma PPD and glucose increased during the [^{14}C]acetone infusion period. Therefore, a minimum estimate

TABLE 3
Initial ketone body concentrations

Patient	Acetone (mM)	AcAc (mM)	β-OHB (mM)
1	4.77	2.34	7.47
2	4.24	3.27	10.31
3	1.21	1.71	4.14
4	3.95	3.99	12.58
5	6.02	4.39	13.35
6	2.61	2.45	5.92
7	0.50	1.71	3.84
Mean ± SEM	3.26 ± 0.79	2.84 ± 0.40	8.23 ± 1.48
Range	0.50–6.02	1.71–4.39	3.84–13.35

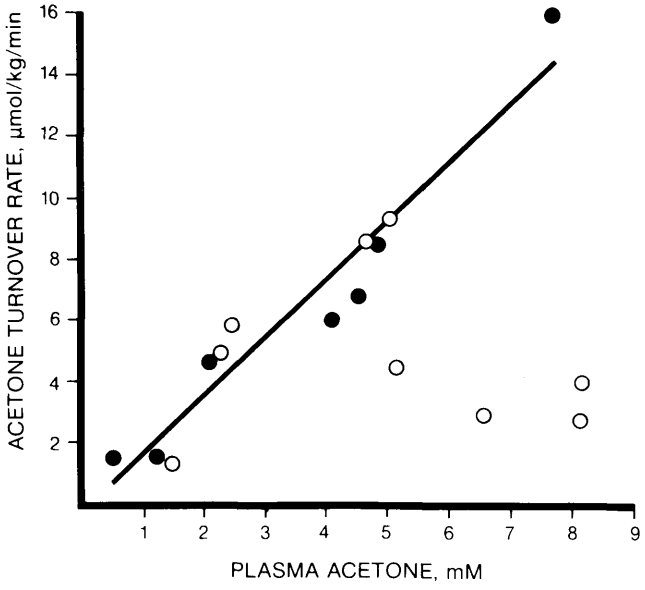

FIGURE 1. Relationship between plasma acetone concentrations and acetone turnover rates. *Closed circles* represent data obtained in present study; *open circles* are data from a previous study included for comparison. *Line* represents derived relationship for present study and is expressed by $y = -0.29 + 1.92x$, where y = acetone turnover rate and x = acetone concentration; $r = 0.97$, $P < 0.001$.

of the percent plasma PPD or plasma glucose derived from plasma acetone was obtained by dividing the last plasma PPD or glucose sp act by the constant mean plasma acetone sp act.

Statistical analyses. Values are expressed as the mean ± SEM. In addition, ranges are given to depict the heterogeneity of the patients studied. The relationships between values were determined by use of the correlation coefficient (r).[12]

RESULTS

Venous plasma ketone body concentrations. As shown in Table 3, initial venous plasma ketone body concentrations in the patients were similar to values previously reported in DKA.[3,13] The wide range of values indicated the heterogeneous nature of the patients.

Acetone turnover rates. Individual acetone turnover rates plotted against plasma acetone concentrations are shown in Figure 1. Data from the present studies with the primed continuous infusion of 2-[^{14}C]acetone are represented by closed circles. For comparative purposes, data obtained previously by the single-injection technique for determining [^{14}C]acetone turnover rates from patients in DKA are shown by open circles.[3] Up to a plasma acetone concentration of ~4–5 mM, there was a direct linear relationship between the plasma acetone concentration and the turnover rate, and the data obtained from both methods of tracer administration are in good agreement. However, above a plasma acetone concentration of 4–5 mM, divergent results were observed. Over the entire concentration range, data from the studies with the single-injection technique suggest no relationship exists between plasma acetone concentrations and turnover rates, whereas data obtained from the continuous-infusion technique showed a linear relationship between plasma acetone concentrations and acetone turnover rates [$y = -0.29 + 1.92x$ ($r = 0.97$, $P < 0.001$)]. The relationship between plasma acetone concentrations and turnover rates obtained by the continuous infusion of tracer was strongly dependent on the single patient whose turnover rate was 15.9 μmol · kg^{-1} · min^{-1} at a plasma acetone concentration of 7.61 mM. We have no reason to suspect that these data are incorrect. Therefore, these primed continuous-infusion studies suggest that the single-injection method underestimates the acetone turnover rate when the acetone pool is large, as reflected by plasma acetone concentrations that exceed 5.0 mM.

Plasma acetone, acetol, and PPD concentrations. The relationships between the plasma acetone, acetol, and PPD concentrations observed during the acetone-turnover study period in five of the patients are shown in Figure 2. Plasma PPD ranged from an undetectable concentration in one patient, whose plasma acetone concentration was 0.5 mM, to the highest PPD concentration of 0.53 mM in another patient, whose plasma acetone concentration was 7.6 mM. Plasma acetol was undetectable in the patient whose plasma acetone concentration was 0.5 mM and was 0.48 mM in the patient whose plasma acetone concentration was 7.6 mM. Data from the five patients showed a direct linear relationship between the concentrations of plasma acetone and PPD [$y = -0.07 + 0.08x$ ($r = 0.99$, $P < 0.001$)] and between plasma acetone and acetol [$y = -0.031 + 0.062x$ ($r = 0.97$, $P < 0.01$)].

Plasma acetone and PPD specific activities. The relationship between the plasma acetone sp act and plasma PPD sp act was determined in four patients. During the continuous infusion of 2-[^{14}C]acetone, the plasma acetone sp act became constant by the 4th h of the infusion period, but plasma PPD sp act continued to increase. This behavior in a typical study is shown in Figure 3. Table 4 shows the average constant plasma acetone sp act, the greatest plasma PPD sp act, and the relative plasma PPD sp act. Because plasma

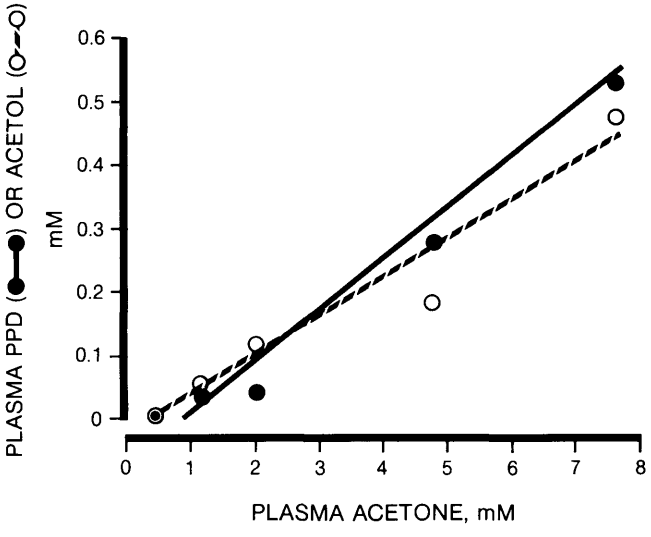

FIGURE 2. Relationship between plasma acetone concentrations and plasma Acetol or PPD concentrations in 5 DKA patients. *Closed circles* and *solid line* show relationship for PPD, which is expressed by $y = -0.069 + 0.08x$; $r = 0.97$, $P < 0.01$. *Open circles* and *dotted line* show relationship for Acetol, which is expressed by $y = -0.031 + 0.062x$; $r = 0.97$, $P < 0.01$.

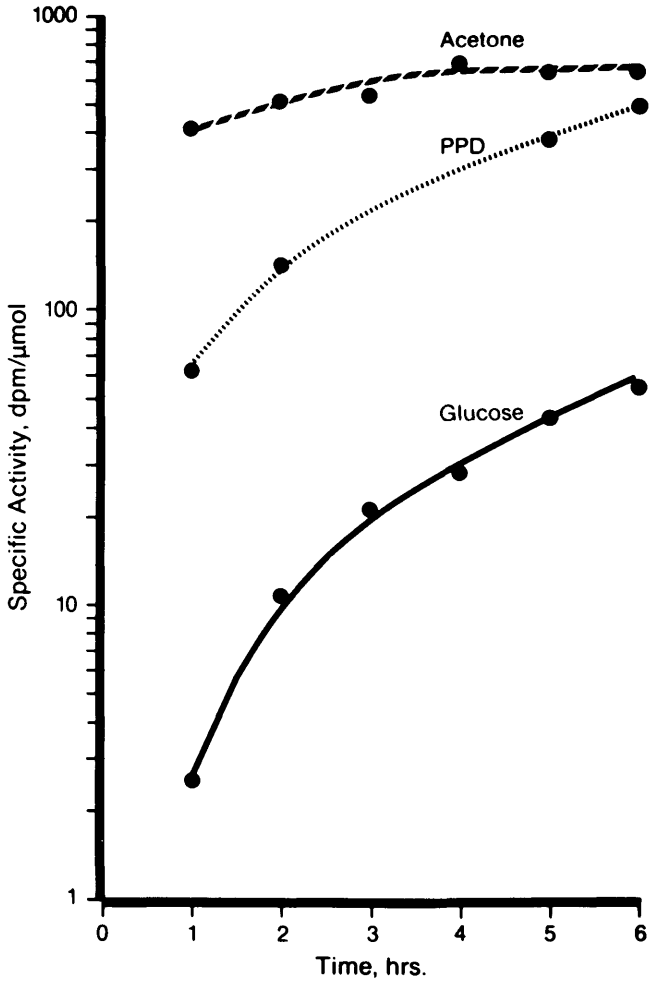

FIGURE 3. Relationship between plasma acetone, PPD, and glucose sp act in patient 1.

PPD sp act had not become constant, the calculated relative sp act must be regarded as minimum estimates of the percent plasma PPD derived from plasma acetone. The relative sp act of PPD ranged from 31 to 121%. In patient 6, recovery of PPD during column purification was low and may have introduced a substantial experimental error in the determination of plasma PPD sp act.

Plasma acetone and glucose specific activities. The relationships between the plasma acetone sp act and plasma glucose sp act are shown in Table 5. Plasma acetone sp act had plateaued by the 4th h after initiating the primed continuous infusion, but plasma glucose sp act continuously increased during the 2-[^{14}C]acetone infusion period. This behavior in a typical study is shown in Figure 3. Table 5 shows the average constant plasma acetone sp act, the greatest plasma glucose sp act, and the plasma glucose relative sp act in each of the diabetic patients studied. Because the plasma glucose sp act had not reached constant values, the calculated relative sp act represented minimum estimates of the percent plasma glucose derived from plasma acetone. These values ranged from 0.5 to 4.1%.

TABLE 4
Plasma acetone and PPD specific activities

Patient	Sp act (dpm/μmol)		Relative sp act* (%)
	Acetone	PPD	
1	653	480	74
3	2313	1594	69
5	332	102	31
6	1127	1364	121

*Relative sp act = (PPD sp act/acetone sp act) × 100.

TABLE 5
Plasma acetone and glucose specific activities

Patient	Sp act (dpm/μmol)		Relative sp act* (%)
	Acetone	Glucose	
1	653	54	4.1
2	542	19	1.8
3	2313	21	0.5
4	1062	40	1.9
7	6196	246	2.0

*Relative sp act = [glucose sp act ÷ 6/(acetone sp act ÷ 3)] × 100.

Distribution of radioactivity in urine glucose. To gain information about the possible pathway by which acetone may be converted to glucose in these patients, the distribution of radioactivity in glucose carbon atoms from the 2-[^{14}C]acetone was determined and is shown in Table 6. In six of seven patients studied, radioactivity was found predominantly in glucose carbons 1, 2, 5, and 6. These results are comparable to those obtained in similar studies in experimental animals and suggest that acetone is converted to pyruvate before conversion to glucose.[14,15] In one male patient (5), radioactivity was predominantly located in glucose carbons 3 and 4. These results suggest that pathways of acetone metabolism may be different in some patients.

DISCUSSION

This study confirms the finding of high plasma acetone concentrations in decompensated diabetic patients.[3,13] Furthermore, it shows a linear relationship between plasma acetone concentrations and acetone production rates when 2-[^{14}C]acetone was given by the primed continuous-infusion technique to measure acetone appearance rates. Plasma acetone concentrations ranged from 0.47 to 7.61 mM, and acetone turnover rates varied from 1.52 to 15.9 μmol · kg^{-1} · min^{-1} (108–1038 μmol · 1.73 m^{-2} · min^{-1}) in patients in moderate to severe DKA (see Figure 1).

In a previous study we used the pulse (single)-injection technique to measure acetone production rates in a similar group of patients in DKA.[3] We reported a direct linear relationship between plasma acetone concentrations and acetone production rates when the plasma acetone concentration was <4–5 mM. At plasma acetone concentrations >4–5 mM, this relationship was lost.[3] The results in this study show excellent agreement between the pulse-injection and continuous-infusion techniques up to a plasma acetone concentration of ~4–5 mM. Above this concentration, divergent results were obtained (Figure 1). The primed continuous-infusion technique showed a linear relationship between plasma acetone concentration and acetone appearance rate. Thus, the present study suggests that pulse administration

TABLE 6
Distribution of radioactivity in urine glucose

Time of collection (h)	Glucose radioactivity in carbons 1, 2, 5, 6, and 3, 4													
	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7	
	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4	1, 2, 5, 6	3, 4
1	40.9	59.1											94.0	6.0
2	83.5	16.5			65.9	34.1	77.8	22.2	38.7	61.2	93.4	6.6	94.5	5.5
3	75.8	24.2	84.8	15.2	73.9	26.1	81.0	19.0	38.3	61.7	93.7	6.3	91.0	9.0
4	74.4	25.6	77.5	22.5	83.6	16.4	71.5	28.5	32.7	67.3	93.2	6.8		
5	82.1	17.9			87.9	12.0	81.2	18.8	49.2	50.9	91.9	8.1	88.8	11.2
6	84.1	15.9			88.5	11.5	74.0	26.0			92.1	7.9	90.0	10.0

of [^{14}C]acetone is inappropriate to determine acetone turnover rates, especially when plasma acetone concentrations are high, because of insufficient mixing of the tracer in large acetone pools.

Partial oxidation of fatty acids in the liver[16] and kidney[17,18] generates AcAc that undergoes either reduction to β-OHB or decarboxylation to acetone. Circulating concentrations of AcAc and β-OHB are curvilinearly and of acetone are linearly related to their production rates.[19,20] The mean plasma AcAc plus β-OHB concentration in this study was ~11 mM. From the previously published information it can be estimated that the mean production rate of AcAc plus its redox couplet, β-OHB, was ~0.9–1.2 mmol · min^{-1} · 1.73 m^{-2}. The mean acetone production rate in this study was 0.53 mmol · min^{-1} · 1.73 m^{-2}. This value is twofold greater than was previously obtained in similar patients who were studied with the single-injection technique of [^{14}C]acetone administration.[3]

Our previous studies showed that the major fraction of acetone produced undergoes further in vivo metabolism.[3] Previously, others identified acetol and PPD as possible early intermediates in the pathways of acetone utilization.[1] After administration of 2-[^{14}C]acetone to rats, Rudney[21] isolated PPD as the phosphate ester from liver and found label solely in carbon 2, indicating that acetone was directly converted to this intermediate. Our demonstration of a direct relationship between the plasma concentrations of acetone, acetol, and PPD, and incorporation of significant quantities of 2-[^{14}C]acetone into PPD, strongly suggests that a similar pathway also exists in humans and becomes manifested during DKA. PPD has been shown to provoke an increase in liver glycogen content[22,23] and blood glucose concentrations[23] in laboratory animals. Recently, glucose production from acetone, acetol, and PPD has been demonstrated in hepatocytes from rats fed acetone in their drinking water.[5] Acetol and PPD may be intermediates in the pathway by which acetone is converted to glucose in humans.

Using the pulse administration 2-[^{14}C]acetone, we previously reported the incorporation of label into plasma glucose in only three of nine DKA patients. In the current studies, with primed continuous infusion of tracer to achieve a constant plasma acetone sp act, incorporation of label into plasma glucose was observed in five of five patients studied. In these patients, plasma glucose sp act were still increasing at the end of the infusion period. Because of this, the relative sp act reflects a minimum estimate of the fraction of glucose derived from acetone that ranges from 0.5 to 4.1%. In animals, radioactivity from 2-[^{14}C]acetone was found to be distributed principally in carbons 1, 2, 5, and 6 of blood glucose and liver glycogen, a pattern of incorporation similar to that observed from 2-[^{14}C]pyruvate.[14,15] This has been interpreted to indicate that acetone is metabolized to the gluconeogenic precursor pyruvate before conversion to glucose.[1] The results obtained in the degradation of urine glucose from the DKA patients support the earlier animal studies. In six of seven of these patients, 70–90% of glucose radioactivity resided in carbons 1, 2, 5, and 6. In one patient the labeling pattern displayed predominant distribution of radioactivity in carbons 3 and 4. This suggests that other pathways of acetone metabolism may exist among subclasses of diabetic patients.

The minimal quantity of plasma glucose derived from acetone during DKA was estimated to be 0.5–4.1% with an average quantity of ~2%. A 2% net gain in new glucose carbon from fat during DKA is not a small quantity of glucose. The production rate of glucose after moderate to severe DKA amounts to 0.8–1.0 mmol · min^{-1} · 1.73 m^{-2}.[24,25] The major fraction of the glucose produced during DKA is derived from recycled lactate and pyruvate and from glycerol. Assuming that the total quantity of new glucose synthesized from amino acids during moderate to severe DKA is reflected by the amount of nitrogen excreted in the urine and that the 1 g of urinary nitrogen equates to the production of 3 g of glucose, net gluconeogenesis from amino acids is ⩾0.2 mmol · min^{-1} · 1.73 m^{-2} in adult humans during moderate to severe DKA.[24] Thus, at least 10% (3 mg · min^{-1} · 1.73 m^{-2}) of the newly gained glucose carbons are derived from acetone during DKA (0.02 × 0.8–1.0 ≈ 0.02 mmol · min^{-1} · 1.73 m^{-2}). This can be placed in perspective by recognizing that this contribution is ~50% as much glucose as alanine contributes during DKA.[24]

In addition to acetol and PPD, pyruvaldehyde also may be derived from acetone.[5] Pyruvaldehyde was the favored glucose precursor at a time when metabolic pathways were virtually unknown.[26] We have been unable to detect pyruvaldehyde in patients with DKA. Nonetheless, we showed that part of the acetone produced by patients in DKA was converted to glucose. The most likely pathway involved acetone → acetol → PPD → pyruvate → oxalacetate → phosphoenolpyruvate → glucose. Glucose production from acetone may have occurred from pyruvaldehyde → glucose.[5]

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