Gluconeogenesis in moderately and severely hyperglycemic patients with type 2 diabetes mellitus

GUENTHER BODEN,² XINHUA CHEN,¹ AND T. PETER STEIN²
¹Division of Endocrinology/Diabetes/Metabolism and the General Clinical Research Center, Temple University Hospital, Philadelphia, Pennsylvania 19140; and the ²Department of Surgery, University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine, Stratford, New Jersey 08084

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Gluconeogenesis in moderately and severely hyperglycemic patients with type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 280: E23–E30, 2001.—We tested the generally accepted concept that increased gluconeogenesis (GNG) and endogenous glucose production (EGP) are the main reasons for postabsorptive hyperglycemia in patients with type 2 diabetes mellitus (T2DM). GNG was measured with the ²H₂O method by use of both the C5-to-C2 ratio (C5/C2, with gas chromatography-mass spectrometry) and the C5-to-2H₂O ratio (C5/2H₂O, with isotope ratio mass spectrometry), and EGP was measured with 3-[¹⁴C]glucose in 27 patients with T2DM [13 with fasting plasma glucose (FPG) >10 mM and 14 with FPG <10 mM] and in 7 weight- and age-matched nondiabetic controls. The results showed 1) that GNG could be determined accurately with ²H₂O by using either C5/C2 or C5/2H₂O; 2) that whereas after an overnight fast of 16 h, GNG was higher in the entire group of patients with T2DM than in controls (6.4 vs. 5.0 mol·kg⁻¹·min⁻¹; P < 0.02), GNG was within normal limits (less than the mean ± 2 SD of controls or <65.3%) in 11/14 (79%) patients with mild to moderate hyperglycemia (FPG <10 mM) and in 5/13 (38%) of patients with severe hyperglycemia (FPG 10–20 mM); 3) that elevated GNG in T2DM was associated with a 43% decrease in prehepatic insulin secretion, i.e., with hepatic insulin deficiency; and 4) that FPG correlated significantly with glucose clearance (insulin resistance) (r = 0.70) and with GNG (r = 0.50) or EGP (r = 0.45). We conclude 1) that peripheral insulin resistance is at least as important as GNG (and EGP) as a cause of postabsorptive hyperglycemia in T2DM and 2) that GNG and EGP in T2DM are increased under conditions of significant hepatic insulin deficiency and thus probably represent a late event in the course of T2DM.

endogenous glucose production; insulin resistance; prehepatic insulin secretion; deuterated water method

HYPERGLYCEMIA AFTER AN OVERNIGHT FAST is a major hallmark and an important diagnostic criterion of diabetes. Postabsorptive hyperglycemia of >7.8 mM in diabetic patients is generally believed to be due to increased endogenous glucose production (EGP), which in turn is believed to be caused by increased rates of gluconeogenesis (GNG) (7, 8, 26, 28, 32, 41). The validity of this widely accepted concept, however, can be questioned. First, the notion that postabsorptive EGP is uniformly elevated in hyperglycemic patients has recently come under attack (1, 17). Second, the data that were the basis for the thesis that patients with high fasting plasma glucose (FPG) had increased rates of GNG were obtained with methods that, for several reasons, did not allow quantitative measurements of GNG. Usually only one (or at most two) GNG precursor was used. To determine total GNG would have required extrapolation from the conversion to GNG from one to all precursors. This is difficult, because it has been shown that infusion of some precursors (for instance glycerol) decreased the fractional conversion of other precursors (for instance amino acids) (16, 38).

Another, more serious problem was that the hepatic GNG precursor specific activity was unknown, because the label was diluted in the oxaloacetate pool, which is shared by GNG and the tricarboxylic acid cycle (19). This usually resulted in a systematic underestimation of GNG (19). Recently, new methods have become available that for the first time have allowed quantitative in vivo determination of GNG in human subjects (13, 20, 22, 23, 33).

In the current study, we used the ²H₂O technique, which was recently developed and validated by Landau and colleagues (22, 23). Major advantages of this method are that it determines GNG from all precursors (including glycerol) and that it avoids the problems, related to unknown precursor specific activity in the liver, that have plagued all previous isotopic methods. We used this new method to examine the hypothesis that GNG was elevated in patients with type 2 diabetes (T2DM) and was responsible for their postabsorptive hyperglycemia. To this end, we measured GNG in 27 patients with T2DM fasted for 16 h who were subdivided into two groups, those who had either mild to moderate (<10 mM) or severe (>10 mM) postabsorptive hyperglycemia.

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In a separate study, designed to determine $^2$H enrichment in plasma water, the fast was extended to 24 h in 14 diabetic patients (7 with plasma glucose of $>10$ mM and 7 with plasma glucose of $<10$ mM) and in the 7 age- and weight-matched controls. Blood samples were collected at 16, 20, and 24 h for measurement of $^2$H enrichment of plasma water (Table 2).

### Analytical Procedures

**Determination of GNG.** This method depends on the incorporation of $^2$H from $^2$H$_2$O into glucose. After $^2$H$_2$O administration, $^2$H enrichment at the glucose carbon 5 ($C_5$) divided by $^2$H enrichment of plasma water or at the glucose carbon 2 ($C_2$) equals the fractional contribution of GNG to EGP. This is so because the conversion of every molecule of pyruvate to glucose involves addition of an H from body water to C2 of the intermediate phosphoenolpyruvate. This carbon becomes C5 of glucose (22, 23).

During conversion of glycerol to glucose, one H from body water is added to C2 of glyceraldehyde 3-phosphate during isomerization with dihydroxyacetone 3-phosphate. That carbon also becomes C5 of glucose. Thus enrichment in C5 of glucose reflects glucose production from pyruvate and glyceral, i.e., from all GNG precursors (22, 23). Therefore, the ratio of $^2$H labeling at C5 of glucose to plasma water is a measure of GNG relative to EGP.

$^2$H enrichment on C2 reflects glucose production from GNG and from glycolgenolysis (GL). This is so because one H from body water is added to C2 of glucose 6-phosphate when fructose 6-phosphate is converted to glucose 6-phosphate during GNG. Furthermore, glucose 6-phosphate, which is also formed as an intermediate during GL, equilibrates extensively with fructose 6-phosphate, resulting in the exchange of the H bound to C2 of the glucose 6-phosphate with that in body water. There is, however, no labeling at C5 of glucose.

### Table 2. $^2$H enrichment in plasma water

<table>
<thead>
<tr>
<th></th>
<th>16 h</th>
<th>20 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_2DM &gt;10$ mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(n = 7)$</td>
<td>$0.502 \pm 0.019$</td>
<td>$0.505 \pm 0.013$</td>
<td>$0.505 \pm 0.013$</td>
</tr>
<tr>
<td>$T_2DM &lt;10$ mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$(n = 7)$</td>
<td>$0.473 \pm 0.031$</td>
<td>$0.500 \pm 0.037$</td>
<td>$0.489 \pm 0.038$</td>
</tr>
<tr>
<td>Controls $(n = 7)$</td>
<td>$0.436 \pm 0.011$</td>
<td>$0.438 \pm 0.009$</td>
<td>$0.436 \pm 0.007$</td>
</tr>
</tbody>
</table>

Values are means ± SE.
Glucose. Therefore, the ratio of 2H labeling at C5 to C2 of glucose is a measure of GNG relative to EGP (22, 23). 2H enrichment of C5 and C2 was determined by gas chromatography-mass spectrometry (Hewlett-Packard 5890 MS, HP 5890 GC) as previously described (5). GNG (μmol·kg⁻¹·min⁻¹) was calculated by multiplying the ratio of C5 to 2H2O (C5/2H2O) or that of C5 to C2 (C5/C2) with EGP. GL was calculated as the difference between EGP and GNG. Thus GL is that part of glycogenolysis that becomes EGP.

Enrichment of 2H in plasma water was determined in all subjects with an isotope ratio mass spectrometer (PDZ Europa, London, UK) by use of an ABCA-G module and a standard curve with known enrichments ranging from 0.25 to 1.0%.

In the current study, GNG was determined with both C5/2H2O and C5/C2. Both methods gave similar results (Table 3). We are, therefore, presenting pooled data obtained with both methods.

**Glucose turnover.** Glucose turnover was determined with 3-[3H]glucose. 3-[3H]glucose was infused intravenously for 2.5 h starting with a bolus adjusted proportionally to the degree of hyperglycemia (40 μCi × mM glucose/5.5) (15), followed by continuous infusion of 0.4 μCi/min. Glucose was isolated from blood for determination of 3-[3H]glucose specific activity as previously described (36). Rates of total body glucose appearance (GAPA) and disappearance (GAD) were calculated using Steele’s equation for non-steady-state conditions (37). The rate of EGP was equal to GAPA, because no glucose was infused during GL. Therefore, the ratio of 2H labeling at C5 to C2 of glucose is a measure of GNG relative to EGP (22, 23). 2H enrichment of C5 and C2 was determined by gas chromatography-mass spectrometry (Hewlett-Packard 5890 MS, HP 5890 GC) as previously described (5). GNG (μmol·kg⁻¹·min⁻¹) was calculated by multiplying the ratio of C5 to 2H2O (C5/2H2O) or that of C5 to C2 (C5/C2) with EGP. GL was calculated as the difference between EGP and GNG. Thus GL is that part of glycogenolysis that becomes EGP.

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Glucose clearance rates were calculated as GAPA/FPG.

**C-peptide kinetics.** Approximately 1 wk before the studies, a 50-nmol intravenous bolus of biosynthetic human C-peptide (Eli Lilly, Indianapolis, IN) was administered to each subject after an overnight fast. Plasma C-peptide concentrations were then measured, and C-peptide kinetic parameters were calculated at frequent intervals for 3 h as described by Polonsky et al. (30).

**Insulin secretory rates.** The C-peptide kinetic parameters were used to calculate prehepatic insulin secretion rates (ISR) for each time interval between successive blood samples by deconvolution of peripheral C-peptide concentrations, according to Polonsky et al. (30) and Eaton et al. (11).

**Substrate and hormone analyses.** Plasma glucose was measured with a glucose analyzer (YSI, Yellow Springs, OH). C-peptide was determined by RIA (Linco, St. Charles, MO). Insulin was determined after deproteinization by RIA by use of an antiserum with minimal (<0.2%) cross-reactivity with proinsulin (Linco). Human growth hormone and glucagon were determined by RIA. Cortisol was measured with a kit (Diagnostic Products, Los Angeles, CA) and epinephrine with a 3H radioenzymatic assay (Amersham, Piscataway, NJ). Plasma free fatty acid (FFA) concentration was determined with a kit from Wako (Richmond, VA). Plasma glycerol, lactate, alanine, glutamine, glutamate, β-hydroxybutyrate (β-OHB), and acetoacetate (AcAc) were determined enzymatically.

### Statistical Analysis

All data are expressed as means ± SE. Statistical analysis was performed using the SAS program (SAS Institute, Cary, NC). ANOVA with repeated measures was used to determine the differences in GNG, GL, and EGP across time points. Pairwise comparison to each time point was then performed if overall comparison was statistically significant. Correlations between GNG and EGP or glucose were determined by least squares regression analysis.

### RESULTS

#### Effects of a 16-h Fast

Postabsorptive (16-h) plasma glucose concentrations were 10.6 ± 0.8 mM in patients with T2DM (n = 27, 14.2 ± 0.8 (range 10.2–19.3) mM and 7.2 ± 0.4 (range 4.7–9.9) mM, respectively, in patients with FPG >10 mM (n = 13) and <10 mM (n = 14)) and were 5.5 ± 0.2 (range 4.9–6.1) mM in controls (n = 7) (Fig. 1).

**GNG**

Rates of GNG were higher in patients with T2DM than in controls (60.4 ± 2.4% of EGP or 6.35 ± 0.25 μmol·kg⁻¹·min⁻¹ vs. 51.4 ± 2.6% or 5.0 ± 0.3 μmol·kg⁻¹·min⁻¹).
GL 

Rates of GL were 39.6 ± 2.4% of EGP (3.9 ± 0.3 μmol·kg⁻¹·min⁻¹) in patients with T2DM, 35.2 ± 3.3% (4.1 ± 0.3 μmol·kg⁻¹·min⁻¹) in the >10 mM glucose group, 43.7 ± 3.1% (3.8 ± 0.4 μmol·kg⁻¹·min⁻¹) in the <10 mM glucose group, and 48.6 ± 2.6% (4.8 ± 0.5 μmol·kg⁻¹·min⁻¹) in the controls. GL in all T2DM and in the >10 mM glucose group was significantly lower than GL in controls (P < 0.03).

EGP 

Rates of EGP were higher in the >10 mM glucose group than in the <10 mM glucose group (12.6 ± 1.2 vs. 8.6 ± 0.8 μmol·kg⁻¹·min⁻¹, P < 0.01) and in the controls (9.8 ± 0.6 μmol·kg⁻¹·min⁻¹, P < 0.05). The differences between all T2DM (10.5 ± 0.8 μmol·kg⁻¹·min⁻¹) and controls and between the <10 mM glucose and control group were not statistically significant.

FPG correlated significantly but modestly with EGP (r = 0.46, P < 0.01; Fig. 2).

Glucose Clearance 

Glucose clearance was used to estimate insulin sensitivity. Rates of glucose clearance were 1.12 ± 0.10, 0.90 ± 0.08, 1.33 ± 0.15, and 1.79 ± 0.10 ml·kg⁻¹·min⁻¹ in all T2DM, the >10 mM and <10 mM groups, and controls, respectively. All of these differences were highly significant (P < 0.01). Glucose clearance correlated closely with FPG (r = 0.70, P < 0.001; Fig. 2).

Hormones and Substrates 

All T2DM had significantly higher plasma insulin, growth hormones, cortisol, FFA, and ketone body levels than controls (Table 4). The >10 mM glucose group had significantly higher plasma insulin and ketone body levels than the <10 mM glucose group and significantly higher plasma insulin, glucagon, FFA, ketone bodies, and GNG precursor levels than the controls.

Elevated vs. Normal GNG 

To gain insight into factors responsible for the increased rates of GNG, we compared the 11 patients (8 from the >10 mM, 3 from the <10 mM group) who had GNG >65.3% (i.e., higher than the mean + 2 SD of controls) with the remaining 16 T2DM patients and with the 7 controls who had normal GNG. Compared with the 16 patients with normal GNG, the 11 patients with high GNG had significantly lower prehepatic ISR (101 ± 18 vs. 178 ± 32 μmol/min, P < 0.05) but the same glucose clearance (1.13 ± 0.12 vs. 1.14 ± 0.15 ml·kg⁻¹·min⁻¹; Fig. 3). They also had higher plasma β-OHB (323 ± 68 vs. 173 ± 32 μmol/l, P < 0.005) and total ketone body levels (393 ± 71 vs. 228 ± 46 μmol/l, P < 0.05) but comparable plasma AcAc (69 ± 10 vs. 55 ± 15 μmol) and FFA levels (638 ± 37 vs. 596 ± 46 μM) (Fig. 4). On the other hand, there were no significant differences in plasma glucagon (68 ± 6 vs. 67 ± 5 pg/ml) and in plasma epinephrine levels (18 ± 3 vs. 20 ± 3 pg/ml). These results indicated that high GNG in patients with T2DM was associated with hepatic insulin deficiency.
DISCUSSION

Can GNG be Accurately Quantitated in T2DM with $^2$H$_2$O?

To assess its role in the pathogenesis of elevated FPG in patients with T2DM, we measured GNG with the recently developed $^2$H$_2$O method (22, 23). This method determines GNG from all precursors (including glycerol) and avoids the problems related to unknown precursor specific activity in the liver that have previously prevented quantitative determination of GNG. The method has been extensively validated in normal subjects (5, 23) and has been used in pregnant women (18) and in patients with cirrhosis of the liver (29). So far, it has not been used in diabetic patients. In this study, GNG was determined in patients with T2DM and in nondiabetic controls by use of C5/C2 and C5/H2O. C5/C2 does not require steady-state conditions, only sufficient $^2$H enrichment to measure C5 and C2. C5/2H2O does need complete mixing of $^2$H and body water. This is obtained; 1 h after the last $^2$H2O ingestion (23). Not surprisingly, therefore, we found that $^2$H enrichment in plasma water did not change between 16 and 24 h, indicating that a steady state existed at 16 h (Table 2). Confirming a previous report from our laboratory, $^2$H enrichment on C2 of glucose and in plasma water was the same in nondiabetic subjects (5). In diabetic patients, $^2$H enrichment of plasma water was slightly but not significantly higher than that on C2.
resulting in GNG rates that were 3–5% higher when C5/C2 was used instead of C5/H2O (Table 2). Both methods can therefore be used to quantitate GNG in patients with T2DM. For this study, C5/C2 as well as C5/H2O was obtained for all data points, and the results were pooled.

GNG in T2DM

We found that patients with T2DM, as a group, had higher rates of GNG than controls (60.4 ± 2.4 vs. 51.4 ± 2.6%, P < 0.03). In one of the two other studies in which GNG was quantitatively determined [with 13C nuclear magnetic resonance spectroscopy (NMR)], Magnusson et al. (24) reported rates of GNG of 88 ± 2% of EGP in seven patients with T2DM (FPG 14.6 ± 1.2 mM) and of 70 ± 6% in five nondiabetic controls. Although both studies agreed that GNG was elevated in T2DM, the GNG values in the Magnusson study were higher than those in our study. The differences, however, were more apparent than real when the differences in methodology are considered. Magnuson et al. determined mean rates of GL and obtained GNG by subtraction of GL from EGP. There are several reasons why this method could underestimate GL and therefore overestimate GNG. 1) The NMR spectroscopy method does not detect renal GL. This may be inconsequential in nondiabetic subjects, whose kidneys contain only trivial amounts of glycogen (2). Patients with T2DM, however, accumulate glycogen in their kidneys and are able to produce glucose by GL (2). This alone could account for much of the difference between the two studies. 1 2) In the Magnusson study, liver glycogen concentrations were much lower in diabetic patients than in controls (131 vs. 282 mmol/l), possibly due to differences in prestudy food intakes. Because GL depends on glycogen levels (40), this could have been a reason for low GL and high GNG rates in the diabetic patients. 3) Magnuson et al. determined average rates of GL from changes in hepatic glycogen concentrations based on NMR measurements obtained between 4 and 22.5 h after the last meal. Therefore, to provide accurate rates of GL, the first NMR measurement needed to coincide with the peak of postmeal hepatic glycogen accumulation. If hepatic glycogen increased after the first NMR measurement (4 h after the meal), which may occur in diabetic patients who not infrequently have delayed absorption, GL would have been underestimated and GNG overestimated. 4) Liver volume (to calculate glycogen content from glycogen concentration) was determined once (14.5 h after the last meal). It was assumed that the decrease in liver volume [observed previously to be 23% over 67 h of fasting (33)]

was linear over time. It appears more likely, however, that liver glycogen decreases dose dependently, i.e., at a faster rate during the early hours of the fast than later (14). Assuming a linear decrease would therefore result in underestimation of the glycogen content and GL and overestimation of GNG during the initial 15 h of fasting. In another study, Tayek and Katz (39), using mass isotopomer [U-13C]glucose analysis, reported GNG rates of 48.8 ± 5.7% of EGP in nine patients with T2DM (FPG 11.8 ± 1.3 mM) and 46.6 ± 4.0% in eight controls (P < 0.05).

When we studied 27 patients with T2DM, it became apparent that there was considerable variation in their rates of GNG. For instance, GNG was elevated infrequently in patients with FPG <10 mM; in fact, only 1 of 14 (7%) had GNG exceeding the mean + 3 SD of controls, whereas 3 of 14 (21%) exceeded the mean ± 2 SD. Elevated GNG was more common in patients with more severe hyperglycemia (FPG >10 mM). Here 5 of 13 (38%) exceeded the mean ± 3 SD and 8 of 13 (61.5%) exceeded the mean ± 2 SD of controls. This also meant, however, that GNG remained within normal limits in more than one-third (5 of 13) of even severely hyperglycemic patients (FPG 10.2–19.3 mM). One patient in this group had discontinued his Glipizide medication only 1 day before being studied. It is, therefore, possible that this patient’s GNG (49.5%) might have been slightly higher had the drug been discontinued 2 days earlier. Thus, whereas there was a trend for GNG to rise with rising FPG levels, the correlation between GNG and FPG was modest (r = 0.50, P < 0.005).

GNG and Insulin

To learn why GNG was high in some diabetic patients but not in others, we compared the 11 patients with elevated GNG (> mean ± 2 SD of controls) with the remaining 16 patients who had normal GNG (Fig. 3). This comparison revealed that the patients with elevated GNG had similar plasma levels of the major GNG-promoting hormones and substrates, including glucagon, epinephrine, cortisol, FFA, and GNG precursors (lactate, alanine, glutamate, glutamine, and glycerol; Table 5). In addition, they were as insulin resistant (as judged by their glucose clearance) as the patients with normal GNG. Noteworthy, however, their livers were exposed to ~40% less insulin (as

| Table 5. Plasma GNG precursor levels in subjects with normal and high rates of GNG |
|-----------------|-----------|-------------|
| Normal GNG      | Controls  | T2DM        |
| (n = 7)         | (n = 16)  |
| Lactate         | 845 ± 74  | 1,148 ± 156 |
| Alanine         | 289 ± 21  | 412 ± 43    |
| Glutamate       | 89 ± 9    | 79 ± 10     |
| Glutamine       | 541 ± 36  | 478 ± 36    |
| Glycerol        | 116 ± 18  | 91 ± 10     |
| Total precursors| 1,832 ± 114| 2,208 ± 191|

High GNG T2DM  (n = 11)

Lactate         1,138 ± 148
Alanine         355 ± 29
Glutamate       91 ± 24
Glutamine       380 ± 52
Glycerol        84 ± 11
Total precursors 2,048 ± 158

Values are means ± SE. *P < 0.05 vs. controls.

1 For instance, if the kidneys contributed 25% of total EGP, as has been reported by Meyer et al. (25), and if 50% of this renal EGP was from GL (a reasonable assumption), then 1.39 μmol·kg⁻¹·min⁻¹ of a total EGP of 11.1 μmol·kg⁻¹·min⁻¹ in the Magnusson study (24) would have been renal GL. Hepatic plus renal GL would have been 2.7 μmol·kg⁻¹·min⁻¹, i.e., 24% of EGP, and GNG would have been 76%, the same as the 75% that we found in seven patients with comparable FPG after 24 h of fasting (this study).

2 The NMR spectroscopy method does not detect renal GL. This may be inconsequential in nondiabetic subjects, whose kidneys contain only trivial amounts of glycogen (2). Patients with T2DM, however, accumulate glycogen in their kidneys and are able to produce glucose by GL (2). This alone could account for much of the difference between the two studies.

3 It was assumed that the decrease in liver volume [observed previously to be 23% over 67 h of fasting (33)]
judged by a ~40% reduction in prehepatic ISR). This suggested that hepatic insulin deficiency was a major cause for the increased GNG in these patients, because insulin is known to suppress GNG (34), and insulin deficiency is known to increase gene transcription of at least three of the four key GNG enzymes (phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, and fructose 1,6-bisphosphatase) (12).

Insulin is also a powerful suppressor of ketone body formation (27). Presence of insulin deficiency in these patients was further supported by the finding that their plasma β-OHB levels were higher, whereas their FFA levels (i.e., the ketone body precursors) were similar compared with those of the diabetic patients with normal GNG.

**GNG and FPG**

Whether EGP (or GNG) is elevated in mildly to moderately hyperglycemic patients with T2DM has remained controversial. Older studies have frequently reported greatly increased rates of EGP, which has led to the conclusion that elevated levels of FPG in T2DM were primarily the result of increased EGP (3, 4, 10, 21). More recently, however, it has become clear that in most of these studies, EGP was overestimated in proportion to the degree of the patient’s hyperglycemia. The main reason for this was incomplete equilibration of the labeled and nonlabeled glucose in the expanded glucose pool. In studies in which an isotopic steady state was achieved, EGP was usually found to be elevated only in patients who had FPG of ≥10 mM (15, 17). In the current study, we used a primed-continuous trace infusion in which the prime dose was adjusted in proportion to the patient’s glucose concentration. This method has been shown to produce steady-state tracer-specific activities within 60 min, even in severely hyperglycemic patients (15).

Our results did not support the currently popular concept that EGP and GNG were primarily responsible for the fasting hyperglycemia >7.8 mM in patients with T2DM (28). Approximately 40% of patients with severe fasting hyperglycemia (10.2–19.3 mM) and all patients with FPG <10 mM had normal rates of EGP. In addition, neither EGP nor GNG correlated closely with FPG. In fact, the correlation coefficients of 0.46 and 0.50 suggested that not more than 20–25% of the hyperglycemia was due to increased EGP or GNG, respectively. On the other hand, of the eight patients in the group with high rates of GNG, six (75%) also had high rates of EGP.

Plasma glucose concentration is the result of glucose production and utilization. Because elevated glucose production did not seem to be predominantly responsible for the hyperglycemia, the data suggested that the elevated FPG had to be due also to impaired glucose disappearance, as had previously been suggested by others (6, 9). This notion was supported by a negative correlation (r = –0.70) between FPG and glucose clearance (Fig. 2).

It needs to be pointed out, however, that the patients in the >10 mM glucose group had not only grossly elevated plasma glucose but also abnormally high serum insulin levels, both of which should have depressed EGP (31, 35). The fact that in over 50% of these patients EGP was within normal limits instead of reduced indicated that these patients had hepatic as well as peripheral insulin resistance.

In summary, our data showed 1) that the deuterated water method (either C5/C2 or C5/H2O) can be used to accurately measure GNG in patients with T2DM; 2) that GNG was infrequently (~20%) elevated in patients with FPG <10 mM but was commonly elevated (~60%) in patients with FPG >10 mM; 3) that hepatic insulin deficiency seemed to be a major reason for increased GNG; and 4) that peripheral insulin resistance together with inappropriate glucose production caused the development of fasting hyperglycemia. On the basis of these findings, we conclude that the widely held concept that FPG of >7.8 mM is mainly due to increased EGP or GNG overemphasizes the importance of EGP/GNG and underemphasizes the importance of insulin resistance.

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