Abnormal renal, hepatic, and muscle glucose metabolism following glucose ingestion in type 2 diabetes

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Submitted 29 January 2004; accepted in final form 3 August 2004

Meyer, Christian, Hans J. Woerle, Jean M. Dostou, Stephen L. Welle, and John E. Gerich. Abnormal renal, hepatic, and muscle glucose metabolism following glucose ingestion in type 2 diabetes. Am J Physiol Endocrinol Metab 287: E1049 –E1056, 2004. First published August 10, 2004; doi:10.1152/ajpendo.00041.2004.—Recent studies indicate an important role of the kidney in postprandial glucose homeostasis in normal humans. To determine its role in the abnormal postprandial glucose metabolism in type 2 diabetes mellitus (T2DM), we used a combination of the dual-isotope technique and net balance measurements across kidney and skeletal muscle in 10 subjects with T2DM and 10 age-, weight-, and sex-matched nondiabetic volunteers after ingestion of 75 g of glucose. Over the 4.5-h postprandial period, diabetic subjects had increased mean blood glucose levels (14.1 ± 1.1 vs. 6.2 ± 0.2 mM, P < 0.001) and increased systemic glucose appearance (100.0 ± 6.3 vs. 70.0 ± 3.3 g, P < 0.001). The latter was mainly due to ~23 g greater endogenous glucose release (39.8 ± 5.9 vs. 17.0 ± 1.8 g, P < 0.002), since systemic appearance of the ingested glucose was increased by only ~7 g (60.2 ± 1.4 vs. 53.0 ± 2.2 g, P < 0.02). Approximately 40% of the diabetic subjects’ increased endogenous glucose release was due to increased renal glucose release (19.6 ± 3.1 vs. 10.6 ± 2.4 g, P < 0.05). Postprandial systemic tissue glucose uptake was also increased in the diabetic subjects (82.3 ± 4.7 vs. 69.8 ± 3.5 g, P < 0.05), and its distribution was altered; renal glucose uptake was increased (21.0 ± 3.5 vs. 9.8 ± 2.3 g, P < 0.03), whereas muscle glucose uptake was normal (18.5 ± 1.8 vs. 25.9 ± 3.3 g, P = 0.16). We conclude that, in T2DM, 1) both liver and kidney contribute to postprandial overproduction of glucose, and 2) postprandial renal glucose uptake is increased, resulting in a shift in the relative importance of muscle and kidney for glucose disposal. The latter may provide an explanation for the renal glycogen accumulation characteristic of diabetes mellitus as well as a mechanism by which hyperglycemia may lead to diabetic nephropathy.

Liver; kidney; gluconeogenesis; meal

There is evidence that postprandial hyperglycemia is an independent risk factor for cardiovascular disease (21), the major cause of mortality in type 2 diabetes mellitus (T2DM) (45). Moreover, people with impaired glucose tolerance, who generally have normal fasting plasma glucose levels, have about a twofold increased risk of dying from cardiovascular disease (50). A key factor responsible for postprandial hyperglycemia in people with impaired glucose tolerance and T2DM is excessive release of glucose into the systemic circulation (44). This has generally been attributed exclusively to hepatic abnormalities [impaired suppression of glucose release and impaired stimulation of glucose uptake (44)], since this organ had been thought to be the sole source of glucose under most physiologic circumstances (10).

Recent studies, however, indicate that the human kidney normally accounts for ~20% of glucose release after an overnight fast (20). Moreover, in contrast to the liver, the kidney normally increases its release of glucose after glucose ingestion, so that renal glucose release actually exceeds hepatic glucose release for several hours (38). In patients with T2DM, glucose release by liver and kidney are both increased to a comparable extent after an overnight fast (42). Furthermore, both renal and hepatic glucose release are regulated by insulin (37), and it appears that both are resistant to suppression by insulin in T2DM (56). It is therefore not unreasonable to expect that, in T2DM, renal glucose release may be excessively increased after meal ingestion and thus be an important factor contributing to postprandial hyperglycemia.

In addition to excessive postprandial glucose release, the kidney may be involved in the abnormal postprandial glucose disposal found in T2DM. After an overnight fast, renal glucose uptake accounts for ~15% of overall tissue glucose uptake in nondiabetic volunteers (7, 41). In people with T2DM, renal glucose uptake has been reported to be increased (42). This increase in renal glucose uptake in T2DM was not merely due to the mass action effects of hyperglycemia but was also due to increased renal glucose fractional extraction (42). Should a similarly increased renal glucose fractional extraction persist after meal ingestion, the kidney would be a site of considerable glucose uptake. Such increased renal glucose uptake could provide an explanation for the paradoxical finding that, in poorly controlled T2DM, postprandial systemic glucose disposal is increased, whereas postprandial muscle glucose uptake is either normal or reduced (18, 19, 25). Moreover, it could provide an explanation for the accumulation of glycogen found in diabetic kidneys (2).

The present studies were therefore undertaken to determine the role of the kidney in the abnormal postprandial glucose metabolism in T2DM. For these purposes, we used a combination of the dual-isotope technique and net balance measurements across the kidney and skeletal muscle in 10 patients with T2DM and 10 nondiabetic controls before and after glucose ingestion.

METHODS

Subjects. Informed written consent was obtained from 20 subjects, 10 with T2DM (6 men and 4 women, Hb A1c 8.1 ± 0.4%) and 10 nondiabetic volunteers (5 men and 5 women), after the protocol had been approved by the University of Rochester Institutional Review Board. Diabetic and nondiabetic subjects were of similar age (52 ± 2
subjects and baseline data of 9 of the 10 diabetic subjects have been previously reported (38, 42, 56).

Calculations. Systemic appearance and systemic disappearance of glucose were determined with steady-state equations under basal conditions (57) and subsequently after glucose ingestion with the non-steady-state equations of DeBoo et al. (12), using a pool fraction of 0.65 and a volume of distribution of 200 ml/kg. The rate of appearance of the oral glucose in the systemic circulation was calculated from [6,6-D3]glucose data with the equation of Chiasson et al. (8). Endogenous glucose release was calculated as the difference between the overall rate of glucose appearance and the rate of appearance of exogenous glucose. Systemic tissue glucose uptake was calculated as total systemic glucose disappearance minus glucosuria. Glucosuria was calculated as the urinary glucose concentration × urinary volume/collection period. Because rates of glucosuria vary postprandially due to different degrees of hyperglycemia, only averages of systemic and renal tissue glucose uptake (see below) over the entire 4.5-h postprandial period are presented in RESULTS.

Net initial splanchnic glucose uptake of the ingested glucose was calculated as renal difference between the amount of glucose ingested and the total appearance of the ingested glucose in the systemic circulation during the 4.5-h postprandial period, assuming that absorption of the ingested glucose had been completed as has been reported by Radziuk et al. (47). Whole body glucose disappearance during the postprandial period was calculated as the sum of systemic glucose disappearance and net initial splanchnic glucose uptake of the ingested glucose.

Renal plasma flow (RPF) was determined by p-aminohippuric acid clearance technique (4), and renal blood flow (RBF) was calculated as RPF/(1 − hematocrit). Renal net balances of glucose were calculated as (arterial concentration − venous concentration) × RBF. Renal glucose fractional extraction (FX) was calculated as (arterial [6,6-D3]glucose specific activity × arterial glucose concentration) − (venous [6,6-D3]glucose specific activity × venous glucose concentration)/(arterial [6,6-D3]glucose specific activity × arterial glucose concentration). Renal glucose disappearance (RGD) was calculated as RBF × arterial glucose concentration × FX. Renal tissue glucose uptake (RTGU) was calculated as RGD × glucosuria. Renal tissue fractional glucose uptake was calculated as RTGU/(RBF × arterial glucose concentration). Glucosuria and RTGU derived from the ingested glucose were calculated as the product of their respective rates and the fraction of the arterial glucose derived from the ingested glucose. The latter was calculated as arterial [6,6-D3]glucose enrichment/[6,6-D3]glucose enrichment of the ingested glucose. Renal glucose release (RGR) was calculated as RGD − renal glucose net balance. Hepatic glucose release was calculated as the difference between endogenous glucose release and renal glucose release. After plasma lactate and glycerol concentrations had been converted to whole blood values by multiplying by 0.86 and 0.9, respectively (3, 14), renal net balances of alanine, lactate, and glycerol were calculated analogously to renal glucose net balance except that RPF was used for alanine, because its tissue exchange occurs via plasma (9).

Forearm balances of glucose, lactate, alanine, and glycerol were calculated analogously to their renal balances, except that FBF or plasma flow were used. Forearm data per 100 ml of tissue were converted to values per kilogram forearm muscle as previously described (24), assuming that 80% of the measured FBF perfused muscle and that muscle comprised 60% of the forearm volume. Assuming that forearm muscle was representative of muscle elsewhere in the body, these values were multiplied by total body skeletal muscle mass, which was calculated from midarm circumference and triceps skinfold thickness with the equation of Heymsfield (23). Muscle uptake of glucose derived from the ingested glucose was calculated as the product of overall muscle glucose uptake and the fraction of the arterial glucose derived from the ingested glucose.

β-Cell function was assessed using the homeostasis model assessment (HOMA) index of insulin secretion, calculated as SECR_{hom} =
insulin (pM) × 3.33/[Glc (mM) − 3.5], where insulin represents the average fasting plasma insulin concentration and Glc the average fasting plasma glucose concentration (34).

Statistical analysis. Data are given as means ± SE and were evaluated using unpaired two-tailed Student’s t-tests. Least squares linear regression was used to assess correlations. A P value of <0.05 was considered statistically significant.

RESULTS

Arterial concentrations of blood glucose and plasma insulin and glucagon. Diabetic subjects started with greater preprandial blood glucose concentrations (9.9 ± 1.1 vs. 4.7 ± 0.1 mM, P < 0.001) and had more prolonged and greater increases after glucose ingestion (Fig. 1). Accordingly, their mean blood glucose concentration during the 4.5-h postprandial period was increased more than twofold (14.1 ± 1.1 vs. 6.2 ± 0.2 mM, P < 0.001).

Despite being hyperglycemic and thus having a greater stimulus for insulin secretion, diabetic subjects had fasting plasma insulin concentrations similar to those of nondiabetic subjects (69 ± 7 vs. 56 ± 5 pM, P = 0.20). With HOMA analysis, this corresponded to a 67 ± 6% reduction in β-cell function. After glucose ingestion, plasma insulin increased more slowly and to a lower peak concentration in the diabetic subjects (166 ± 26 at 120 min vs. 325 ± 45 pM at 90 min, P < 0.02). Consequently, despite their prolonged hyperglycemia, diabetic subjects had mean plasma insulin levels during the postprandial period that were significantly reduced (129 ± 15 vs. 213 ± 28 pM, P < 0.02; Fig. 1).

Although hyperglycemia normally suppresses glucagon secretion (52), fasting plasma glucagon concentrations in diabetic subjects were similar to those of nondiabetic volunteers (74 ± 6 vs. 69 ± 5 ng/l, P = 0.55). During the postprandial period, mean plasma glucagon concentrations were greater in the diabetic subjects (67 ± 4 vs. 54 ± 4 ng/l, P < 0.05), implying that α-cell function is impaired in the postprandial as well as in the preprandial state in T2DM (Fig. 1). The abnormal postprandial plasma glucagon and insulin responses resulted in a markedly reduced plasma insulin-to-glucagon ratio (2.0 ± 0.3 vs. 4.2 ± 0.6 pm/ng, P < 0.01), which would be expected to increase hepatic glucose release (52).

Arterial substrate concentrations. Fasting plasma lactate concentrations were greater in diabetic subjects (1,154 ± 125 vs. 610 ± 30 μM, P < 0.01), whereas alanine (277 ± 30 vs. 228 ± 16 μM, P = 0.18) and glycerol concentrations (78 ± 7 vs. 74 ± 9 μM, P = 0.73) were not significantly different in both groups. During the postprandial period, diabetic subjects had greater mean plasma lactate (1,458 ± 150 vs. 786 ± 28 μM, P < 0.01) and glycerol concentrations (52 ± 9 vs. 32 ± 3 μM, P < 0.05), whereas their plasma alanine concentrations were similar to those of nondiabetic volunteers (322 ± 31 vs. 258 ± 18 μM, P = 0.10).

Despite the basal hyperglycemia, which should have reduced plasma FFA (6), fasting plasma FFA concentrations were similar in diabetic and nondiabetic subjects (777 ± 60 vs. 761 ± 96 μM, P = 0.89). After glucose ingestion, plasma FFA decreased in both groups, but mean levels were ~50% greater in diabetic subjects (428 ± 93 vs. 287 ± 31 μM, P = 0.21).

Systemic glucose release and systemic appearance of the ingested glucose. Before glucose ingestion, systemic glucose release (sum of hepatic and renal glucose release) was significantly greater in diabetic subjects (100.0 ± 6.3 vs. 70.0 ± 3.3 g, P < 0.001; Table 1, Fig. 2). Assuming complete absorption of the ingested glucose during the 4.5-h

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Subjects (n = 10)</th>
<th>Diabetic Subjects (n = 10)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Total systemic glucose release*</td>
<td>70.0±3.3</td>
<td>100.0±6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic appearance of ingested glucose*</td>
<td>53.0±2.2</td>
<td>60.2±1.4</td>
<td>&lt;0.02</td>
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<tr>
<td>Endogenous glucose release*</td>
<td>17.0±1.8</td>
<td>39.8±5.9</td>
<td>&lt;0.002</td>
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<tr>
<td>Hepatic, %</td>
<td>39.0±12.7</td>
<td>49.0±4.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Renal, %</td>
<td>61.0±12.7</td>
<td>51.0±4.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Whole body glucose disappearance*</td>
<td>91.9±2.3</td>
<td>110.5±4.7</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Net initial splanchnic glucose uptake*</td>
<td>22.0±2.2</td>
<td>14.8±1.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Systemic glucose disappearance*</td>
<td>69.9±3.6</td>
<td>95.7±5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucosuria*</td>
<td>0.2±0.1</td>
<td>13.4±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic tissue glucose uptake*</td>
<td>69.8±3.5</td>
<td>82.3±4.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Muscle, %</td>
<td>38.3±5.0</td>
<td>25.0±2.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Kidney, %</td>
<td>13.0±2.5</td>
<td>26.3±4.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Other, †%</td>
<td>48.7±3.6</td>
<td>48.7±3.4</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values are means ± SE. *g per 4.5 h; †total minus sum of initial splanchnic, muscle, and renal glucose uptake.
Renal and hepatic glucose release. Before glucose ingestion, diabetic subjects had greater renal (4.69 ± 0.69 vs. 1.12 ± 0.25 μmol·kg⁻¹·min⁻¹, \( P < 0.01 \)) and hepatic glucose release (11.5 ± 0.9 vs. 8.34 ± 0.34 μmol·kg⁻¹·min⁻¹, both \( P < 0.01 \); Fig. 3), consistent with a previous report (42).

After glucose ingestion, patterns of renal and hepatic glucose release were similar in both groups; renal glucose release increased to peaks at 30–90 min and remained above baseline for 2–3 h, whereas hepatic glucose release decreased immediately and remained suppressed during the entire postprandial period. However, in diabetic subjects, mean rates of renal glucose release were approximately twice as great as in nondiabetic subjects (4.68 ± 0.74 vs. 2.34 ± 0.54 μmol·kg⁻¹·min⁻¹, \( P < 0.03 \)), and mean rates of hepatic glucose release were approximately three times as great as in nondiabetic subjects (4.58 ± 0.82 vs. 1.45 ± 0.53 μmol·kg⁻¹·min⁻¹, \( P < 0.01 \)). Accordingly, during the 4.5-h postprandial period, diabetic subjects had 9 g greater glucose release by kidney (19.6 ± 3.1 vs. 10.6 ± 2.4 g, \( P < 0.05 \)) and 14 g greater glucose release by liver (20.2 ± 4.2 vs. 6.4 ± 2.1 g, \( P < 0.02 \)).

Systemic glucose disposal. Before glucose ingestion, systemic tissue glucose uptake (systemic glucose disappearance minus glucosuria: 15.4 ± 1.0 vs. 9.2 ± 0.5 μmol·kg⁻¹·min⁻¹, \( P < 0.001 \)) was significantly greater in diabetic subjects. Because glucose clearance, an index of the efficacy of glucose disposal in peripheral tissues, was not significantly reduced in diabetic subjects (1.69 ± 0.15 vs. 1.96 ± 0.09 ml·kg⁻¹·min⁻¹, \( P = 0.17 \)), these results suggest that the primary metabolic abnormality responsible for fasting hyperglycemia was increased systemic glucose release.

During the postprandial period, systemic glucose disappearance was nearly 40% increased in diabetic subjects (95.7 ± 5.2 vs. 69.9 ± 3.6 g, \( P < 0.001 \)). As a result, despite the decreased net initial splanchnic sequestration of the ingested glucose, whole body glucose disappearance, the sum of systemic glucose disappearance and net initial splanchnic glucose sequestration, was also increased in the diabetic subjects (110.5 ± 4.7 vs. 91.9 ± 2.3 g, \( P < 0.003 \)). When systemic glucose disappearance was corrected for glucosuria, tissue uptake of glucose from the systemic circulation was still greater in diabetic subjects (82.3 ± 4.7 vs. 69.8 ± 3.5 g, \( P < 0.05 \); Table 1). However, because diabetic subjects were markedly hyperglycemic, their postprandial systemic glucose clearance was significantly reduced (1.52 ± 0.20 vs. 2.66 ± 0.12 ml·kg⁻¹·min⁻¹, \( P < 0.001 \)).

Renal glucose uptake. Fasting (1.512 ± 132 vs. 1.414 ± 74 ml/min, \( P = 0.56 \)) and postprandial renal blood flows (1.477 ± 107 vs. 1.484 ± 60 ml/min, \( P = 0.95 \)) were not significantly different between the diabetic and nondiabetic subjects.

Renal tissue glucose fractional extraction before glucose ingestion was greater in diabetic subjects (2.65 ± 0.40 vs. 1.27 ± 0.24%, \( P < 0.02 \)). However, during the postprandial period, renal tissue glucose fractional extraction increased in nondiabetic subjects, but not in diabetic subjects, so that they no longer significantly different (2.07 ± 0.19 vs. 2.16 ± 0.44%, \( P = 0.86 \)).

Postabsorptive renal tissue glucose uptake (overall renal glucose net balance corrected for glucose release and glucosuria) was greater in diabetic subjects (4.41 ± 0.80 vs. 0.90 ± 0.16 μmol·kg⁻¹·min⁻¹) and accounted for a greater propor-

Fig. 2. Total, ingested, and endogenous glucose appearance in the systemic circulation after glucose ingestion in nondiabetic and diabetic subjects.

Fig. 3. Renal and hepatic glucose release after glucose ingestion in nondiabetic and diabetic subjects.
During the postprandial period, mean FBF increased ~10% in both groups and remained comparable. Mean muscle glucose fractional extraction in nondiabetic subjects increased about twofold to 6.20 ± 0.85% but only ~1.5-fold in diabetic subjects to 2.42 ± 0.18% (*P < 0.01). Nevertheless, due to their hyperglycemia, the diabetic subjects’ muscle glucose uptake was not significantly different from that in nondiabetic subjects (18.5 ± 1.8 vs. 25.9 ± 3.3 g, *P = 0.16). However, diabetic subjects’ muscle glucose uptake accounted for lesser proportions of systemic tissue glucose uptake (25.0 ± 2.7 vs. 38.3 ± 5.0%, *P < 0.05) and the disposal of the ingested glucose (11.4 ± 0.9 vs. 21.5 ± 3.4%, *P < 0.02; Tables 1 and 2).

Muscle net balances of gluconeogenic substrates. Before glucose ingestion, muscle net release of lactate (0.96 ± 0.27 vs. 0.80 ± 0.23 mmol·kg⁻¹·min⁻¹, *P = 0.71), alanine (1.00 ± 0.22 vs. 0.67 ± 0.18 mmol·kg⁻¹·min⁻¹, *P = 0.34), and glyceral (0.05 ± 0.02 vs. 0.01 ± 0.03 mmol·kg⁻¹·min⁻¹, *P = 0.37) was not significantly different in the two groups. During the postprandial period, muscle net release of lactate was greater in diabetic subjects (1.19 ± 0.29 vs. 0.36 ± 0.19 mmol·kg⁻¹·min⁻¹, *P < 0.05), whereas net releases of alanine (0.63 ± 0.15 vs. 0.48 ± 0.16 mmol·kg⁻¹·min⁻¹, *P = 0.58) and glyceral (0.02 ± 0.03 vs. 0.00 ± 0.02 mmol·kg⁻¹·min⁻¹, *P = 0.46) were comparable in both groups.

DISCUSSION

The present study demonstrates that abnormalities in kidney, liver, and muscle glucose metabolism are involved in the dysregulation of postprandial glucose homeostasis in patients with T2DM.

During the postprandial period, ~31 g more glucose reached the systemic circulation in the diabetic subjects. Consistent with previous reports (5, 18, 19, 25, 36, 44, 46), this was primarily due to impaired suppression of endogenous glucose release (~24 g) and to a lesser extent to reduced initial splanchnic glucose sequestration of the ingested glucose load (~7 g), as found in splanchnic balance studies using the hepatic venous catheter technique (16, 17, 32) and some (18, 19, 44), but not all, previous studies using the dual-isotope technique (5, 25, 36, 46). The increased postprandial endogenous glucose release, formerly thought to be solely of hepatic origin, may be due to the diabetic state.

Table 2. Disposition of 75-g ingested glucose in nondiabetic and diabetic subjects

<table>
<thead>
<tr>
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<th>Nondiabetic Subjects (n = 10)</th>
<th>Diabetic Subjects (n = 10)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Net initial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>splanchnic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose uptake</td>
<td>22.0 ± 2.2 (29.3 ± 2.9)</td>
<td>14.8 ± 1.4 (19.7 ± 1.8)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Muscle glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uptake</td>
<td>16.1 ± 2.5 (21.5 ± 3.4)</td>
<td>8.5 ± 0.6 (11.4 ± 0.9)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Renal tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose uptake</td>
<td>6.2 ± 1.4 (8.2 ± 2.0)</td>
<td>10.6 ± 1.4 (14.2 ± 2.0)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>0.1 ± 0.1 (0.1 ± 0.1)</td>
<td>6.5 ± 1.5 (8.7 ± 2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other*</td>
<td>30.6 ± 2.7 (40.8 ± 3.6)</td>
<td>34.6 ± 2.9 (46.1 ± 3.9)</td>
<td>&lt;0.39</td>
</tr>
</tbody>
</table>

Values are means ± SE in g/4.5 h; values in parentheses are % ingested glucose. *Total ingested minus sum of net initial splanchnic, muscle, and renal glucose uptake and glucosuria.

Table 3. Fasting and postprandial renal net balances of gluconeogenic substrates in nondiabetic and diabetic subjects

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Subjects (n = 10)</th>
<th>Diabetic Subjects (n = 10)</th>
<th>P</th>
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<tbody>
<tr>
<td>Renal glucose net balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>−0.22 ± 0.14</td>
<td>−0.29 ± 0.51</td>
<td>=0.90</td>
</tr>
<tr>
<td>Postprandial*</td>
<td>−0.15 ± 0.29</td>
<td>0.37 ± 0.30</td>
<td>=0.28</td>
</tr>
<tr>
<td>Renal lactate net uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>1.65 ± 0.15</td>
<td>3.03 ± 0.76</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Postprandial*</td>
<td>2.07 ± 0.21</td>
<td>4.22 ± 0.73</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Renal glyceral net uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>0.58 ± 0.06</td>
<td>0.62 ± 0.12</td>
<td>=0.78</td>
</tr>
<tr>
<td>Postprandial*</td>
<td>0.29 ± 0.02</td>
<td>0.47 ± 0.11</td>
<td>=0.15</td>
</tr>
<tr>
<td>Renal alanine net release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>0.10 ± 0.04</td>
<td>0.34 ± 0.07</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Postprandial*</td>
<td>0.19 ± 0.08</td>
<td>0.33 ± 0.11</td>
<td>=0.36</td>
</tr>
</tbody>
</table>

Values are means ± SE in mmol·kg⁻¹·min⁻¹. *Average during the 4.5-h postprandial period.
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POSTPRANDIAL ORGAN GLUCOSE KINETICS IN T2DM

origin, was due to increased glucose release by both kidney and liver. The kidney accounted for ~9 g or 40% of the increased postprandial endogenous glucose release.

Several possible mechanisms could explain the excessive postprandial glucose release by liver and kidney. First, in T2DM, glucose overproduction predominantly involves gluconeogenesis in the postabsorptive state (33, 53), and increases in both renal and hepatic gluconeogenic enzyme activity have been found in experimental diabetic animals (30, 43). Presumably, this increased enzymatic activity could persist in diabetic patients after meal ingestion. Second, insulin suppresses both hepatic and renal glucose release (7, 37). Therefore, the reduced postprandial insulin secretion and the insulin resistance characteristically found in T2DM also probably played a role.

Third, FFA, whose postprandial plasma concentrations were ~50% greater in diabetic subjects, may have contributed, since FFA have been shown to stimulate gluconeogenesis in liver and kidney (28, 55). Finally, in vitro studies indicate that an increased availability of gluconeogenic precursors increases both hepatic and renal gluconeogenesis to a comparable extent (22). Our laboratory (41) previously reported that, in postabsorptive nondiabetic volunteers, liver and kidney account for ~60 and 40%, respectively, of systemic gluconeogenesis from both lactate and glycerol, whereas the liver is almost exclusively responsible for alanine gluconeogenesis. In the present study, plasma lactate and glycerol, but not alanine, were increased in diabetic subjects. Thus, by extrapolation from the above data in postabsorptive nondiabetic volunteers, postprandial renal and hepatic glucose release in diabetic subjects would be expected to increase by 40 and 60%, respectively, i.e., essentially identical to the increases actually observed.

Normally, renal glucose release is largely, if not exclusively, due to gluconeogenesis (20). One would therefore expect that the increased renal glucose release in T2DM subjects would result mainly from increased gluconeogenesis. In the present studies, the sum of net renal uptake of lactate, alanine, and glycerol was approximately twofold greater in diabetic subjects during the postprandial period than was their renal glucose release. Nevertheless, net substrate balance could account for only ~5.4 of the ~9.0 g increased renal glucose release if these substrates were used wholly for gluconeogenesis. These observations raise the possibility that the increased postprandial renal glucose release found in diabetic subjects might have involved glycolysis. It should be noted, however, that we did not determine renal uptake of glutamine, another important renal gluconeogenic precursor (41), and that our renal net balance measurements underestimated true renal uptake of gluconeogenic precursors to the extent that they were simultaneously released. Moreover, due to the methodological limitations in the precise quantification of renal substrate fluxes, it is possible that renal uptake of gluconeogenic precursors was underestimated or that renal glucose release was overestimated in the diabetic subjects. It therefore remains unclear whether the diabetic subjects’ increased postprandial renal glucose release was attributable exclusively to increased gluconeogenesis or to both increased gluconeogenesis and glycolysis.

Most previous studies have found that, in T2DM, postprandial systemic tissue glucose uptake is increased but that muscle glucose uptake is either normal (18, 19) or reduced (25). These observations therefore suggest that, in T2DM, there is a redistribution of glucose disposal such that muscle may play a proportionately lesser role in postprandial glucose disposal and that other tissues may compensate for reduced muscle glucose uptake. The kidney appeared to be a likely candidate for this because, in T2DM, postabsorptive renal glucose uptake is increased not merely due to the mass action effects of hyperglycemia but also because of increased renal glucose fractional extraction (42).

The present studies clearly confirmed this suspicion. Over the postprandial period, ~13 g more glucose was taken up from the systemic circulation by tissues in diabetic subjects. Approximately 85% of this (~11.2 g) was accounted for by increased renal glucose uptake. As a consequence, the renal contribution to postprandial systemic tissue glucose disposal was approximately twofold greater in diabetic subjects (26.3 ± 4.7 vs. 13.0 ± 2.5%, P < 0.03). Because the diabetic subjects’ renal blood flow and renal glucose fractional extraction were normal in the postprandial state, the mass action effects of hyperglycemia wholly accounted for their increased renal glucose uptake. In contrast to the kidney, muscle glucose uptake, although not significantly different in absolute terms in both groups, accounted for a lesser proportion of postprandial systemic tissue glucose disposal in the diabetic subjects (25.0 ± 2.7 vs. 38.3 ± 5.2%, P < 0.05). Our findings therefore suggest that the distribution of postprandial systemic tissue glucose uptake is abnormal in poorly controlled T2DM, whereby the kidney partially compensates for the relatively reduced glucose uptake by skeletal muscle (see Table 1).

Although the present studies do not provide insight into the fate of glucose taken up by the kidney, there are several potential explanations for the excessive renal glucose utilization in T2DM. Diabetes is generally associated with increased tubular reabsorption of sodium (13, 29, 54), which is largely dependent on the activity of Na⁺/K⁺-ATPase and thus energy requiring (49). In streptozotocin-induced diabetic rats, increased activity of Na⁺/K⁺-ATPase has been found in the thick ascending limb of Henle’s loop and the cortical and medullary collecting tubules (26), i.e., nephron segments that have high activities of glycolysis (49). In addition, increased activities of Na⁺/K⁺/glucose cotransporter have been found in proximal tubules of streptozotocin-induced diabetic rats that were linked to the stimulation of the Na⁺/glucose cotransporter by hyperglycemia (27). Although proximal tubules usually have little glycolytic activity (49), it is possible that hyperglycemia also stimulates the Na⁺/glucose cotransporter located in the outer medulla (51), where the glycolytic activity is high (49). Thus the increased renal glucose uptake that we observed in the diabetic subjects might have been used for glycolysis to meet the increased renal energy demand. Moreover, although the normal kidney contains negligible amounts of glycogen, there is excessive glycogen accumulation in the kidney of diabetic humans (2). The increased renal glucose uptake in our diabetic subjects may therefore explain this phenomenon. Finally, some of the excessive glucose taken up by the kidney in our diabetic subjects might have entered pathways that have been implicated in the development of diabetic nephropathy, i.e., the polyol pathway, the hexosamine pathway, formation of diacylglycerol and activation of protein kinase C, or nonenzymatic glycosylation of renal proteins (15, 48).

As with all studies, certain limitations of the methods employed need to be taken into consideration.
First, because renal blood flow is high, analytic imprecision in measuring relatively small arterial-renal venous differences in substrate and tracer concentrations can lead to substantial errors in calculating renal (and hepatic) fluxes, as discussed in detail elsewhere (20).

Second, with regard to renal and muscle fluxes, a potential source of imprecision might have been the use of the “hot-hand technique” to obtain arterialized venous blood as opposed to the use of arterial blood, since there might have been venous contamination. In our studies, oxygen saturation in arterialized venous blood samples exceeded 90%, indicating little or no contamination. Nevertheless, glucose concentrations have been found to be slightly lower in arterialized venous blood than in arterial blood in some (31, 35) but not all studies (1), the weighted average difference being ~1.5 mg/dl. If this were the case in the present study, postprandial glucose uptake by kidney and muscle would have been underestimated by ~6 and 5 g, respectively, in both groups. As a result, the contributions of kidney and muscle to postprandial tissue glucose uptake of the ingested glucose would have increased from ~8 to ~13% and from ~22 to ~26% in the nondiabetic subjects and from ~14 to ~18% and from ~11 to ~14% in the diabetic subjects. Of note, underestimation of arterial blood glucose concentrations due to the hot-hand technique would not have affected renal glucose release, since glucose specific activities, which nearly exclusively determine renal glucose release, are identical in arterialized venous and arterial blood (1).

Furthermore, there might have been imprecision in renal and muscle glucose fluxes during the postprandial period due to non-steady-state conditions, since the Fick principle, on which these measurements are based, assumes a steady state. However, in both diabetic and nondiabetic subjects, blood glucose concentrations at the end of the 270-min postprandial period were similar to those before glucose ingestion, so that imprecision in glucose fluxes during rising blood glucose concentrations was cancelled out by those during falling blood glucose concentrations. The precision of mean and cumulative glucose fluxes across kidney and muscle during the postprandial period was therefore probably very little affected by non-steady-state conditions. With regard to the kidney, it should also be pointed out that the transit time of blood across this organ is only a few seconds because of its high blood flow (39), so that there is probably very little imprecision in renal flux measurements throughout the postprandial period as a result of systemic non-steady-state conditions.

Finally, a limitation of our studies might have been the use of [6,6-2H2]glucose in the oral glucose solution for determination of the rate of appearance of the ingested glucose in the systemic circulation. [6,6-2H2]glucose retains its label during systemic circulation. [6,6-2H2]glucose retains its label during glycogenolysis. Because glucose ingestion does not totally suppress glycogenolysis, glycogen synthesis and glycogenolysis may potentially occur simultaneously, or glycogen labeled immediately following meal ingestion can subsequently be degraded. Consequently, hepatic glucose release resulting from glycogen cycling of the labeled ingested glucose would be erroneously viewed as continued systemic glucose appearance of the ingested glucose, not as hepatic glucose release. Thus hepatic glucose overproduction in the diabetic patients might have been underestimated to the extent that hepatic glycogen cycling was increased. However, Butler and Rizza (5) demonstrated that hepatic glycogen cycling of ingested glucose was similar in diabetic and nondiabetic subjects using a meal that contained both [2-3H]glucose (an isotope that extensively detritiates during hepatic glucose cycling) and [6-2H]glucose (an isotope that is not detritiated during hepatic glucose cycling).

Given the aforementioned potential limitations of the precision of our measurements, data involving renal, muscle, and hepatic fluxes including differences between nondiabetic and diabetic subjects should not be considered strictly quantitative. In all likelihood, however, these limitations applied similarly to both groups so that only more “noise” was introduced in the differences between the diabetic and nondiabetic subjects. As this would have diminished statistical significance, our findings can be considered quite robust.

In conclusion, the present studies indicate that, in patients with T2DM, 1) both liver and kidney contribute to the postprandial overproduction of glucose; 2) postprandial renal glucose uptake is increased, resulting in a shift in the relative importance of muscle and kidney for glucose disposal; and 3) increased postprandial glucose uptake by the kidney could provide an explanation for the renal glycogen accumulation characteristic of diabetes mellitus as well as a mechanism by which hyperglycemia may lead to diabetic nephropathy.

ACKNOWLEDGMENTS

We thank Becky Miller for excellent editorial assistance and the nursing and laboratory staff of the General Clinical Research Center for superb help. Dr. H. J. Woerle is now located at Ludwig-Maximilians-University of Munich, Munich, Germany. Dr. J. Dostou is now located at University of North Carolina, Chapel Hill, NC.

GRANTS

The present work was supported in part by Division of Research Resources-GCRC Grant SM01-RR-00044, National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-20411, and an American Diabetes Association Career Development Award to C. Meyer.

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