Relationship Between Hepatic Glucose Production and Fasting Plasma Glucose Concentration in Patients With NIDDM

Chii-Yuan Jeng, Wayne H-H. Sheu, Martin M-T. Fuh, Y-D. Ida Chen, and Gerald M. Reaven

This study was initiated to reevaluate the changes in basal hepatic glucose production (HGP) rate that occur in patients with non-insulin-dependent diabetes mellitus (NIDDM). Measurements were made in 51 volunteers: 18 with normal glucose tolerance and 33 with newly diagnosed NIDDM of varying degrees of severity. To avoid the methodological problems associated with quantifying HGP over short time periods, using non-steady-state isotopic kinetics, radiolabeled glucose was infused for a 12-h period, from 10 P.M. to 10 A.M. with HGP quantified from 9 to 10 A.M.. The results showed that fasting plasma glucose (FPG) concentration and HGP were significantly correlated (r = 0.68, P < 0.001) in patients with NIDDM. However, when the 33 patients with NIDDM were divided into three groups of 11 each on the basis of FPG concentration, it became clear that the relationship between FPG and HGP was complex. Thus, values for HGP in patients with NIDDM and FPG <180 mg/dl were not higher than in the normal population (1.67 ± 0.07 vs. 1.69 ± 0.04 mg·kg^{-1}·min^{-1}, NS). Significant increases (P < 0.01) in HGP above normal were seen in the 11 patients with NIDDM and FPG concentrations between 180 and 250 mg/dl (2.05 ± 0.07 mg·kg^{-1}·min^{-1}), as well as in those with FPG >250 mg/dl (2.18 ± 0.13 mg·kg^{-1}·min^{-1}). Although those with the highest FPG concentrations tended to have the greatest values for HGP, the difference between the latter two groups of patients with NIDDM was not statistically significant. Finally, HGP rates in the 11 patients with FPG concentrations >250 mg/dl were only 29% higher than values in the control population. These data indicate that HGP rates determined under steady-state isotopic conditions are not higher than normal until FPG concentration is >180 mg/dl, and that the increase in HGP is still relatively modest in magnitude (~29%) in patients with the most severe degree of fasting hyperglycemia (FPG >250 mg/dl). *Diabetes* 43:1440–1444, 1994

From the Division of Endocrinology and Metabolism (C-Y.J., W.H-H.S, M.M-T.F.), Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; and the Division of Endocrinology, Gerontology and Metabolism (Y-D.I.C., G.M.R.), Department of Medicine, Stanford University School of Medicine, Stanford, California.

Address correspondence and reprint requests to Chii-Yuan Jeng, M.D., Division of Endocrinology and Metabolism, Tri-Service General Hospital, #8, Ting-Chow Rd., Sect. 3, Taipei, Taiwan 100.

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FPG, fasting plasma glucose; HGP, hepatic glucose production; NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; R_a, rate of glucose appearance; R_d, rate of glucose disappearance.

Considerable evidence has been published (1–12) describing the relationship between fasting plasma glucose (FPG) concentration and hepatic glucose production (HGP) in patients with non-insulin-dependent diabetes mellitus (NIDDM). These observations have led to the widespread belief that the magnitude of fasting hyperglycemia in patients with NIDDM is a direct function of the increase in HGP. Although this is an attractive point of view, recent observations suggest that the situation may be somewhat more complicated (13–16). In particular, there are several reasons why the notion that an increase in HGP plays the major role in regulation of fasting hyperglycemia merits further analysis. In the first place, it has been shown that simple fasting will lead to a fall in both FPG concentration and HGP in patients with NIDDM (13,17). Indeed, the HGP of patients with fasting hyperglycemia became equal to that of normal subjects by 2 P.M., 20 h after dinner the evening before (13). Despite the similarity of HGP in the two groups, the patients with NIDDM were still extremely hyperglycemic, with a more than twofold increase in plasma glucose pool size (13). Obviously, in this situation, an increase in HGP cannot be responsible for fasting hyperglycemia in patients with NIDDM. Perhaps the best explanation for the discrepancy between the general hypothesis and the data described above is that earlier studies have measured HGP in patients with NIDDM by methods that provide falsely high values for HGP and the greater the degree of hyperglycemia, the greater the error in measurement of HGP (13–16). More specifically, the problem comes from the fact that previous measurements of basal HGP in patients with NIDDM have been based on estimates of the non-steady-state turnover rate of radiolabeled glucose, attempting to correct for the fact that isotopic steady-state was never attained. We (13,14) and others (15,16) have emphasized the inadequacy of this approach, pointing out that the corrections used in these earlier studies to compensate for the lack of isotopic steady-state do not work and that the inevitable outcome is an overestimation of HGP in patients with NIDDM (13–16). There are several ways to deal with this problem (13–16), but we believe the simplest is to quantify HGP over a time period in which isotopic steady-state conditions are reached. We have used this approach in this study to measure HGP in 18 normal subjects and 33 NIDDM patients.

RESEARCH DESIGN AND METHODS

For these studies, 51 individuals were recruited: 33 with NIDDM and 18 normal volunteers. NIDDM had been newly diagnosed in all patients.

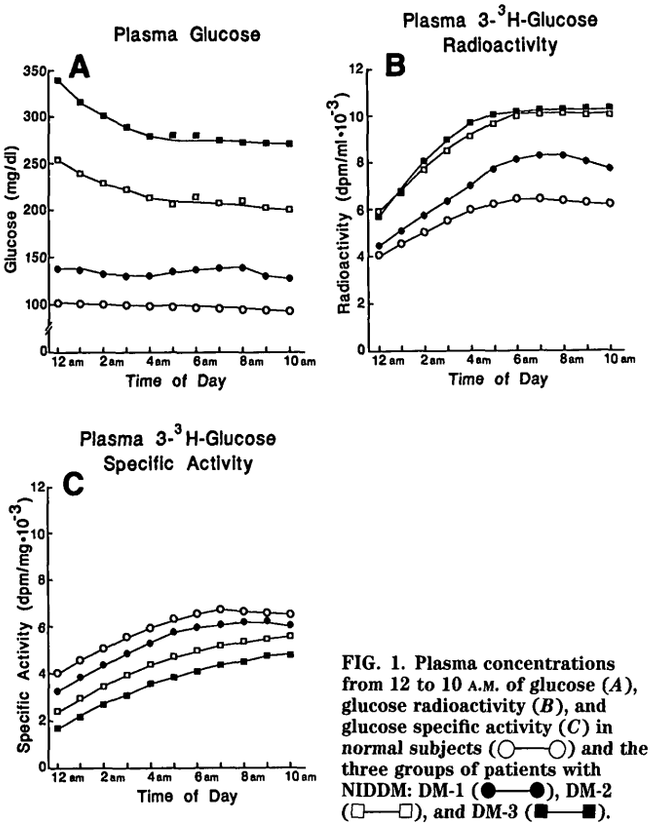

FIG. 1. Plasma concentrations from 12 to 10 A.M. of glucose (*A*), glucose radioactivity (*B*), and glucose specific activity (*C*) in normal subjects (○—○) and the three groups of patients with NIDDM: DM-1 (●—●), DM-2 (□—□), and DM-3 (■—■).

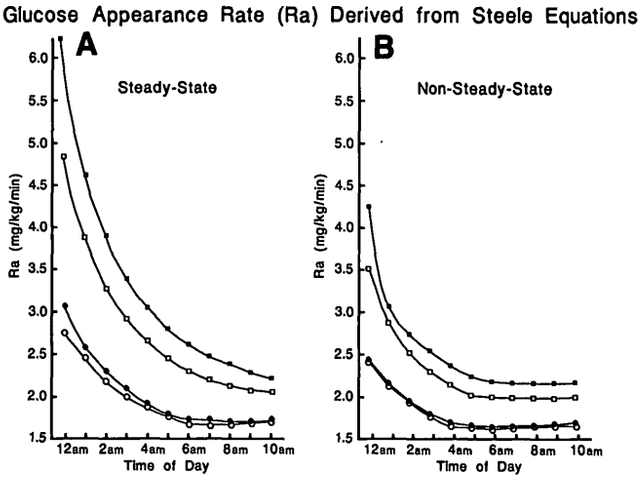

FIG. 2. Values for R_a from 12 to 10 A.M. using either the steady-state (*A*) or non-steady-state (*B*) equations of Steele in normal subjects (○—○) and patients with NIDDM: DM-1 (●—●), DM-2 (□—□), and DM-3 (■—■).

These patients were between 35 and 70 years of age with a body mass index (BMI) ≤30 kg/m^2, were otherwise healthy, and were taking no medication known to affect glucose metabolism. Patients with NIDDM were divided into three groups of 11 each on the basis of their FPG concentrations as follows: DM-1, FPG <180 mg/dl; DM-2, FPG = 180–250 mg/dl; and DM-3, FPG >250 mg/dl. The patients with NIDDM were divided into these three groups based on the fact that significant glycosuria does not occur when the FPG concentration is <180 mg/dl and previous studies from our laboratory in which a FPG concentration >250 mg/dl was used as the definition of severe fasting hyperglycemia (17). The 18 normal volunteers were similar in age distribution and BMI and had normal glucose tolerance by conventional criteria (18). After informed consent had been obtained, volunteers were admitted to the Clinical Research Center of Tri-Service General Hospital for measurement of basal [^{3}H]glucose turnover rate.

Subjects ate an identical meal at 6 P.M. with no additional food allowed until the study was completed. Intravenous catheters were then placed, one for the infusion of 3-[^{3}H]glucose and the other used to draw blood samples. At 10 P.M., 30 μCi of 3-[^{3}H]glucose was given as a bolus, followed by a continuous infusion of radiolabeled glucose (0.3 μCi/min) until 10 A.M. the following morning. Blood was obtained at hourly intervals in prechilled tubes containing EDTA, and plasma was stored at −70°C until assayed.

Plasma glucose (19) and insulin (20) concentrations were measured as described previously. To determine the specific activity of glucose, an aliquot of plasma was precipitated by $Ba(OH)_2$ and $ZnSO_4$ and centrifuged, and the protein-free supernatant was used for glucose and radioactivity measurements. A portion of supernatant was evaporated to dryness at 60°C in a scintillation vial under compressed air to eliminate ^3H_2O. Five milliliters of scintillation solution was added, and radioactivity was determined in a liquid scintillation spectrophotometer. Glucose concentration was also determined in the supernatant (21). The rates of glucose appearance (R_a) and disappearance (R_d) were calculated by Steele's equations (22). Because there was no exogenous glucose infusion, the rate of R_a was assumed to equal HGP.

One-way analysis of variance was used to evaluate the difference in the R_a values of the four groups. The difference between each two groups was further compared by the adjusted t test of Bonferroni and/or the χ^2 test. Correlation between the HGP and the glucose level was assessed by linear regression. Data are expressed as means ± SE. All statistical analysis was performed using the SAS program.

RESULTS

Figure 1 displays the changes in plasma concentration of glucose, 3-[^{3}H]glucose radioactivity, and 3-[^{3}H]glucose specific activity in the control subjects and in the three groups of patients with NIDDM from midnight until 10 A.M.. Obviously, the fall in plasma glucose concentration was much greater and values for specific activity were lower in patients with NIDDM. Note that the plasma glucose concentration continued to fall, and glucose specific activity continued to increase at a slow rate throughout the duration of the study in patients with significant fasting hyperglycemia.

Figure 2 displays the values for R_a throughout the study using Steele's equations. As can be seen in Fig. 2*A*, when the steady-state equation was used, the R_a in normal subjects and patients with NIDDM in the absence of significant hyperglycemia was constant during the last 4 h of the study. However, this was not the case in the two groups of patients with significant hyperglycemia, who demonstrated a continuous slow decline during this same period. Note that the primary bolus of tritiated glucose was similar in all subjects, not adjusted for plasma glucose pool size. This undoubtedly explains the initial rapid decline in R_a from 12 A.M. to 4 A.M. in the two groups of patients with significant hyperglycemia. However, when the non-steady-state equations of Steele were used, the values for R_a were constant in all four groups during the last 4 h of the study (Fig. 2*B*).

Figure 3 depicts the relationship between FPG concentration and HGP in the entire 51 experimental subjects. It can be seen that HGP values tended to be higher in patients with NIDDM, and the correlation coefficient between FPG concentrations and HGP in the entire population was statistically significant ($r = 0.68$, $P < 0.001$). Furthermore, when normal subjects were excluded from the analysis, a statistically significant relationship ($r = 0.67$, $P < 0.001$) remained between HGP and FPG concentrations in patients with NIDDM.

On the other hand, when the data in Fig. 3 were looked at in more detail, there did not appear to be a progressive increase in HGP throughout the range of FPG concentrations in patients with NIDDM. To examine this relationship more closely, the 33 patients with NIDDM were divided into the three groups as defined in METHODS. The FPG and HGP for the

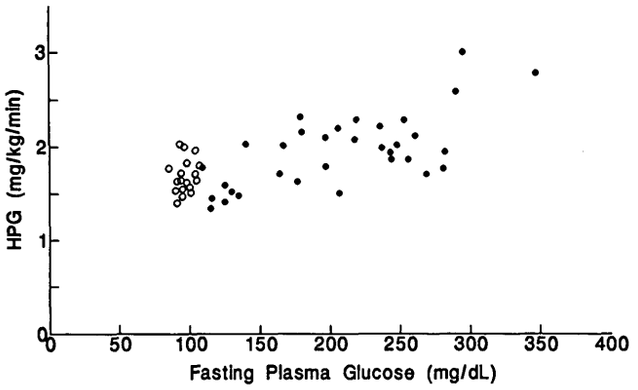

FIG. 3. Relationship between FPG concentration and HGP in normal subjects (○) and patients with NIDDM (●).

normal population and the three groups of patients with NIDDM are shown in Fig. 4. Mean ± SE FPG was 97 ± 2, 137 ± 7, 211 ± 7, and 275 ± 9 mg/dl, and HGP was 1.69 ± 0.04, 1.67 ± 0.07, 2.05 ± 0.07, and 2.18 ± 0.13 mg · kg^{-1} · m^{-2} for normal, DM-1, DM-2, and DM-3 subjects, respectively. Thus, FPG was higher in patients with NIDDM and increased with similar magnitude (~55 mg/dl) from groups DM-1 to DM-2 to DM-3. In contrast, the data shown indicated that HGP for normal subjects and patients with NIDDM in group DM-1 were essentially identical. However, HGP for DM-2 and DM-3 patients was significantly higher ($P < 0.01$) than in either the control population or DM-1 patients. Although the mean HGP for the DM-3 patients was slightly higher than that for the DM-2 patients, the difference was not statistically significant by either the adjusted t test of Bonferroni or the χ^2 test. Finally, note that the mean HGP of DM-3 patients (FPG >250 mg/dl) was only 29% higher than the value in the control population, whereas the mean FPG of DM-3 patients was three times that seen in normal subjects.

DISCUSSION

The results shown in Fig. 1 illustrate the difficulty in accurately measuring HGP in patients with NIDDM and significant fasting hyperglycemia (FPG >180 mg/dl). It can be seen that these individuals had a very large and slowly turning over plasma glucose pool and that the plasma glucose concentration continued to decline at a slow, but continuous, rate throughout the period of observation. Thus, in these patients, plasma glucose specific activity never reached a true plateau, but, at best, only attained a quasi–steady state. Furthermore, even when calculated by Steele's non-steady-state equation, R_a values did not become constant until 4 A.M., 6 h after the initiation of the tracer infusion (Fig. 2). Thus, the data in Figs. 1 and 2 emphasize the technical problems of arriving at a true plateau of specific activity, as well as valid R_a values, in patients with significant fasting hyperglycemia. The fact that the values of R_a were somewhat higher from 2 to 4 A.M. than from 4 to 10 A.M. in all subjects is most likely simply a function of the prolonged time necessary before plasma radioactivity reaches a quasi–plateau level. The alternative that the early R_a values are correct and the fall with time is a function of fasting seems unlikely in view of our previous demonstration that, when the same patients with NIDDM were studied on two occasions, the measurements of R_a varied as a function of duration of tracer administration, not time after the removal of food, until a quasi–steady state of radioactivity was reached (14).

On the other hand, it could be argued that our approach to avoiding the non-steady-state dilemma could be confounded by possible prelabeling of hepatic glycogen with 3-[^{3}H]glucose during glucose cycling (23,24). If this were to occur, the co-release of this radioactive glucose with cold glucose during glycogenolysis would have led to the blinding of a certain proportion of glucose released from the liver, thus leading to an underestimate of HGP. Since Efendic et al. (23,24) have shown increased glucose cycling in individuals with NIDDM, this may further confuse the comparison of HGP between normal subjects and NIDDM patients. However, we were aware of the importance of this potential problem using 3-[^{3}H]glucose as tracer and have attempted to resolve this issue by injecting a bolus of glucagon 4–6 h after the initiation of tracer infusion. While this led to an immediate increase in plasma glucose of ~100 mg/dl 10, 20, 30, 40, 50, and 60 min after the glucagon injection, there was no additional radioactivity released from the liver; indeed, specific activity of 3-[^{3}H]glucose decreased as a result of the increase in cold glucose. Thus, we do not believe that significant incorporation of [^{3}H]glucose into glycogen occurred during the overnight infusion of tracer. Furthermore, it appears (23,24) that the degree of glucose cycling in patients with NIDDM only accounts for ~14% of total HGP at the most. However, because a substantial proportion of glucose labeled with tritium in the 3rd position loses the label as it is converted to a 3-carbon fragment during glycolysis, the underestimate will actually be even less. Thus, the quantitative impact of glucose cycling on the values of R_a obtained in this study should be extremely modest in magnitude.

If we now turn our attention to the relationship between HGP and FPG concentration, the results in Fig. 3 show that there is a significant correlation ($r = 0.68$, $P < 0.001$) between HGP and FPG concentration in patients with NIDDM, confirming results of previous studies (1–12). However, the quantitative nature of this relationship was quite different from that described in those earlier studies. More specifically, it can be seen from the results in Figs. 3 and 4 that the HGP was only increased by ~30% in patients with the highest FPG concentrations, not the two- to threefold increase described in studies in which a quasi–steady state of tritiated glucose was not reached (1–12). Indeed, as can be seen from Fig. 4, the mean HGP of patients with NIDDM and FPG concentrations <180 mg/dl was not different from the mean value in the control population. Of interest in this context are the results of a paper published by our research

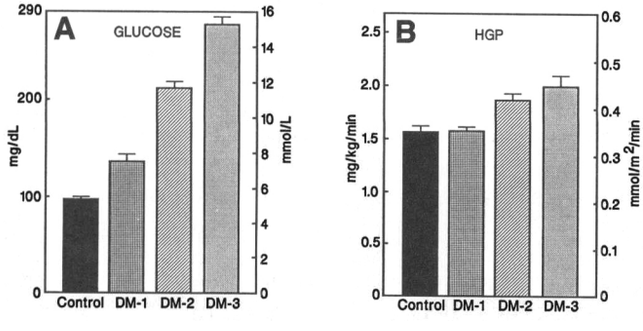

FIG. 4. FPG concentration (*A*) and HGP (*B*) in normal subjects ($n = 18$) and three groups of patients with NIDDM (DM-1, DM-2, and DM-3). The patients with NIDDM were divided into three groups of 11 each on the basis of their FPG concentrations: DM-1, <180 mg/dl; DM-2, 180–250 mg/dl; and DM-3, >250 mg/dl.

group ~25 years ago (25), which also demonstrated that HGP was similar in normal subjects and patients with NIDDM and FPG concentrations ≤180 mg/dl.

Although results of the current studies are quite different from most previous reports of the relationship between HGP and FPG concentrations, in which values for HPG in patients with significant fasting hyperglycemia were two to three times as high as in normal control subjects, the reason for the disparity is straightforward. Studies reporting that HGP values were substantially higher than normal in patients with NIDDM were performed with isotopic techniques that were self-fulfilling (1–12). Both our group (13,14) and Hother-Nielsen and Beck-Nielsen (15,16) have shown that the time period during which HGP was measured in these earlier studies did not allow for the attainment of a quasi–steady state of plasma glucose specific activity, and the greater the FPG pool size, the greater would be the overestimation of HGP. Thus, the conclusion from the other studies that a greater than normal HGP is the direct cause of fasting hyperglycemia cannot be sustained. We have responded to this dilemma by increasing the duration of the infusion period of radiolabeled glucose, whereas Hother-Nielsen and Beck-Nielsen have proposed that the problem can be solved by increasing the size of the bolus of tritiated glucose given at the start of the isotope infusion in proportion to the glucose pool size. We have tried their approach, and it seems to us to be a less satisfactory solution. More specifically, given the relatively short period of infusion time, the bolus used has a significant impact on the duration of time before constant values for R_a can be obtained. In general, the duration of infusion needed to obtain constant values for R_a will vary as a function of the bolus, the infusion rate of the tracer, the plasma glucose pool size, and the glucose turnover rate. Thus, it is not easy to know exactly what the best bolus is to achieve a condition that permits a valid estimate of R_a and what is the most appropriate shortened time period to achieve that goal. Indeed, the time it takes to obtain a valid estimate of R_a can vary if the bolus is either too small or too large. We have tried to calculate the best bolus as suggested by Hother-Nielsen and find that the time it takes varies considerably from patient to patient, and if a shortened fixed time period were to be used for all patients, the R_a obtained will in some patients differ from the true R_a. On the other hand, the goal of our study was not to see which of these alternative approaches provided the best way to measure HGP, and either technique seems more desirable than what has been conventionally done in the past.

We also must disagree somewhat with the conclusions of a recent study by Hother-Nielsen and Beck-Nielsen as to values of HGP in patients with NIDDM. As mentioned earlier, this research group has also recognized (15,16) the overestimation of HGP in previous studies and recently reported that HGP was similar in normal subjects and patients with NIDDM (16). Although these results are much closer to ours than those in most previous publications, they differ in that these authors were unable to discern any increase above normal in the HGP of patients with NIDDM. However, they studied only 22 diabetic patients (10 lean and 12 obese), and the mean FPG concentrations of the two groups were 12.7 (230 mg/dl) and 11.0 mmol/l (200 mg/dl), respectively. No subjects appeared to have a FPG concentration >13.8 mmol/l (250 mg/dl). Thus, it seems most likely that their inability to detect any increase in HGP in patients with NIDDM may be due to the selection of the patients they studied.

Although the results of this study and the findings of Hother-Nielsen and Beck-Nielsen (16) demonstrate that HGP values in patients with NIDDM are quite similar to the values seen in normal subjects, these findings should not be interpreted to mean that the liver is acting normally in patients with NIDDM. Obviously, a normal rate of HGP in the face of a greatly expanded plasma glucose pool is an extremely abnormal response on the part of the liver. Furthermore, the fact that the absolute values for HGP were only ~30% higher in patients with very high plasma glucose concentrations does not mean that the liver does not contribute to the increase in plasma glucose pool size in patients with fasting hyperglycemia. It seems that the results of this study support the view that there are two defects that play significant roles in the development of fasting hyperglycemia in patients with NIDDM and that this change would not occur in the absence of either abnormality. Specifically, a value for HGP similar in magnitude to that seen in nondiabetic individuals could not lead to fasting hyperglycemia unless there was a concomitant defect in peripheral glucose disposal rate. Conversely, a defect in peripheral glucose disposal rate can only result in fasting hyperglycemia when HGP cannot be suppressed by an increase in plasma glucose concentration. Thus, the major pathophysiological implication of these studies is that it does not seem appropriate to differentiate between a hepatic and a peripheral cause for the appearance of fasting hyperglycemia in patients with NIDDM—the presence of both defects was necessary.

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