28 Regulation of Fasting and Post-Prandial Glucose Metabolism

Keywords: Type 2 Diabetes, endogenous glucose production, splanchnic glucose uptake, gluconeo-genesis, glycogenolysis, glucose effectiveness.
Abstract: Type 2 Diabetes Mellitus (T2DM) is characterized by both fasting and post-prandial hyperglycemia. Abnormalities in hepatic glucose metabolism i.e. excessive glucose production and decreased glucose uptake have been shown to contribute to both fasting and post-prandial hyperglycemia in individuals with T2DM. Insulin induced suppression of endogenous glucose production (EGP) and splanchnic glucose uptake (SGU) are considerably impaired in T2DM when compared to nondiabetic subjects (ND) matched for age, gender and degree of body fatness. Additionally, the effect of glucose per se on suppression of endogenous glucose production is also impaired in people with T2DM. Furthermore, it has been shown that the "nonsuppressability" of post-prandial glucagon concentrations in people with T2DM contributes to post-prandial hyperglycemia through stimulation of hepatic glucose production. Additionally both higher rates of gluconeogenesis (GNG) and lack of suppression of glycogenolysis (GGL) contribute to excessive hepatic glucose production in T2DM. Therefore, dysregulation of hepatic glucose metabolism contributes significantly to both fasting and post-prandial hyperglycemia typically observed in individuals with T2DM.

BOTH GLUCOSE PRODUCTION AND DISAPPEARANCE MODULATE FASTING AND POST-PRANDIAL GLUCOSE CON-CENTRATIONS IN DIABETIC AND NON-DIABETIC HUMANS.

Glucose production is regulated by a variety of factors of which perhaps the most important are the prevailing plasma concentrations of glucose, insulin and glucagon. After an overnight fast glucose concentrations are generally in the range of 80-95 mg/dL, in healthy non-diabetic humans. At that time, endogenous glucose production (EGP) closely approximates glucose utilization (GU). Following a meal, depending on the type and amount of carbohydrate ingested, plasma glucose begins to rise 15-20 minutes after eating, reaches a peak at 45-60 minutes and then returns to pre-prandial values within 2-3 hours Fig. 1. This rise in glucose is accompanied by a rapid rise in insulin secretion while glucagon secretion falls.[1] As a result there is prompt suppression of EGP and increased SGU which in turn limits the amount of glucose that reaches the systemic circulation for disposal by peripheral tissues, i.e. muscle. Thus plasma glucose concentrations in healthy young ND humans rarely exceed 160-170 mg/dl following a mixed meal.

The situation is quite different in people with T2DM. Fasting glucose concentrations increase with increasing severity of type 2 diabetes (Fig. 1) due to inappropriately increased rates of EGP and inappropriately decreased rates of GU.[2-4] Since hyperglycemia per se suppresses EGP and stimulates GU[5] and since insulin concentrations also increase as glucose increases in people with T2DM (albeit at a reduced rate due to impaired beta cell function), glucose concentrations eventually stabilize when EGP again equals GU. In many instances, loss of glucose in the urine accounts for a substantial proportion of postprandial glucose disappearance. The concentration at which the glucose eventually equilibrates depends on a variety of factors including insulin secretion and action.

Fasting hyperglycemia is almost invariably accompanied by an excessive increase in glucose following carbohydrate ingestion Fig. 1. Whereas the integrated increase in plasma insulin commonly does not differ in T2DM and ND subjects following carbohydrate ingestion (at least in

the initial stages of T2DM)[1], the rate of increase in insulin is delayed and the amount secreted is not appropriate for the elevated glucose concentrations. In addition, glucagon secretion does not suppress and may even paradoxically increase following carbohydrate ingestion in T2DM. EGP suppression also is delayed resulting in excessive postprandial hepatic release of glucose Fig. 2. However, the rate of appearance of the ingested glucose does not differ in T2DM and ND individuals and therefore cannot account for the greater postprandial rise in glucose concentrations.[6] However, since hyperglycemia stimulates hepatic glucose uptake, the equivalent rate of meal appearance in T2DM despite much higher glucose concentrations, implies that hepatic glucose uptake also is impaired. Furthermore, the equivalent rates of overall GU despite substantially higher plasma glucose con-centrations, suggests a concomitant decrease in glucose uptake by extra-hepatic tissues.

TYPE 2 DIABETES IMPAIRS INSULIN INDUCED SUPPRESSION OF HEPATIC GLUCOSE PRODUCTION

The hyperinsulinemic euglycemic clamp method[7] allows insulin action to be assessed under conditions in which glucose and insulin concentrations are matched in diabetic and non-diabetic subjects. The amount of exogenous glucose that has to be infused to maintain euglycemia equals the algebraic sum of insulin induced stimulation of glucose uptake and suppression of glucose production. Insulin dose response curves for glucose production and uptake can be generated by infusing insulin at differing rates and by measuring glucose turnover by concurrently infusing either a radioactive or stable isotope of glucose. When glucose concentrations are clamped at constant values, glucose appearance equals glucose disappearance. Fig. 3 shows data from experiments in which glucose turnover was measured under moderate hyperglycemia in the presence of a pancreatic clamp (somatostatin-basal hormone replacement). EGP measured under these conditions was higher in the T2DM than ND subjects when insulin concentrations were matched at ~75 and ~150 pmol/l clearly documenting the presence of hepatic insulin resistance.[8] On the other hand, EGP no longer differed in the T2DM and ND subjects at insulin concentrations ~300 pmol/l and higher Fig. 4 indicating that glucose production suppresses in people with T2DM.[9] provided sufficient insulin is given. Of interest, the insulin concentrations of ~300 pmol/l were produced by infusing insulin at a rate of 1.0 mU/kg/min. Therefore, hepatic insulin resistance would have been missed if only this infusion rate had been used. This emphasizes the point that low insulin concentrations are required to assess insulin induced suppression of EGP whereas higher insulin concentrations can be used to measure insulin induced stimulation of GU. To further determine the mechanism of hepatic insulin resistance i.e. whether it was due to impaired insulin induced suppression of GNG or glycogenolysis (GGL), lean ND, obese ND and obese T2DM subjects were studied after an overnight fast using the deuterated water method and a hyperinsulinemic-euglycemic clamp. At baseline, GNG was higher in T2DM than the obese ND subjects and GGL was higher in T2DM than the lean ND subjects Fig. 5. During the clamp when glucose and insulin concentrations were matched and glucagon suppressed, both GNG and GGL were higher in T2DM than both lean and obese ND subjects. Furthermore both GNG and GGL were higher in the obese versus lean ND subjects, thus providing evidence that defects in the regulation of GGL and GNG cause hepatic insulin resistance in obese ND and T2DM humans.[10]

TYPE 2 DIABETES IMPAIRS INSULIN INDUCED SUPPRESSION OF SPLANCHNIC GLUCOSE PRODUCTION (SGP) AND STIMULATION OF SPLANCHNIC GLUCOSE UPTAKE (SGU)

EGP represents the sum of all glucose produced in the body. Multiple tissues possess the enzymes necessary to produce glucose including the liver, intestine, kidney and perhaps even muscles. In order to determine whether insulin induced suppression of hepatic glucose release

was also impaired, the hepatic vein was catheterized in the above experiments. This enabled SGP and net splanchnic glucose uptake (NSGU) (reflecting the algebraic sum of glucose production and uptake by the liver and the gut) to be measured concomitantly with EGP. As shown in Fig. 6, SGP was higher in T2DM than ND subjects at insulin concentrations of ~150 pmol/l with comparable rates being observed at insulin concentrations of ~300 pmol/l.[8] Thus excessive insulin induced suppression of SGP also is impaired in T2DM. While these studies in humans cannot distinguish hepatic from intestinal glucose release, experiments in animals suggest that rates of the latter are quite low implying increased hepatic glucose release in people with type 2 diabetes.[11]

Numerous studies have shown that insulin induced stimulation of muscle glucose uptake is reduced in type 2 diabetes.[12-15] As is evident from Fig. 7, insulin induced stimulation of SGU also is reduced. SGU was slightly but not significantly lower in the T2DM than ND subjects at insulin concentrations of ~75 pmol/l and SGU increased in ND subjects when insulin was increased to ~150 pmol/l. In contrast, SGU did not change in T2DM when insulin concentration was increased to ~150 pmol/l.[8] This resulted in rates of SGU that were significantly lower in the T2DM than ND subjects. Thus both insulin induced stimulation of SGU and insulin induced suppression of SGP are impaired in T2DM. In a similar experiment in ND subjects, an increase in insulin from ~150 to ~350 pmol/l resulted in maximal suppression of EGP, whereas SGU continued to increase when insulin was increased to ~700 pmol/l Fig. 8. In contrast, EGP progressively decreased and SGU progressively increased in the T2DM subjects as insulin increased from ~150 to ~700 pmol/l. SGU was lower in the T2DM subjects at all doses of insulin tested. On the other hand, in contrast to net glucose uptake and overall glucose disposal, the increment in SGU in response to increments in insulin did not differ between T2DM and ND subjects, implying a right shifted but parallel dose-response curve.[16]

In order to gain insight into the cause of the decrease in SGU, UDP-flux also was measured using the acetaminophen glucuronide method. As shown in Fig. 9, UDP-glucose flux measured at insulin concentrations of ~350 pmol/l was lower in T2DM than ND subjects implying that the lower rates of SGU were accompanied by decreased hepatic glycogen synthesis. Of interest, the decrease in UDP-glucose flux was entirely accounted for by a decrease in the contribution of extracellular glucose since the contribution of intracellular glucose to hepatic UDP-glucose flux did not differ between groups.[8,17] Since glucose uptake by the liver is believed to be limited by phosphorylation of glucose by hepatic glucokinase, these data strongly suggests that activation of glucokinase by insulin is impaired inT2DM and agents that enhance SGU (e.g. glucokinase activators) are likely to improve glucose tolerance.

THE EFFECTS OF TYPE 2 DIABETES ON GLUCOSE INDUCED SUPPRESSION OF GLUCOSE PRODUCTION

Glucose per se is a potent regulator of its own metabolism. In the presence of basal insulin the effect of glucose to modulate its own production and uptake is referred to as "glucose effectiveness" (GE). In order to determine whether glucose can regulate its own metabolism in people with T2DM, glucose was infused in a pattern similar to the meal appearance rates commonly observed following ingestion of 50 grams of glucose (i.e. prandial glucose profile) in the presence of somatostatin and exogenous basal insulin infusion in T2DM and ND subjects. As shown in Fig. 10, despite basal insulin concentrations, glucose con-centrations (upper panel) in ND subjects increased to ~10 mmol/l and returned to basal values within 4 hours whereas glucose concentrations in T2DM increased to ~13 mmol/l and remained elevated five hours later indicating a decrease in net GE. Tracer glucose (lower panel) was concurrently administered to determine whether the defect was in inability to suppress production or stimulate uptake. Despite the identical rates of tracer infusion T2DM subjects had higher concentrations of plasma tracer glucose than ND subjects. This was due to slower clearance and decreased mass action of

glucose to stimulate disappearance. "Minimal model" indices of GE (hot and cold) were also lower in T2DM subjects. The data indicated that GE was abnormal in people with T2DM.[5]

EGP did not differ between groups. Since glucose concentrations were higher in T2DM subjects, this implied but did not prove that glucose induced suppression of EGP also was impaired. Hawkins, et al have reported impaired glucose induced suppression of EGP in diabetic individuals with chronic poor glycemic control.[18] These authors subsequently showed that glucose induced suppression of EGP but not stimulation of GU, returned to normal when glycemic control was improved.[19] Thus, glucose induced stimulation of GU remains impaired, glucose induced suppression of EGP likely reverses with improved glycemic control in T2DM.

The Contribution of Glucagon to Excess Glucose Production in Type 2 Diabetes

Glucagon concentrations tend to be higher in T2DM following an overnight fast.[1] In order to determine whether the response to glucagon also is altered in T2DM, ND and T2DM subjects were studied on three occasions with different doses of glucagon (Fig. 11). This resulted in glucagon concentrations remaining constant at ~110 pg/ml or increasing to ~200 and ~300 pg/ml respectively in both the diabetic and non-diabetic subjects. Plasma glucose concentration and endogenous glucose production did not differ between groups indicating that hepatic sensitivity to glucagon does not differ in diabetic and non-diabetic subjects.[20]

While the above study argued against enhanced hepatic sensitivity to glucagon, they did not rule out the possibility that the lack of post-prandial suppression of glucagon contributes to excessive endogenous glucose production in people with type 2 diabetes. Healthy non-diabetic volunteers were studied on four occasions in random order. On each occasion 35 grams of glucose was infused in a pattern similar to the meal appearance rates commonly observed following ingestion of 50 grams of glucose.[21] Somatostatin along with insulin was infused to create either a "diabetic" or "non-diabetic" plasma insulin profile. On two occasions, basal glucagon infusion prevented a fall in plasma glucagon concentrations referred to as the "non-suppressed glucagon" study days, while on the other two occasions, the glucagon infusion allowed plasma glucagon concentra-tions to fall by ~50 pg/ml during the first two hours of the experiment referred to as the "suppressed glucagon" study days Fig. 12. This study demonstrated that lack of post-prandial suppression of glucagon in the presence of delayed increase in insulin such as occurs in diabetic individuals exacerbates post-prandial hyperglycemia in T2DM.

THERAPIES FOR TYPE 2 DIABETES

New and existing therapies are directed toward correcting these abnormalities of glucose metabolism. Insulin secretagogues such as sulfonylureas increases total insulin secretion. Shorter acting secretagogues such as repaglinide and nateglinide increase early postprandial insulin secretion. Incretins, incretin analogues, and inhibitors of incretin degradation such as GLP-1, exenatide, and sitagliptin increase glucose dependent insulin secretion, decrease glucagon secretion, and delays gastric emptying. Other analogues of islet peptides such as pramlintide also delay gastric emptying and inhibits glucagon secretion. Agents that improve insulin action such as thiazolidinediones increases both muscle and fat glucose uptake. Used alone or in combination, these or newer therapeutic agents have the potential of normalizing fasting and postprandial glucose concentrations in people with type 2 diabetes mellitus.

SUMMARY AND CONCLUSION

As it is evident from the above discussion, regulation of hepatic glucose metabolism is a complex and dynamic process. Glucose production is inappropriately increased and glucose disappearance inappropriately decreased in people with type 2 diabetes. Excessive post-prandial

glucose production occurs in the presence of decreased and delayed insulin secretion and hyperglucagonemia. Hyperglucagonemia contributes to post-prandial hyperglycemia by stimulating glycogenolysis. These abnormalities in hormone secretion, coupled with impaired insulin induced suppression of glucose production and stimulation of splanchnic glucose uptake likely account in large part for the excessive amounts of glucose that reach the systemic circulation for disposal by peripheral tissues following food ingestion. In contrast, when adequate basal insulin concentrations are present, neither glucagon induced stimulation of glucose production nor glucose induced suppression of glucose production differ in diabetic and non-diabetic subjects matched for gender, age and degree of obesity. Alterations in the ability of insulin, glucagon and glucose alone or in combination to regulate endogenous glucose production could contribute to the pathogenesis of hyperglycemia in people with type 2 diabetes. Normalization of hepatic glucose production i.e. GNG, GGL or ideally both are likely to improve glycemic control in people with type 2 diabetes mellitus. This would require normalization of insulin and glucagon secretion as well as hepatic insulin action.

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MULTIPLE CHOICE QUESTIONS

1. **What are the causes of fasting hyperglycemia in people with T2 DM?**
   A. Increased glucose production
   B. Decreased glucose uptake
   C. Combination of both
2. **Endogenous glucose production is regulated by the following:**
   A. Glucose
   B. Insulin
   C. Glucagon
   D. All the above
3. **Splanchnic glucose uptake is stimulated by all *except:***
   A. Hyperinsulinemia
   B. Hyperglycemia
   C. Hyperglucagonemia
   D. Following a meal
4. **In order to study post-prandial hyperglycemia all the following techniques may be utilized *except:***
   A. Mixed Meal Test
   B. Euglycemic clamp
   C. Hyperglycemic clamp
   D. OGTT
5. **Extra-hepatic Insulin action is measured by all the following *except:***
   A. IVGTT
   B. Fixed Meal Test
   C. Euglycemic Hyperinsulinemic clamp using very low dose insulin
   D. Euglycemic Hyperinsulinemic clamp using high dose insulin
6. **Hepatic Insulin action is measured most accurately by which of the following:**
   A. Mixed Meal Test
   B. Hyperinsulinemic euglycemic clamp using a low dose insulin
   C. Fasting insulin/glucagon ratio
   D. A and B only
   E. All of the above

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1. C 2. D 3. C 4. B 5. C 6. D