Renal substrate exchange and gluconeogenesis in normal postabsorptive humans

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RELEASE OF GLUCOSE BY THE KIDNEY has been reported to be accounted for nearly 30% of systemic glucose release. Renal substrate exchange and gluconeogenesis in normal postabsorptive humans. Am J Physiol Endocrinol Metab 282: E428–E434, 2002. First published October 23, 2001; 10.1152/ajpendo.00116.2001.—Release of glucose by the kidney in postabsorptive normal humans is generally regarded as being wholly due to gluconeogenesis. Although lactate is the most important systemic gluconeogenic precursor and there is appreciable net renal lactate uptake, renal lactate gluconeogenesis has not yet been investigated. The present studies were therefore undertaken to quantify the contribution of lactate to renal gluconeogenesis and the role of the kidney in lactate metabolism. We determined systemic and renal lactate conversion to glucose as well as renal lactate net balance, fractional extraction, uptake, and release in 24 postabsorptive humans by use of a combination of isotopic and renal balance techniques. For comparative purposes, accumulated similar data for glutamine, alanine, and glycerol are also reported. Systemic lactate gluconeogenesis (1.97 ± 0.12 μmol·kg⁻¹·min⁻¹) was about threefold greater than that from glycerol, glutamate, and alanine. The sum of gluconeogenesis from these precursors, corrected for tricarboxylic acid (TCA) cycle carbon exchange, explained 34% of systemic glucose release. Renal lactate uptake (3.33 ± 0.28 μmol·kg⁻¹·min⁻¹) accounted for nearly 30% of its systemic turnover. Renal gluconeogenesis from lactate (0.78 ± 0.10 μmol·kg⁻¹·min⁻¹) was 3.5, 2.5, and 9.6-fold greater than that from glycerol, glutamate, and alanine. The sum of renal gluconeogenesis from these precursors equaled ~40% of the sum of their systemic gluconeogenesis. When the isotopically determined rates of systemic and renal gluconeogenesis were corrected for TCA cycle carbon exchange, gluconeogenesis from these precursors accounted for 43% of systemic glucose release and 89% of renal glucose release. We conclude that 1) in postabsorptive normal humans, lactate is the dominant precursor for both renal and systemic gluconeogenesis; 2) the kidney is an important organ for lactate disposal; 3) under these conditions, renal glucose release is predominantly, if not exclusively, due to gluconeogenesis; and 4) liver and kidney are similarly important for systemic gluconeogenesis.

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METHODS

Subjects

Informed written consent was obtained from 49 normal volunteers after the protocol had been approved by The University of Rochester Institutional Review Board. The subjects (29 men, 20 women) were 30 ± 1 yr of age (range 20–51 yr), had a body mass index of 24.3 ± 0.5 kg/m² (range 18–33 kg/m²), and had normal physical examinations, routine laboratory tests, and glucose tolerance (World Health Organization criteria) (54). In addition, they had no family history of diabetes mellitus and were not taking any medications known to affect glucose metabolism. For 3 days before the study, all subjects had been on a weight-maintaining diet containing ≥200 g of carbohydrate and had abstained from alcohol.

Protocol

Subjects were admitted to the University of Rochester General Clinical Research Center between 6:00 and 7:00 PM the evening before experiments. They consumed a standard meal between 6:30 and 8:00 PM (10 kcal/kg; 50% carbohydrate, 35% fat, 15% protein) and fasted thereafter until experiments were completed.

At ~5:30 AM, an antecubital vein was cannulated, and a primed continuous infusion of [6-3H]glucose (~25 μCi, ~0.25 μCi/min) was begun in all subjects (n = 49). In addition, either [U-14C]glutamine (~20 μCi, ~0.20 μCi/min, n = 37) or [U-14C]glycerol (~20 μCi, ~0.20 μCi/min, n = 10) and either [3-13C]lactate (~1,300 μmol, ~13 μmol/min, n = 24) or [3-13C]alanine (~2,000 μmol, ~20 μmol/min, n = 10) were started. All radioactive isotopes were obtained from Amer sham Biosciences (Arlington Heights, IL), and all stable isotopes were obtained from Cambridge Isotope Laboratories (Andover, MA). Seventeen subjects simultaneously received [3-13C]lactate and [U-14C]glutamine isotopes, five subjects simultaneously received [3-13C]lactate and [U-14C]glycerol isotopes, and two subjects received only [3-13C]lactate. Eight subjects simultaneously received [U-14C]glutamine and [3-13C]alanine isotopes, and 12 subjects received [U-14C]glu tamine only. Two subjects simultaneously received [U-14C] glycerol and [3-13C]alanine isotopes, and three subjects received [U-14C]glycerol only. Some of the results of glutamine (n = 32) and alanine (n = 6) data have been previously reported (34, 35, 47).

At ~8:00 AM, an infusion of p-aminohippuric acid (12 mg/min) was started for determination of renal blood flow. Between 8:00 and 9:00 AM, a renal vein was catheterized through the right femoral vein under fluoroscopy, and the position of the catheter tip was ascertained by injecting a small amount of iodinated contrast material. The catheter was then continuously infused with saline (heparinized at 5.6 U/min) to maintain patency. At ~9:00 AM, a dorsal hand vein was cannulated and kept in a thermoregulated Plexiglas box at 65°C for sampling arterialized venous blood (5). Starting at ~10:00 AM, after allowing 4 h to achieve isotopic steady state, three blood samples were collected simultaneously from the dorsal hand vein and the renal vein at 30-min intervals (240, 270, 300 min) for determination of glucose, lactate, glycerol, glutamine, and alanine concentrations and their 3H and 14C specific activities (SA) or 13C enrichments and for determination of p-aminohippuric acid concentrations.

Analytical procedures. Blood samples were collected for glucose, lactate, glycerol, glutamine, and alanine concentrations and SA or enrichments in oxalate-fluoride tubes. Whole blood glucose was immediately determined in triplicate with a glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH). For high-performance liquid chromatography (HPLC) analysis of plasma alanine and glutamine concentrations as well as [14C]glutamine SA, an internal standard (25 nmol p-fluorophenylalanine) was added to 4.00 ml of plasma; the pH was adjusted to 4.80–5.00, and samples were frozen for later analysis as described previously (29). For other determinations, samples were placed immediately in a 4°C ice bath, and plasma was separated within 30 min by centrifugation at 4°C. Plasma [3H]- and [14C]glucose SA as well as [14C]glutamine SA were determined in duplicate by HPLC (39). [14C]glucose and [13C]alanine enrichments were determined in duplicate by selected ion monitoring gas chromatography-mass spectroscopy (GC-MS) of the acetylbutylibor onate (glucose) or t-butyldimethylsilyl (alanine) ester derivatives (44, 51). Some of the [13C]glucose enrichments in our lactate studies were measured by GC combustion isotope ratio mass spectrometry (Hewlett-Packard 5890, Europa spectrometer 20–20) because of low plasma glucose enrichments (3). Plasma [13C]lactate enrichments were determined in duplicate by ion monitoring GC-MS of the bis-trimethylsilyl derivates (53). Plasma p-aminohippuric acid concentrations were measured by a colorimetric method (6), and plasma lactate and glycerol concentrations were measured by standard microfluorometric assays (32, 52).

Calculations

Assumptions and methodological limitations of the combined net balance and isotopic approach for determining glucose release and gluconeogenesis by the kidney have been previously discussed in detail (24, 36, 47). Arterial and renal venous [3H]glucose, [14C]glutamine, and [14C]glycerol specific activities and [13C]lactate and [13C]alanine enrichments at 240, 270, and 300 min were not statistically significantly different from one another (ANOVA), consistent with isotopic steady state having been achieved. However, isotopic steady state was apparently not achieved for [13C]- and [14C]glucose, as evidenced by the fact that values at 240 min were significantly different from those at 300 min (paired Student’s t-test). Consequently, we used non-steady-state equations for calculating systemic gluconeogenesis from the labeled precursors (13). Systemic (overall) release and uptake of glucose, lactate, glutamine, and alanine were determined with standard steady-state equations (53). Renal plasma flow (RPF) was determined by the p-aminohippuric acid clearance technique (6), and renal blood flow (RBF) was calculated as RPF/(1 – hematocrit). Renal glucose fractional extraction (FX) was calculated as: (arterial [6-3H]glucose SA × arterial glucose concentration – renal vein [6-3H]glucose SA × renal vein glucose concentration)/arterial [6-3H]glucose SA × arterial glucose concentration). Renal glucose uptake (RGU) was calculated as RBF × arterial glucose concentration × FX. Renal glucose net balance (NB) was calculated as RBF × (arterial glucose concentration – renal vein glucose concentration). Renal glucose release was calculated as RGU – NB (15). Analogous equations were used for renal net balance, uptake, and release of lactate, glutamine, and alanine, except that renal plasma flow was used for glycerol, glutamine, and alanine, because tissue exchange of these substrates occurs via plasma (14, 41). For lactate, blood flow was used; plasma values were corrected to whole blood val-
ues by multiplying by 0.86, because whole blood values are 86% of plasma values (1).

Renal lactate gluconeogenesis was calculated as [renal vein \(^{13}\)C glucose enrichment \times \text{renal vein glucose concentration} – \text{arterial \(^{13}\)C enrichment} \times \text{arterial glucose concentration} \times (1 – \text{\(^{3}\)H glucose FX})/\text{renal vein \(^{13}\)C lactate enrichment \times 2} \), i.e., the renal \(^{13}\)C glucose production divided by renal vein lactate \(^{13}\)C enrichment corrected for differences in carbons in glucose and lactate (18). Rates of renal gluconeogenesis from glycerol, glutamine, and alanine were calculated analogously. Because of carbon exchange in the TCA cycle, the isotopic method used underestimates gluconeogenesis from lactate, glutamine, and alanine by 15–50\% (33, 53).

To correct for an assumed underestimation of 25\%, isotopically determined rates of systemic and renal gluconeogenesis from lactate, glutamine, and alanine were multiplied by 1.33, i.e., 1/(1 – 0.25).

**Statistical Analysis**

Unless stated otherwise, data are expressed as means ± SE. Rates of systemic and renal gluconeogenesis from various substrates are given in glucose equivalents. The data were analyzed as obtained, without rerunning what in the past we had considered erroneous measurements (e.g., negative glucose fractional extractions) to avoid possible bias (23). Paired two-tailed Student’s \(t\)-tests were used to compare arterial and renal venous substrate concentrations and SA. Differences of various parameters of systemic and renal metabolism among lactate, glycerol, glutamine, and alanine were analyzed using analysis of variance followed by Scheffé’s post hoc test (55). A \(P\) value < 0.05 was considered statistically significant.

Table 1. Arterial values and arterial-renal venous differences of substrate concentrations and their SA/enrichments in postabsorptive healthy humans

<table>
<thead>
<tr>
<th>Glucose Conc, mM</th>
<th>(-60) min</th>
<th>(-30) min</th>
<th>0 min</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-v</td>
<td>4.57 ± 0.05</td>
<td>4.57 ± 0.05</td>
<td>4.57 ± 0.05</td>
<td>4.57 ± 0.05</td>
</tr>
<tr>
<td>([\text{(^{13})C}]\text{glucose Enr, APE})</td>
<td>0.68 0.39</td>
<td>0.68 0.39</td>
<td>0.68 0.39</td>
<td>0.68 0.39</td>
</tr>
<tr>
<td>Lactate Conc, (\mu)M</td>
<td>18 ± 3</td>
<td>25 ± 4</td>
<td>20 ± 2</td>
<td>21 ± 2</td>
</tr>
<tr>
<td>a-v</td>
<td>648 ± 29</td>
<td>615 ± 35</td>
<td>596 ± 29</td>
<td>619 ± 29</td>
</tr>
<tr>
<td>([\text{(^{13})C}]\text{lactate Enr, APE})</td>
<td>1.45 ± 0.20</td>
<td>1.54 ± 0.22</td>
<td>1.49 ± 0.21</td>
<td>1.49 ± 0.21</td>
</tr>
<tr>
<td>Glycerol Conc, (\mu)M</td>
<td>59 ± 15</td>
<td>62 ± 17</td>
<td>63 ± 17</td>
<td>63 ± 17</td>
</tr>
<tr>
<td>a-v</td>
<td>240 ± 94</td>
<td>345 ± 114</td>
<td>115 ± 86</td>
<td>233 ± 86</td>
</tr>
<tr>
<td>([\text{(^{14})C}]\text{glycerol SA, dpm/\mu mol})</td>
<td>261 ± 37</td>
<td>278 ± 38</td>
<td>269 ± 37</td>
<td>269 ± 37</td>
</tr>
<tr>
<td>a-v</td>
<td>7.0 ± 2.7</td>
<td>7.4 ± 2.9</td>
<td>6.5 ± 2.5</td>
<td>6.5 ± 2.5</td>
</tr>
<tr>
<td>Glutamine Conc, (\mu)M</td>
<td>30 ± 14</td>
<td>32 ± 5</td>
<td>38 ± 5</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>a-v</td>
<td>1,240 ± 76</td>
<td>1,298 ± 79</td>
<td>1,290 ± 77</td>
<td>1,290 ± 77</td>
</tr>
<tr>
<td>([\text{(^{14})C}]\text{glutamine SA, dpm/\mu mol})</td>
<td>62 ± 10</td>
<td>60 ± 12</td>
<td>59 ± 8</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>a-v</td>
<td>11 ± 5</td>
<td>11 ± 6</td>
<td>3 ± 8</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>Alanine Conc, (\mu)M</td>
<td>322 ± 20</td>
<td>303 ± 23</td>
<td>297 ± 22</td>
<td>307 ± 21</td>
</tr>
<tr>
<td>a-v</td>
<td>30 ± 14</td>
<td>32 ± 5</td>
<td>38 ± 5</td>
<td>33 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE. Conc, concentration; SA, specific activity; Enr, enrichment; a-v, arterial-venous; art, arterial; APE, atom % excess.
tive arterial values, indicating uptake of these substrates by the kidney. Renal FX of glucose, lactate, glycerol, glutamine, and alanine averaged 2.19 ± 0.21, 27.5 ± 1.9, 55.2 ± 3.5, 9.74 ± 0.68, and 9.63 ± 0.64%, respectively. Renal uptake of glucose, lactate, glycerol, glutamine, and alanine averaged 1.88 ± 0.17, 3.33 ± 0.28, 0.64 ± 0.07, 0.68 ± 0.05, and 0.35 ± 0.05 μmol·kg⁻¹·min⁻¹, respectively, and accounted for 16.4 ± 1.4, 26.7 ± 2.4, 32.4 ± 3.8, 13.0 ± 1.1, and 8.3 ± 1.1% of their systemic disposal.

Renal venous SA/enrichments of glucose (P < 0.001), lactate (P < 0.002), glycerol (P < 0.003), glutamine (P < 0.001), and alanine (P < 0.005) were significantly lower than arterial values, indicating that renal release of these substrates was occurring simultaneously with their renal uptake. Renal release of glucose, lactate, glycerol, glutamine, and alanine averaged 2.48 ± 0.17, 0.50 ± 0.15, 0.04 ± 0.02, 0.29 ± 0.03, and 0.35 ± 0.05 μmol·kg⁻¹·min⁻¹, respectively, and accounted for 21.4 ± 1.4, 4.4 ± 1.2, 2.3 ± 0.8, 5.7 ± 0.6, and 6.6 ± 1.6% of their systemic release.

**Systemic and Renal Lactate, Glycerol, Glutamine, and Alanine Gluconeogenesis**

Systemic gluconeogenesis from lactate, glycerol, glutamine, and alanine was similar to previously reported values (7, 15, 25, 42, 48) (Table 3). As expected, lactate was the most important systemic gluconeogenic precursor, being about threefold greater than that from glycerol, glutamine, and alanine, each of which averaged ~0.6 μmol·kg⁻¹·min⁻¹ (all P < 0.001). Together, gluconeogenesis from these substrates accounted for 34% of overall glucose release when uncorrected for TCA cycle carbon exchange.

For renal gluconeogenesis, lactate was also the most important precursor. Production of glucose from lactate was 4.7-, 2.5-, and 9.6-fold greater than that from glycerol, glutamine, and alanine, respectively (all P < 0.001). The sum of gluconeogenesis from these precursors, uncorrected for TCA cycle carbon exchange, accounted for ~70% of renal glucose release. The sum of their renal gluconeogenesis equaled nearly 40% of the sum of their systemic gluconeogenesis.

**DISCUSSION**

The principal findings of the present studies are 1) that in postabsorptive normal humans, lactate is the dominant precursor for both renal and systemic gluconeogenesis, 2) that, on the assumption that 50% of endogenous glucose release was due to gluconeogenesis, the sum of systemic gluconeogenesis from lactate, glycerol, glutamine, and alanine, after correction for values (7, 15, 25, 42, 48) (Table 3). As expected, lactate was the most important systemic gluconeogenic precursor, being about threefold greater than that from glycerol, glutamine, and alanine, each of which averaged ~0.6 μmol·kg⁻¹·min⁻¹ (all P < 0.001). Together, gluconeogenesis from these substrates accounted for 34% of overall glucose release when uncorrected for TCA cycle carbon exchange.

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**DISCUSSION**

The principal findings of the present studies are 1) that in postabsorptive normal humans, lactate is the dominant precursor for both renal and systemic gluconeogenesis, 2) that, on the assumption that 50% of endogenous glucose release was due to gluconeogenesis, the sum of systemic gluconeogenesis from lactate, glycerol, glutamine, and alanine, after correction for
TCA cycle carbon exchange, could account for nearly all of systemic gluconeogenesis, 3) that the sum of renal gluconeogenesis from these precursors could account for nearly all renal glucose release, 4) that renal gluconeogenesis accounts for nearly 40% of systemic gluconeogenesis, and finally 5) that the kidney is an important organ for lactate and glycerol disposal.

In the present studies, with values uncorrected for TCA cycle carbon exchange, systemic lactate gluconeogenesis accounted for ~15% of systemic glucose release, whereas systemic gluconeogenesis from glycerol, glutamine, and alanine each accounted for ~5–6% of systemic glucose release, similar to previous reports (7, 15, 25, 42, 48). Thus gluconeogenesis from these substrates could explain, at a minimum, approximately one-third of systemic glucose release. As indicated earlier, the isotopic method used to study gluconeogenesis underestimates conversion of lactate, glutamine, and alanine to glucose because of TCA cycle carbon exchange. This underestimate has been reported to be between 15 and 50% (33, 53). By multiplying the isotopically determined rates of systemic gluconeogenesis by 1.33 to correct for an assumed underestimate of 25%, the sum of lactate, glycerol, glutamine, and alanine gluconeogenesis would account for 43% of systemic glucose release.

This value is within the range of the contribution of systemic gluconeogenesis to systemic glucose release (36–55%) in postabsorptive humans, estimated with techniques using the mass isotopomer distribution analysis (26), deuterated water (30), and MNR measurements of hepatic glycogen depletion (40). From these data, one can estimate that, in postabsorptive humans, glucose production from lactate, glycerol, glutamine, and alanine could account for ≥78% (i.e., 43% × 1.33) and as much as 120% (i.e., 43% × 1.33 × 1.33) of overall systemic gluconeogenesis. It thus appears that, although amino acids other than glutamine and alanine may be converted to glucose by liver and kidney, their individual contribution to gluconeogenesis is normally quite small in the postabsorptive state. This conclusion is consistent with data indicating that most of the carbons of amino acids originating from proteolysis are transferred through plasma as glutamine and alanine (21).

Regarding renal gluconeogenesis, we found that lactate was also the most important precursor. Assuming the same factor as discussed to correct for renal TCA cycle carbon exchange, renal gluconeogenesis from lactate exceeded the sum of renal gluconeogenesis from glycerol, glutamine, and alanine. Together, gluconeogenesis from these substrates accounted for ~90% of renal glucose release. Given the limits of analytical precision in the methods we used, the fact that we did not measure gluconeogenesis from all amino acids and that we used a conservative value for correction of TCA cycle carbon exchange, our results are consistent with the view that renal glucose release is predominantly, if not exclusively, due to gluconeogenesis in healthy postabsorptive humans.

Of interest, renal gluconeogenesis from these substrates accounted for a weighted average of ~40% of their systemic gluconeogenesis. Because, as discussed earlier, these substrates represent most of the carbons used for gluconeogenesis, one may infer that kidney and liver account for nearly equal proportions of systemic gluconeogenesis in postabsorptive humans. It should be pointed out that our data apply only to the postabsorptive state and that the renal contribution to systemic gluconeogenesis might change under different conditions, i.e., diabetes, hypoglycemia, the postprandial state, acid-base disorders.

That lactate accounted for such a large proportion of renal glucose release in the present studies is not unexpected. The rate of gluconeogenesis from a substrate by the kidney depends on its rate of delivery, its uptake, and the efficiency of its conversion to glucose. Substrate delivery to the kidney in turn depends on the concentration of the substrate in the circulation and on the renal blood flow. In the present studies, plasma lactate concentrations were similar to those of glutamine and significantly greater than those of alanine and glycerol. Because lactate is transported through the circulation by whole blood whereas glutamine, alanine, and glycerol are all transported by plasma (14, 41), the delivery of lactate to the kidney was greater than that of the other substances. Renal carbon uptake from lactate, which reflects renal rates of delivery and renal fractional extraction, exceeded the sum of renal carbon uptake from glutamine, alanine, and glycerol.

Our net renal balance data for alanine, glycerol, and glutamine are in general agreement with previous reports (9, 12, 16, 31, 49, 50). Our data for renal lactate net uptake (~170 μmol/min) are essentially identical to those reported by Cersosimo and colleagues (9, 12) (~170 μmol/min). These net uptakes are much greater than those reported by Björkman et al. (4), Ekberg et al. (16), and Brundin and Wahren (6a) (~25 μmol/min). The reason for these differences is unclear; however, the 95% confidence limits for the net renal lactate uptake reported by Brundin and Wahren (6a) and Ekberg et al. (16) would include the mean values obtained by ourselves and Cersosimo and colleagues.

It is of note that the proportions of the different substrates taken up by the kidney used for gluconeogenesis were not significantly different from one another (P = 0.86, ANOVA). This suggests that renal substrate uptake was the main factor responsible for renal gluconeogenesis and that there may be no preferential intracellular use of substrates for gluconeogenesis by the kidney. This view is consistent with the fact that renal gluconeogenesis from individual substrates correlated significantly with renal uptake from respective substrates (r = 0.71, P < 0.001). Nevertheless, we wish to point out that these conclusions apply to the normal postabsorptive state. Dose response and hormonal perturbation experiments will be needed to determine whether alterations in substrate delivery and hormonal milieu preferentially affect renal gluconeogenesis from individual precursors.
Net balance measurements for the major renal gluconeogenic precursors (lactate, glutamine, and glycerol) were highly correlated with their isotopically determined rates of uptake \( (r = 0.80, P < 0.0001; r = 0.77, P < 0.0001; \text{and } r = 0.98, P < 0.0005) \). These observations are relevant to a potential limitation of using isotopes due to isotopic exchange. For example, a molecule of lactate could be converted to pyruvate with loss of label and then reconverted to lactate. In such a situation, there would be no net difference in lactate balance, but the loss of label would result in a lower venous lactate specific activity and radioactivity indicating renal uptake and production. Furthermore, our renal net balance measurements of lactate, glycerol, glutamine, and alanine indicate that these substrates could have accounted for \(~75\%\) of renal glucose release if one assumes that all net renal uptake of these substrates was used solely for gluconeogenesis. This is similar to the proportion of renal glucose release accounted for by isotopically determined rates of renal gluconeogenesis when corrected for TCA cycle carbon exchange \((~90\%)\). These observations suggest that isotopic exchange did not materially affect the interpretation of our data regarding the relative importance and contribution of individual gluconeogenic precursors.

Although renal uptake accounted for only a small proportion of the systemic disposal of alanine and glutamine \((~10\%)\), it did account for a considerable proportion of systemic lactate and glycerol disposal \((~25–30\%)\). Previous studies have shown that liver and kidney are the predominant sites for glycerol disposal in humans \((27)\). However, an important role of the kidney for lactate disposal has not been previously appreciated. This finding may be relevant to the increased propensity of people with chronic renal failure to develop lactic acidosis \((43)\) and hypoglycemia \((19, 20)\), since reduced renal lactate uptake could lead to lactate accumulation and decreased renal glucose release.

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REFERENCES


