Pathogenesis of Fasting and Postprandial Hyperglycemia in Type 2 Diabetes: Implications for Therapy

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Objective: To gain a greater understanding of the cause of fasting and postprandial hyperglycemia in people with type 2 diabetes.

Overview: Endogenous glucose production is excessive before eating and fails to appropriately suppress after eating in people with type 2 diabetes. This is due in part to impaired insulin induced suppression of endogenous glucose production which is observed early in the evolution of type 2 diabetes. Increased rates of gluconeogenesis and perhaps glycogenolysis contribute to hepatic insulin resistance. Insulin induced stimulation of hepatic glucose uptake and hepatic glycogen synthesis are reduced in people with type 2 diabetes primarily due to decreased uptake of extracellular glucose presumably because of inadequate activation of hepatic glucokinase. Delayed insulin secretion results in higher peak glucose concentrations particularly when suppression of glucagon is impaired whereas, insulin resistance prolongs the duration of hyperglycemia which can be marked when both hepatic and extra-hepatic insulin resistance are present.

Conclusions: The premise of these, as well as studies performed by many other investigators, is that an understanding of the pathogenesis of type 2 diabetes will enable the development of targeted therapies that are directed toward correcting specific metabolic defects in a given individual. I, as well as many other investigators believe that such therapies are likely to be more effective and to have a lower risk than would occur if everyone were treated the same regardless of the underlying cause of their hyperglycemia. While we do not yet have sufficient knowledge to truly individualize therapy, in my opinion this approach will be the norm in the not too distant future.

The discovery of insulin by Banting and Best forever changed the lives of people with diabetes. When properly used, insulin prevents death from ketoacidosis in people with type 1 diabetes and reduces the symptoms from severe hyperglycemia in people with type 2 diabetes. However, unfortunately as currently used, insulin does not completely prevent the chronic microvascular or macrovascular complications of diabetes. This likely is because insulin, as well as all other available therapies, does not fully normalize glucose, or for that matter, lipid, or protein metabolism. The premise of research that my collaborators and I have conducted over the years is that the only way to maximize benefit and minimize risk is to tailor therapy to each individual’s needs and the only way to do so is to understand the cause of hyperglycemia in that particular person. While much remains to be learned, I think we have moved along way toward this goal. The data that I will review in this articleprimarily focuses on the cause of fasting and postprandial hyperglycemia in type 2 diabetes mellitus. However in general, the principles also pertain to people with type 1 diabetes mellitus.

Figure 1 shows the results from a series of experiments conducted by Dr Peter Butler in which the pattern of change in glucose, insulin and glucagon concentrations in people with type 2 diabetes were compared to those observed in age, gender and weight matched non-diabetic subjects (1). Fifty grams of glucose was ingested at time zero. Glucose concentrations in the non-diabetic subjects averaged ~5 mmol/L before glucose ingestion, increased to only ~8 mmol/L
mg/dl after glucose ingestion, and returned to pre-prandial concentrations within two hours. The reason why this occurred was because insulin concentrations rapidly increased as glucose rose reaching a peak within 30 minutes of glucose ingestion. Furthermore, glucagon concentrations fell as glucose rose and rose as glucose fell back to preprandial concentrations.

The situation is quite different in people with diabetes. People with so called “mild” type 2 diabetes have both fasting and postprandial hyperglycemia. In these studies, fasting glucose averaged ~7.2 mmol/L before glucose ingestion and increased to ~11 mmol/L after glucose ingestion. Despite higher glucose concentrations, peak insulin concentrations did not differ from those observed in the non-diabetic subjects. Furthermore, they were not achieved until two hours after glucose ingestion. People with so called “severe” type 2 diabetes have still higher fasting glucose concentrations, in this instance ~10 mmol/L, and experience marked and prolonged hyperglycemia after eating. Once again insulin secretion was delayed and peak insulin concentrations did not occur until two hours after glucose ingestion. In addition, insulin concentrations during the two hours after eating were lower than those observed in either people with “mild” diabetes or in people who did not have diabetes. Glucagon concentrations tended to be higher in people with either “mild” or “severe” diabetes before glucose ingestion and did not suppress and if anything paradoxically increased after glucose ingestion.

The data from this study (1), as well as those from studies conducted by many other investigators (2-7; 8) established that insulin and glucagon secretion are abnormal in people with type 2 diabetes following carbohydrate ingestion. Insulin secretion is decreased and delayed and glucagon does not suppress. The question then arises as to whether these abnormalities, either alone or in combination with insulin resistance, cause hyperglycemia? If so, to what extent do alterations in hepatic glucose metabolism contribute to fasting and postprandial hyperglycemia?

Figure 2 shows a simplified portrayal of glucose metabolism in the post-absorptive state (9). Following an overnight fast, glucose is released by the liver into the blood stream and taken up by insulin sensitive tissues such as muscle and tissues with limited response to insulin such as the brain. Glucose released from the liver is derived from the breakdown of glycogen and synthesis of new glucose via the gluconeogenic pathway. The difference between the rate of glucose entering and the rate of glucose leaving the blood stream determines whether glucose rises, falls or remains the same. Things become more complicated after eating. Glucose derived from a meal enters the portal vein after absorption from the gut. It then can pass through the liver and be released into systemic circulation, incorporated into glycogen via the direct pathway, or first degraded to three carbon precursors such as lactate and alanine then re-synthesized via the indirect gluconeogenic pathway back to glucose-6-phospate which in turn can then be either incorporated into glycogen or dephosphorylated and released into the systemic circulation as glucose.

In order to determine why glucose concentrations are too high in people with type 2 diabetes both before and after eating, Dr. Dick Firth used a multiple tracer approach to simultaneously measure the total rate of glucose appearance as well as its components which are the rate of appearance of the ingested glucose and the rate of endogenous glucose production (10). The upper panel in figure 3 shows the total rate of glucose appearance. As is evident, the rate of glucose appearance was higher in the people with type 2 diabetes, before and after glucose ingestion. Thus, too much glucose entered the systemic circulation both before and after eating. The systemic rate of appearance of the ingested glucose, measured by tracing the rate of appearance of a tracer contained in the meal, is shown in the middle panel of figure 3. Somewhat to our surprise, the rate of appearance of the ingested glucose did not differ between groups.
Therefore the excessive rise in postprandial glucose concentrations was not due to too much glucose entering from the gut. However, since the glucose concentrations were markedly elevated in the people with the diabetes and since hyperglycemia stimulates hepatic glucose uptake (11-14), these data should not be interpreted as indicating postprandial hepatic glucose uptake is normal in type 2 diabetes.

What then was the cause of the excessive rate of glucose appearance? The rates of endogenous glucose production are shown in the lower panel of Figure 3. Endogenous glucose production was higher in the diabetic than non-diabetic subjects before eating. In addition, whereas endogenous glucose production rapidly decreased in the non-diabetic subjects after glucose ingestion, suppression of endogenous glucose production was slower in the people with diabetes requiring approximately six hours for a nadir to be reached. The excess amount of glucose released due to slower suppression of endogenous glucose production entirely accounted for the higher postprandial rates of glucose appearance (10).

What about glucose disappearance. Was hyperglycemia due to lower rates in the diabetic subjects? As is evident from this side the answer is no. As is evident from the upper panel of Figure 4, if anything rates of glucose disappearance were higher in the diabetic than non-diabetic subjects both before and after glucose ingestion. Urinary glucose loss and muscle glucose uptake both contribute to glucose disappearance. Urinary glucose loss can be substantial when glucose concentrations exceed the renal glucose threshold as commonly happens after eating. To gain insight regarding muscle glucose uptake, Dr. Firth used the forearm catheterization method to measure forearm glucose uptake. As is evident from the lower panel of Figure 4 in contrast, to the higher rates of total body glucose disappearance, forearm glucose uptake did not differ in the diabetic and non-diabetic subjects (10). Taken together, these data indicate that people with type 2 diabetes have excessive rates of endogenous glucose production both before and after eating contributing to both fasting and postprandial hyperglycemia. In addition, while meal appearance and muscle glucose uptake did not differ in the diabetic and non-diabetic subjects, they were not appropriate for the prevailing glucose concentration.

The obvious next question was why was endogenous glucose production increased in people with type 2 diabetes? Is this due to hepatic insulin resistance? As shown in figure 5, Dr. Rita Basu addressed this question by clamping glucose at ~8 mmol/L, a concentration commonly observed after eating, that is sufficiently high to stimulate hepatic glucose uptake, but not so high as to fully suppress endogenous glucose production (15). Glucose concentrations were maintained at this level by means of an infusion of glucose in people with type 2 diabetes, or in people who did not have diabetes. Insulin was infused at rates that resulted in insulin concentrations that spanned the physiologic range. Somatostatin also was infused in order to inhibit hormone secretion along with replacement amounts of glucagon to ensure that portal insulin and glucagon concentrations were constant and equal throughout the experiment in the diabetic and non-diabetic subjects.

Rates of endogenous glucose production present during the final 30 minutes of each insulin infusion are shown in the upper panel of Figure 6. Endogenous glucose production was suppressed in the people who did not have diabetes when insulin was increased from 150 to 300 pmol with no further suppression being observed when insulin was subsequently increased to 600 pmol. In contrast, despite matched glucose and insulin concentrations, endogenous glucose production was higher in the diabetic than non-diabetic subjects at insulin concentrations of 150 pmol/l indicating hepatic insulin resistance. Endogenous glucose production progressively decreased when insulin concentrations were increased to 300 then 600 pmol/l. Of note, while the
rates of endogenous glucose production were slightly higher in the people with diabetes, the differences were no longer significant at insulin concentrations above 150 pmol/l. Thus, people with type 2 diabetes have hepatic insulin resistance. These data also explain why hepatic insulin resistance will be missed when insulin action only is assessed at high insulin concentrations. A different pattern is observed for glucose disappearance. As shown in the lower panel of Figure 6, glucose disappearance progressively increased in both groups when insulin concentrations were increased from 150 to 300 to 600 pmol/l. However, glucose disappearance was lower in the people with diabetes at all three insulin concentrations.

Why was insulin induced stimulation of glucose disappearance lower in the people with diabetes? Is insulin induced stimulation of hepatic glucose uptake, muscle glucose uptake or a combination of both decreased in people with type 2 diabetes? In order to address this question, Dr. Ananda Basu used the splanchnic catheterization method whose development was pioneered by Dr John Wahren (16). With this method, blood samples are simultaneously obtained from an artery and from the hepatic vein. Splanchnic blood flow is measured by infusing indocyanine green. Since both flow and glucose concentration are known, net splanchnic glucose balance, abbreviated in Figure 7 as NSGB, can be calculated by subtracting the amount of glucose leaving the splanchnic bed from the amount of glucose entering. Splanchnic glucose uptake, abbreviated as SGU, also can be calculated if a glucose tracer is infused. For example, if 10 labeled molecules of glucose enter the splanchnic bed and 9 leave, then splanchnic glucose uptake must have been one. Since the ratio of labeled to unlabeled glucose in the artery is known, total splanchnic glucose uptake can be determined. Splanchnic glucose production, here abbreviated as SGP, then is calculated as the algebraic sum of net splanchnic balance and splanchnic glucose uptake.

Figure 8 shows splanchnic glucose production measured in the presence of comparably elevated glucose and insulin concentrations in the diabetic and non-diabetic subjects. The pattern is virtually identical to that observed with endogenous glucose production in that the rate of splanchnic glucose production was increased in the people with type 2 diabetes at low insulin concentrations but no longer differed from people who did not have diabetes at higher insulin concentrations (16). These data indicate that insulin induced suppression of splanchnic glucose production is impaired in people with type 2 diabetes. Since the liver is presumed to be the primary source of splanchnic glucose production, these data strongly imply that people with type 2 diabetes have increased rates of hepatic glucose release.

Is insulin stimulated hepatic glucose uptake also impaired in people with type 2 diabetes? Figure 9 shows that it is. Splanchnic glucose uptake, shown in the upper panels, was slightly lower in the people with type 2 diabetes at low insulin concentrations and significantly lower at higher insulin concentrations. The same pattern was observed for leg glucose uptake, shown in the lower panel, with leg glucose uptake being slightly lower at low insulin concentrations and significantly lower at higher insulin concentrations. When total muscle mass was estimated using measurements obtained with DEXA scanning, under these experimental conditions, muscle accounted for approximately two thirds and liver one third of the decrease in total body glucose disappearance that was observed in the people with type 2 diabetes (16).

Why is splanchnic glucose uptake decreased in people with type 2 diabetes? To gain insight into this question, Dr. Basu used a method pioneered by the late Dr Bernie Landau and colleagues where acetaminophen is used to sample the hepatic UDP glucose pool during infusion of labeled galactose (17). A schematic of this method is shown in Figure 10. When infused in trace amounts, galactose is converted to UDP-galactose within hepatocyte which in turn
equilibrates with the UDP-glucose pool. Enrichment of UDP-glucose can be determined by giving acetaminophen and measuring the enrichment of UDP-glucuronide in the urine. Since UDP-glucose is the obligate precursor of glycogen, flux through the UDP-glucose pool into glycogen can be calculated. The enrichment of the intravenously infused glucose tracer also can be measured in the same manner allowing estimation of the proportion of the hepatic UDP-glucose pool that is derived from uptake of extracellular glucose.

As is evident in Figure 11, UDP flux was lower in the people with diabetes implying decreased rates of hepatic glycogen synthesis. Of particular interest, the decrease in UDP glucose flux was entirely accounted for by a decrease in the rate of uptake of extracellular glucose with no difference in the proportion derived from intracellular sources. Since phosphorylation of glucose by glucokinase is the rate limiting step in uptake of extracellular glucose by the liver (18; 19), these data strongly suggest a defect in hepatic glucokinase activity. This conclusion is supported by studies that have shown decreased activity of this enzyme in people with type 2 diabetes (20) and by the observation that hepatic glucose uptake is reduced in people with genetic defects in glucokinase activation (21). Thus, people with type 2 diabetes have excessive rates of hepatic glucose release, impaired hepatic glucose uptake, decreased hepatic glycogen synthesis and decreased uptake of extracellular glucose.

These data established that endogenous glucose production is increased in people with type 2 diabetes. However these studies (1; 10; 16), as well as many other studies in the literature at that time (22-27), were performed in people whose fasting glucose concentrations generally were substantially above the non-diabetic range elevated (e.g. 10-13 mmol/L). The question then arose as to whether endogenous glucose production is increased in people with “mild” as well as “severe” type 2 diabetes. If so this would suggest that increased rates of endogenous glucose production contribute to rather than are caused by the abnormal metabolic milieu that accompanies elevated glucose concentrations.

To address this question, Dr. Rita Basu (28) performed hyperglycemic, hyperinsulinemic clamps in people with so called “severe” diabetes, whose fasting glucose concentrations averaged approximately 12 mmol/L mg/dl, in people with “mild” diabetes whose fasting glucose concentrations averaged approximately 8 mmol/L, and in people who did not have diabetes whose fasting glucose concentrations averaged approximately 5 mmol/l (upper panel figure 12). On each occasion, Dr. Rita Basu began an infusion of somatostatin, insulin and glucagon at time zero to be sure that portal concentrations of insulin and glucagon were constant and equal in all groups during the clamp. She also infused sufficient glucose to raise glucose concentration to approximately 11 mmol/L in the subjects with either “mild” diabetes or no diabetes. Glucose concentrations in the people with “severe” diabetes remained elevated at concentrations that averaged approximately 13 mmol/Ll. Fasting insulin concentrations in the people with “mild” diabetes were higher than those present in the people who did not have diabetes implying higher hepatic insulin concentrations (lower panel figure 12). In contrast, insulin concentrations were comparable in all groups during the clamp. The Somatostatin infusion and glucagon infusions resulted in near complete suppression of C-peptide and constant but equal plasma glucagon concentrations in both groups (data not shown).

The left side of Figure 13 shows the rates of endogenous glucose production that were present before the clamp. Consistent with previous studies (22-26) and those discussed above (1; 10; 16; 27), endogenous glucose production was increased in people with “severe” diabetes but did not differ in people with “mild” diabetes or no diabetes. However, since people with “mild” diabetes had higher glucose and insulin concentrations this implied abnormal regulation of
endogenous glucose production. This became evident during the clamp. As shown on the right side of Figure 13, when glucose and insulin concentrations were matched, endogenous glucose production was higher in both the “mild” and “severe” diabetes groups. Dr. Gerlies Bock (29) recently used a similar experimental design to establish that insulin induced suppression of endogenous glucose production also is impaired in people with pre-diabetes (data not shown). Thus, abnormal regulation of hepatic glucose metabolism occurs early in the evolution of type 2 diabetes strongly suggesting it is involved in the pathogenesis of the disease.

Increased rates of endogenous glucose production can be caused by increased rates of gluconeogenesis, increased rates of glycogenolysis or a combination of both. Figure 14 (upper panel) shows the rates of gluconeogenesis measured using the deuterated water method that was pioneered by Dr. Bernie Landau (30). This method is based on the fact that following ingestion of deuterated water, the fifth carbon of glucose is labeled with deuterium during gluconeogenesis whereas the second carbon of glucose is labeled with deuterium during both the gluconeogenesis and glycogenolysis (30). While the assumptions of this method continue to be evaluated (31; 32), it is widely accepted as providing an index of gluconeogenesis. Consistent with previous studies (23; 25), the data on the left side of the slide indicate that gluconeogenesis was increased in the people with “severe” diabetes before the clamp. However as shown on the right side of slide, perhaps due to the fact that glucagon was lowered to comparable levels by the somatostatin infusion, the rates of gluconeogenesis that were present during the clamp no longer differed amongst the groups.

Rates of glycogenolysis can be estimated by subtracting the rate of gluconeogenesis from the rate of endogenous glucose production. As shown in the lower panel of Figure 14 (lower panel), the rate of glycogenolysis was increased in the people with “severe” diabetes before the clamp but did not differ in people with “mild” diabetes or no diabetes. However, hyperglycemia is known to be a potent suppressor of glycogenolysis (33). This is evident from the data shown on the right side since rates of glycogenolysis in the people who did not have diabetes were almost completely suppressed when their glucose was raised to 200 mg/dl. In contrast, minimal suppression occurred in the people with either “mild” or “severe” diabetes indicating that the rates of glycogenolysis were not inappropriate for the prevailing glucose and insulin concentrations.

What about insulin secretion? Do alterations in insulin secretion and insulin action have the same effect on postprandial glucose concentrations? Dr Ananda Basu attempted to answer this question by determining the metabolic effects of “diabetic” and “non-diabetic” insulin profiles in insulin sensitive and insulin resistant people (34). Figure 15 shows the insulin concentrations that were observed after Dr. Andy Basu fed people who had either “severe” type 2 diabetes or no diabetes a carbohydrate containing meal. As anticipated, the meal resulted in a prompt increase in insulin concentrations in people who did not have diabetes with levels peaking at approximately 45 minutes. In contrast, there was a delay in insulin release in the people with type 2 diabetes with concentrations not reaching a peak until approximately two hours after eating.

Dr. Basu then studied separate groups of lean non-diabetic subjects, obese non-diabetic subjects and obese subjects with type 2 diabetes on two occasions. On each occasion he infused somatostatin to inhibit endogenous insulin secretion and used a computer to infuse the identical amount of insulin as either a “non-diabetic” or “diabetic” profile (34). Figure 16 shows the resultant insulin concentrations. The insulin concentrations peaked at 30 minutes during the “non-diabetic” profile and at 120 minutes during the “diabetic” profile. Note that this resulted in
substantially lower insulin concentrations during the first hour of the “diabetic” insulin profile in all three groups. Dr. Basu also infused glucose in a pattern and amount that mimicked the meal appearance rate that normally occurs following ingestion of a meal containing 50 grams of glucose. Thus, both groups received the identical amounts of glucose and insulin on all occasions. Only the pattern of the insulin infusion differed. Figure 17 shows the resultant glucose concentrations. The “diabetic” insulin profile caused a higher peak glucose concentration than did the “non-diabetic” profile in all three groups. However, this difference was transient with glucose concentrations falling within three hours to values that no longer differed from those observed during the “non-diabetic” insulin profile. These data indicate that a delay in the rate of rise of insulin resulted in a higher peak glucose concentration but only minimally prolonged the duration of hyperglycemia.

In order to evaluate the effects of differences in insulin action, the results observed during the “non-diabetic” profile are shown in the upper panel of Figure 18 and those observed during the “diabetic” profile are shown in the lower panel. Peak glucose concentrations did not differ in the lean and obese subjects regardless of whether insulin was infused as a “non-diabetic” profile, shown in the upper panel, or “diabetic” profile, shown in the lower panel of figure 18. However the duration of hyperglycemia was more prolonged in the obese non-diabetic subjects, then in the lean non-diabetic subjects, shown in blue. The duration of hyperglycemia was even more prolonged in the people with type 2 diabetes, during both the “non-diabetic” and “diabetic” insulin profiles. Thus, insulin resistance prolonged the duration of hyperglycemia but had a minimal effect on the peak glucose concentration. Note that the glucose concentrations were substantially higher in the obese diabetic subjects than in the obese non-diabetic subjects.

Why did this happen? Figure 19 shows the rates of glucose clearance in the lean and obese individuals who did not have diabetes (34). Despite identical insulin concentrations and higher glucose concentrations, the rates of glucose clearance were lower in the obese individuals documenting the presence of insulin resistance. Glucose clearance also was lower in the obese subjects with type 2 diabetes. However, rates did not differ from those observed in the obese subjects who did not have diabetes whether measured during the “non-diabetic” or “diabetic” insulin profiles. Therefore, the higher glucose concentrations in the obese diabetic were not due to lower rates of glucose clearance.

Figure 20 shows rates of endogenous glucose production. Endogenous glucose production was comparably suppressed in the lean and obese non-diabetic subjects. On the other hand, suppression of endogenous glucose production was markedly impaired in the subjects with type 2 diabetes whether measured during the “non-diabetic” or “diabetic” insulin profiles. Thus, a delay in insulin secretion results in higher peak glucose concentrations and a decrease in insulin action results in prolonged hyperglycemia which is particularly severe when decreased glucose clearance is accompanied by excessive rates of endogenous glucose production.

What about glucagon. Does lack of suppression of glucagon contribute to postprandial hyperglycemia? As illustrated in the bottom panel of Figure 1, glucose ingestion suppresses glucagon concentrations in people who do not have diabetes. In contrast, glucagon concentrations either do not decrease or paradoxically increase in people with type 2 diabetes (1; 3; 8; 35). Can the 40-50 pg/ml difference in glucagon concentration that arises from the lack of suppression of glucagon cause postprandial hyperglycemia? In order to address this question, Dr. Pankaj Shah studied a group of healthy non-diabetic subjects on two occasions (36). He infused insulin as a “non-diabetic” insulin profile on both occasions. On one occasion glucagon was suppressed whereas on the other occasion it was not. He used the same experimental design in a
separate set of subjects except he infused a “diabetic” insulin profile on both occasions. Figure 21 shows that the resultant insulin concentrations were virtually identical on the suppressed and the non-suppressed study days. However as expected, the “non-diabetic” profile resulted in insulin concentrations that peaked at 30 minutes, shown in the upper panel, whereas the “diabetic” profile resulted in insulin concentrations that peaked at 120 minutes, shown in the lower panel.

Figure 22 shows the glucagon concentrations that were achieved during the experiments. To create these patterns, Dr. Shah infused somatostatin from 0 to 360 minutes on both occasions in order to inhibit glucagon release. On one occasion, he infused glucagon at a rate of 0.65 ng/kg/minute throughout the experiment which resulted in a slight increase in peripheral glucagon concentrations. Since endogenous secretion decreased, this meant that portal glucagon concentrations either did not change or minimally increased during the experiment. In contrast, on the other occasion he delayed starting the glucagon infusion until 120 minutes. This resulted in an approximate 50 pg/ml difference in glucagon on the two study days that was only present during the first two hours of the experiment (36).

The upper panel of Figure 23 shows the glucose concentrations that resulted when 35 grams of glucose also was infused in the same prandial profile as used in the experiments by Basu et al (34). Of note, in the presence of the “non-diabetic” profile, the peak glucose concentrations were the same whether or not glucagon was suppressed. While the glucose area above basal was significantly higher on the suppressed than non-suppressed study days, the difference was small.

An entirely different outcome was observed in the presence of the “diabetic” insulin profile. As shown in the lower panel of figure 23, lack of suppression of glucagon resulted in peak glucose concentrations that were ~50-60 mg/dl higher than were observed when glucagon was suppressed. Also of interest, despite the delayed rise in insulin that occurred during the “diabetic” profile, glucose concentrations on the suppressed glucagon study day peaked at only 145 mg/dl. These data suggest that an agent that suppresses glucagon in the presence of a rapid increase in insulin concentration will have a minimal effect on postprandial glucose concentrations. On the other hand, if insulin secretion is delayed, as typically occurs in people with diabetes, then an agent that suppresses glucagon likely will substantially lower postprandial glucose concentrations.

As indicated in figure 24, many factors contribute to fasting and postprandial hyperglycemia. People with type 2 diabetes have excessive rates of endogenous glucose production that fail to appropriately suppress after eating (10; 16; 28). Rates of gluconeogenesis and perhaps glycogenolysis are increased early in the evolution of diabetes (28; 37). Insulin induced stimulation of hepatic glucose uptake is impaired in people with type 2 diabetes. This leads to lower rates of hepatic glycogen synthesis primarily due to reduced uptake of extracellular glucose presumably because of inadequate activation of hepatic glucokinase (16; 38). Delayed insulin secretion results in higher peak glucose concentrations particularly when suppression of glucagon is impaired whereas, insulin resistance prolongs the duration of hyperglycemia which can be marked when both hepatic and extra-hepatic insulin resistance are present (36).

The premise of all of these, as well as other studies that my colleagues and I have performed, is that an understanding of the pathogenesis of type 2 diabetes enables the development of targeted therapies that are directed toward correcting specific metabolic defects in a given individual. I, as well as many other investigators believe that such therapies are likely
to be more effective and to have a lower risk than would occur if everyone were treated the same regardless of the underlying cause of their hyperglycemia. While we do not yet have sufficient knowledge to truly individualize therapy, in my opinion this approach will be the norm in the not too distant future.

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**Figures legends**

Figure 1. Glucose, insulin and glucagon concentrations observed in people who did not have diabetes, had “mild” type 2 diabetes or had “severe” type 2 diabetes. Fifty grams of glucose was ingested at time zero (1).

Figure 2. Simplified portrayal of glucose metabolism in the post-absorptive (upper panel) and postprandial (lower panel) states (9).

Figure 3. Rates of total body glucose appearance, meal derived glucose appearance and endogenous glucose production observed in people with or without type 2 diabetes. Fifty grams of glucose was ingested at time zero (10).

Figure 4. Rates of total body glucose disappearance and forearm glucose uptake observed in people with or without type 2 diabetes. Fifty grams of glucose was ingested at time zero (10).

Figure 5. Plasma glucose and insulin concentrations observed in people with or without type 2 diabetes. Infusions of glucose, insulin, somatostatin, glucagon and growth hormone started at time zero (15).

Figure 6. Rates of endogenous glucose production (upper panel) and total body glucose disappearance (lower panel) observed during the final thirty minutes of a hyperinsulinemic clamp when glucose concentrations were clamped at ~8 mmol/L in people with or without type 2 diabetes (15). * p<0.05 versus no diabetes

Figure 7. A schematic portrayal of the splanchnic catheterization method. HA represents the hepatic artery; PV represents the hepatic vein; HV represents the hepatic vein; NSGB represents net splanchnic glucose balance; SGU represents splanchnic glucose uptake; and SGP represents splanchnic glucose production (16).

Figure 8. Rates of splanchnic glucose production observed during the final thirty minutes of a hyperinsulinemic clamp when glucose concentrations were clamped at ~8 mmol/L in people with or without type 2 diabetes (16). * p<0.05 versus no diabetes

Figure 9. Rates of splanchnic glucose uptake (upper panel) and leg glucose uptake (lower panel) observed during the final thirty minutes of a hyperinsulinemic clamp when glucose concentrations were clamped at ~8 mmol/L in people with or without type 2 diabetes (16). * p<0.05 versus no diabetes

Figure 10. Schematic portrayal of glucose metabolism in the blood, liver and urine when labeled glucose and galactose are infused intravenously and acetaminophen is given by mouth in order to sample UDP-glucuronide in the urine (16).
Figure 11. The contribution of extracellular and intracellular glucose to the hepatic UDP-glucose pool when glucose pool when glucose is clamped at ~145 mg/dl and insulin at ~300 pmol/l in people with or without type 2 diabetes (16). * p<0.05 versus no diabetes

Figure 12. Plasma glucose and insulin concentrations observed in people without diabetes, people with “mild” type 2 diabetes and people with “severe” type 2 diabetes. Infusions of glucose, insulin, somatostatin, glucagon and growth hormone started at time 0. (28)

Figure 13. Rates of endogenous glucose production observed in people who did not have diabetes, had “mild” diabetes or had “severe” diabetes either before (basal) or during a hyperglycemic clamp (28). * p<0.05 versus no diabetes

Figure 14. Rates of gluconeogenesis (upper panel) and glycogenolysis (lower panel) observed in people who did not have diabetes, had “mild” diabetes or had “severe” diabetes either before (basal) or during a hyperglycemic clamp (28). * p<0.05 versus no diabetes

Figure 15. Plasma insulin concentrations observed in people who with and without type 2 diabetes following ingestion of a meal at time zero (34).

Figure 16. Plasma insulin concentrations observed in lean non-diabetic subjects (upper panel), obese non-diabetic subjects (middle panel), and obese people with type 2 diabetes (lower panel) in the presence of either a “non-diabetic” or “diabetic” insulin profile. A prandial glucose infusion and infusions of somatostatin, insulin, glucagon and growth hormone were started at time zero (34).

Figure 17. Glucose concentrations observed in lean non-diabetic subjects (upper panel), obese non-diabetic subjects (middle panel), and obese people with type 2 diabetes (lower panel) in the presence of either a “non-diabetic” or “diabetic” insulin profile. A prandial glucose infusion and infusions of somatostatin, insulin, glucagon and growth hormone were started at time zero (34).

Figure 18. Glucose concentrations observed in lean non-diabetic subjects, obese non-diabetic subjects, and obese people with type 2 diabetes in the presence of either a “non-diabetic” insulin profile (upper panel) or “diabetic” insulin profile (lower panel). A prandial glucose infusion and infusions of somatostatin, glucagon and growth hormone also were started at time zero (34).

Figure 19. Rates of glucose clearance observed in lean non-diabetic subjects, obese non-diabetic subjects, and obese people with type 2 diabetes in the presence of either a “non-diabetic” insulin profile (upper panel) or “diabetic” insulin profile (lower panel). A prandial glucose infusion and infusions of somatostatin, glucagon and growth hormone also were started at time zero (34).

Figure 20. Rates of endogenous glucose production observed in lean non-diabetic subjects, obese non-diabetic subjects, and obese people with type 2 diabetes in the presence of either a “non-diabetic” insulin profile (upper panel) or “diabetic” insulin profile (lower panel). A prandial glucose infusion and infusions of somatostatin, insulin, glucagon and growth hormone also were started at time zero (34).
Figure 21. Plasma insulin concentrations observed during “non-diabetic” or “diabetic” insulin profiles when glucagon concentrations were either maintained constant by glucagon infusion started at time zero (non-suppressed study day), or permitted to decrease by delaying the glucagon infusion until 120 minutes. A prandial glucose infusion and infusions of somatostatin and growth hormone also were started at time zero (36).

Figure 22. Plasma glucagon concentrations observed during “non-diabetic” or “diabetic” insulin profiles when glucagon concentrations were either maintained constant by glucagon infusion started at time zero(non-suppressed study day), or permitted to decrease by delaying the glucagon infusion until 120 minutes. A prandial glucose infusion and infusions of somatostatin and growth hormone also were started at time zero (36).

Figure 23. Plasma glucose concentrations observed during “non-diabetic” or “diabetic” insulin profiles when glucagon concentrations were either maintained constant by glucagon infusion started at time zero (non-suppressed study day), or permitted to decrease by delaying the glucagon infusion until 120 minutes. A prandial glucose infusion and infusions of somatostatin and growth hormone also were started at time zero (36).

Figure 24. Schematic summary of alterations in glucose metabolism observed in people with type 2 diabetes. An arrow pointing up indicates an increase and an arrow pointing down indicates a decrease in flux.
Pathogenesis of hyperglycemia

Figure 2

Figure 3

Graphs showing glucose appearance and meal-derived glucose appearance with and without diabetes.
Pathogenesis of hyperglycemia

**Figure 4**

**Glucose Utilization**

- Oral glucose
- No diabetes
- Type 2 diabetes

**Glucose Appearance**

- Oral glucose

**Figure 5**

**Glucose**

- No diabetes
- Type 2 diabetes

**Insulin**

- Units: pmol/L
Pathogenesis of hyperglycemia

**Endogenous Glucose Production**

- No diabetes
- Type 2 diabetes

**Glucose Disappearance**

- ~150 pmol/L
- ~300 pmol/L
- ~600 pmol/L

Figure 6

**Figure 7**
Pathogenesis of hyperglycemia

Splanchnic Glucose Production

- No diabetes
- Type 2 diabetes

Figure 8
Pathogenesis of hyperglycemia

**Figure 9**

**Splanchnic Glucose Uptake**

- **μmol/kg/min**
  - No diabetes
  - Type 2 diabetes

**Leg Glucose Uptake**

- **μmol/kg/min**
  - ~150 pmol/L
  - ~300 pmol/L

**Figure 10**

**Blood** → **Hepatocyte** → **Urine**

- "Galactose" → UDP-"Galactose" → UDP-"Glucose" → UDP-Glucose
- "Glucose" → Glucokinase → "Glucose-6-P"
- "Glucose-6-P" → Pyruvate
- acetaminophen → UDP-"Gluconuride" → UDP-Glucuronide
- UDP-Glucuronide

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Pathogenesis of hyperglycemia

**Figure 11**

Contribution of Extracellular and Intracellular Glucose to Hepatic UDP Glucose Flux

![Graph showing the contribution of extracellular and intracellular glucose to hepatic UDP glucose flux.](Image)

- **UDP flux**
- **Extracellular**
- **Intracellular**

Insulin: ~300 pmol/L

**Figure 12**

Glucose

![Graph showing glucose levels in different diabetes groups.](Image)

- **No diabetes**
- **Mild type 2**
- **Severe type 2**

Glucose Disappearance

![Graph showing glucose disappearance over time.](Image)

**Figure 12 (continued)**

- **Minutes**
- **mmol/L**
Pathogenesis of hyperglycemia

Endogenous Glucose Production

![Bar chart showing endogenous glucose production at different glucose levels (Basal and Clamp) for no diabetes, mild diabetes, and severe diabetes.](chart1)

Gluconeogenesis

![Bar chart showing gluconeogenesis at different glucose levels (Basal and Clamp) for no diabetes, mild diabetes, and severe diabetes.](chart2)

Glycogenolysis

![Bar chart showing glycogenolysis at different glucose levels (Basal and Clamp) for no diabetes, mild diabetes, and severe diabetes.](chart3)

Figure 13

Figure 14
Pathogenesis of hyperglycemia

Postprandial Insulin Profile

- No diabetes
- Type 2 diabetes

Figure 15

Lean, No Diabetes

"Nondiabetic" profile
"Diabetic" profile

Obese, No Diabetes

Obese, Type 2 Diabetes

Figure 16
Pathogenesis of hyperglycemia

**Glucose Clearance**

Nondiabetic Insulin Profile
- **Lean, no diabetes**
- **Obese, no diabetes**
- **Type 2 diabetes**

**Diabetic Insulin Profile**

Figure 19

**Endogenous Glucose Production**

Nondiabetic Insulin Profile
- **Lean, no diabetes**
- **Obese, no diabetes**
- **Type 2 diabetes**

Diabetic Insulin Profile

Figure 20
Pathogenesis of hyperglycemia

### Insulin

**Nondiabetic Insulin Profile**

- Suppressed glucagon
- Nonsuppressed glucagon

**Diabetic Insulin Profile**

- Suppressed glucagon
- Nonsuppressed glucagon

*Figure 21*

### Glucagon

**Nondiabetic Insulin Profile**

- Suppressed glucagon
- Nonsuppressed glucagon

**Diabetic Insulin Profile**

- Suppressed glucagon
- Nonsuppressed glucagon

*Figure 22*
