Insulin Sensitivity: Normal and Abnormal

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Definition

Insulin is the major anabolic hormone in the human body. Secreted by the \(\beta\) cells of the pancreatic islets, typically in response to a meal, it is fundamental in maintaining normal glucose homeostasis. Its main effect on glucose metabolism is to suppress hepatic glucose production and to stimulate whole body glucose uptake in insulin sensitive tissues, i.e., muscle, liver and fat. Abnormal/impaired insulin sensitivity or ‘insulin resistance’ therefore signifies a state of reduced peripheral and hepatic responsiveness to the biological actions of insulin.

In addition insulin has multiple and vital effects on protein (suppresses proteolysis) and fat (suppresses lipolysis) metabolism. Other recently appreciated effects include those on cellular growth, prevention of apoptosis, stimulation of the sodium-potassium pump and on vascular endothelial function.

Significance

Metabolic syndrome X or the ‘insulin resistance syndrome’ has recently caught the attention of physicians and researchers worldwide as a potentially devastating and formidable health hazard for the coming years. Impaired insulin sensitivity is the hallmark of this portfolio of metabolic abnormalities that include type-2 diabetes, obesity, dyslipidemia, hypertension and hypercoagulability. Type-2 diabetes, which is the prototypical insulin-resistant state, is projected to affect over 200 million individuals by the year 2010. South Asia will see a staggering rise of 57% in the number of people affected by the disease to an estimated 120 million [1].
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**Measurement**

Insulin sensitivity has been measured in various ways. Some of the methods are enumerated here.

**Fasting Plasma Insulin Concentrations**

This has been suggested as a simple way to measure insulin action due to its ease of measurement. However, this suffers from a number of interpretive problems and is therefore correlated very weakly to in vivo estimates of insulin action [2, 3]. The extreme variability of most insulin assays and dependence on fasting glucose levels makes this a poor index of insulin action.

**Homeostatic Model Assessment (HOMA)**

In population-based studies, the proponents of this method have used the product of fasting plasma glucose and fasting plasma insulin divided by 22.5 as an index of insulin action [4]. At best, the correlation to ‘gold standard’ measurements of insulin action is still weak (r = ~0.5–0.6) in various studies. This is not surprising due to the various assumptions this model makes. These are: (a) degree to which fasting plasma glucose is increased in individuals with impaired β-cell function reflects the shape of the normal insulin secretory response to a glucose challenge. This is unlikely to be true except in a most general sense. (b) The fasting plasma insulin concentration is directly related to the severity of insulin resistance, and hepatic and peripheral insulin resistances are the same. Clinical studies have clearly shown that to be untrue, i.e., hepatic and peripheral insulin resistances are not the same.

**Quantitative Insulin Sensitivity Check Index**

Recently Katz et al. [5] have proposed the Quantitative Insulin Sensitivity Check Index (QUICKI) derived from the logarithmic transformation of fasting glucose and insulin levels as a measure of estimating insulin sensitivity. Like most other indices, the correlation of this measure to the gold standard euglycemic clamp is modest (r = ~0.5–0.6) at best in various studies.

**Frequently Sampled Intravenous Glucose Tolerance Test**

Bergman et al. [6] devised a mathematical model, which allowed measurement of insulin sensitivity (SI) from insulin and glucose concentrations obtained from a frequently sampled intravenous glucose tolerance test (FSIVGTT). They referred to the model as ‘minimal’ because it was a simplistic model that could reliably identify physiological descriptors of glucose kinetics. The development of the minimal model was based on several assumptions and premises: (a) the dynamics of glucose kinetics following an intravenous bolus was described by a single compartment; (b) there was a lag effect of insulin on glucose effectiveness which was due to the time necessary
for insulin to traverse the capillary endothelium and elevate interstitial fluid insulin levels; (c) glucose inhibition of its production and stimulation of its utilization was proportional to its plasma concentration, and (d) insulin inhibition of glucose production and stimulation of glucose utilization was proportional to the insulin concentration in a compartment remote from plasma. Based on the above principles, the minimal model began to be used widely for estimations of $S_I$. The protocol used for the FSIVGTT entailed the administration of a glucose bolus of 300 mg/kg followed 20 min later by a bolus of regular insulin (0.03 U/kg) or intravenous tolbutamide. Fitting the resultant glucose and insulin values to the model provided estimates of $S_I$. Saad et al. [7] directly compared with each other and with the glucose clamp, estimates of insulin sensitivity obtained from the tolbutamide-boosted and insulin-boosted protocols. They found that although these indices derived from each of the protocols correlated with each other ($r = 0.7$), they were quantitatively different. Subsequently, modifications of this method that included use of glucose tracers enabled investigators to distinguish between the effects of insulin on peripheral glucose uptake and hepatic glucose production [8–10]. The advantages this technique offers include the relative simplicity of execution and the reasonable reliability in the assessment of insulin sensitivity in clinical studies.

**Oral Glucose Tolerance Test**

The standard 75-gram oral glucose tolerance test (OGTT) also provides an estimate of overall glucose tolerance and has been used to diagnose diabetes mellitus or impaired glucose tolerance. Prior to the advent of more sophisticated and reliable techniques to measure insulin sensitivity, the glucose to insulin ratio obtained from the OGTT had been used as an estimate of insulin action. But due to its poor reproducibility, the variability of glucose absorption and the variability of insulin secretion and assay are some of the innumerable confounders that detract from the reliability of this measurement.

**Insulin Tolerance Test**

In an overnight fasted individual, the glucose response over 80 min to a fixed intravenous bolus dose of regular insulin has been proposed to be a measure of insulin sensitivity. The $K_{ITT}$ represents the percent decline in plasma glucose levels per minute and is determined by the ratio of $0.693/t_{1/2}$ where the denominator is the half-life of plasma glucose decay [11]. Several practical issues limit its use. This includes the likelihood of symptomatic unpleasant hypoglycemia in those tested and a consequent rise in counterregulatory hormones which tend to offset insulin action, hence its measurement.

**Insulin Suppression Test**

This test is now rarely used. In an overnight fasted individual, 5 mg of propranolol is given as an intravenous bolus. Thereafter, infusions of glucose
(6 mg/kg/min), epinephrine (6 μg/min), propranolol (0.08 mg/min) and regular insulin (80 mU/min) are started and maintained for 180 min. Steady state plasma glucose and insulin (SSPG and SSPI) are obtained in the last hour of the test. The higher the SSPG, the lesser the insulin sensitivity [12]. Although this test ultimately heralded the concept of the euglycemic insulin clamp technique, it had multiple problems especially with use of epinephrine and propranolol on insulin action and the cardiovascular system.

**Euglycemic Insulin Clamp**

The insulin clamp technique is purported to be the gold standard for assessment of insulin sensitivity [13]. Modified with the use of glucose tracers with or without somatostatin (to inhibit pancreatic hormone secretion), this technique, though labor-intensive and operator-dependent, does provide accurate estimates of peripheral and hepatic insulin sensitivity. In the present and most advanced stage, the clamp technique involves the following: in the presence of somatostatin infusion to inhibit endogenous insulin production, intravenous infusions of insulin are used at predetermined rates to ensure constant insulin concentration. The level of insulin desired is investigator-dependent and can thus vary from the physiological to the pharmacological (hyperinsulinemic) concentrations. Concomitant basal infusions of glucagon and growth hormone ensures controlled metabolic milieu. The effect of glucose on peripheral and hepatic glucose metabolism can also be estimated with a hyperglycemic insulin clamp technique [14, 15].

**Hepatic Insulin Action**

Insulin secreted by the pancreas, directly enters the portal circulation and reaches the liver where it exerts significant metabolic effects on both glucose production and uptake.

**Glucose Production**

It is now clear from studies in animals and humans that insulin exerts a marked inhibitory effect on glucose production by the liver. It appears that the half normal suppression of hepatic glucose production occurs with an ambient insulin concentration of \( \sim 25 \mu \text{U/ml} \) [16]. This occurs due to insulin’s inhibitory effect on glycogenolysis and gluconeogenesis. Recent studies [17] have shown that a greater amount of insulin is needed to suppress gluconeogenesis than glycogenolysis in healthy humans. Insulin’s effect on hepatic glucose production is both direct by suppressing the enzymatic pathways that stimulate glycogenolysis and gluconeogenesis, stimulate glycogen synthesis, and indirect by inhibiting lipolysis and proteolysis and hence restricting the supply of 3-carbon gluconeogenic substrates like alanine, pyruvate and lactate to the liver, hence inhibiting gluconeogenesis. In the basal post-absorptive
state, under euglycemic clamp conditions [18], individuals with insulin resistance (obese nondiabetic and those with type-2 diabetes) have been shown to have greater glucose production than their lean counterparts (fig. 1). In the post-absorptive state, fasting hyperglycemia has been shown to be due to a defect in insulin-induced suppression of hepatic glucose production and stimulation of peripheral glucose uptake. Recent studies have shown [Basu R et al., submitted] that this is due to both increases in glycogenolysis and gluconeogenesis in those with mild and severe diabetes. Several studies have also shown a direct correlation between the severity of fasting hyperglycemia and the rate of endogenous glucose production in diabetic individuals (fig. 2).

Studies in the postprandial state have also shown impaired suppression of endogenous glucose production in humans after a meal [19]. It is, however, still unclear whether the systemic appearance of meal-derived glucose is altered in those with type-2 diabetes mellitus or not. Experiments using the dual tracer technique have suggested that the systemic appearance of meal-derived glucose is not altered in individuals with type-2 diabetes. However,

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**Fig. 1.** The dose response of insulin to glucose production (a) and utilization (b) in diabetic and nondiabetic humans. From Firth et al. [18].
the significant fluctuations in the tracer to tracee ratios that are inherent to these methods make the estimation of glucose turnover especially the systemic appearance of meal glucose erroneous. Recent methods applying the triple-tracer technique [20] have served to reduce significantly the non-steady-state errors of calculating glucose turnover postprandially in nondiabetic humans. Currently, experiments calculating the meal glucose turnover in diabetic individuals, using the triple-tracer technique, are under way.

Apart from the liver, recent evidence points to a small contribution of the kidneys to basal glucose production. This is so since the kidneys, like the liver, contain gluconeogenic enzymatic machinery. It is suggested [21] that, in those with type-2 diabetes, renal glucose production is increased compared to nondiabetic individuals. However, even in these individuals, the percent contribution of the kidneys to whole body glucose production is minor.

**Glucose Uptake**

Like muscle, liver also utilizes and takes up glucose from the circulation especially after a meal. However, unlike muscle, where glucose transport through glut-4 transporters is rate-limiting in the liver, the glut-2 transporters are not rate limiting for glucose entry into the liver. Once inside the liver cell, it is up to the phosphorylating enzyme glucokinase to covert glucose to glucose-6-phosphate. This enzyme is purported to be rate-limiting in hepatic glucose uptake. Unlike hexokinase in the muscle, glucokinase is not inhibited by the amount of glucose-6-phosphate present in the hepatocyte. Once inside the hepatocyte, extracellular glucose is partly stored as glycogen (direct

![Fig. 2. Elevated endogenous glucose production in diabetic humans when compared to nondiabetic individuals after a meal. From Firth et al. [19].](image-url)
pathway of glycogen synthesis) or is metabolized via glycolysis, the pentose phosphate pathway and others for energy production while the remaining amount is released into the circulation. It is also known that while insulin is the main driver of muscle glucose uptake, the glucose concentration is the primary driving force of splanchnic (hepatic) glucose uptake while insulin serves as a facilitator [Basu et al., submitted]. It stands to reason that the amount of glucose taken up by the liver (collectively termed as splanchnic glucose uptake) will influence the amount of meal-derived glucose that enters the circulation. Hence, the greater the splanchnic glucose uptake after a meal, the lesser the amount of glucose entering the circulation after a meal and vice versa (fig. 3).

Early studies [22, 23] using splanchnic catheterization techniques suggested that net splanchnic release of glucose was greater in the diabetic than nondiabetic subjects. However, the glucose and insulin concentrations were not matched between groups. Subsequent experiments done with the oral glucose euglycemic hyperinsulinemic clamp technique showed conflicting results in diabetic humans [24–26]. Recent studies using a combination of

![Fig. 3. Reduced splanchnic glucose extraction and uptake in diabetic compared to nondiabetic individuals. From Basu et al. [14].](image-url)
splanchnic catheterization and isotope dilution techniques have clearly shown that under comparable physiological hyperinsulinemia and hyperglycemia, splanchnic glucose uptake is reduced by about 50% in individuals with type-2 diabetes when compared to their nondiabetic counterparts [14]. Furthermore, using tracer techniques, the main defect in splanchnic glucose uptake has been shown to be due to a defect in the direct pathway of glycogen synthesis thereby signifying a qualitative defect in the activity of the rate-limiting hepatic enzyme glucokinase. This abnormality in these individuals holds whether glucose is delivered intravenously or through the gut as a continuous infusion through a duodenal tube [27]. Nuclear magnetic resonance studies have clearly shown that net glycogen accretion (postprandial and fasting) is reduced in individuals with type-2 diabetes compared to their nondiabetic counterparts, thus providing corroborative evidence to the putative defect in glucokinase activity [28, 29]. It remains to be seen whether the same defect holds true following a meal in those with insulin resistance.

**Muscle Insulin Action**

Muscle is the primary insulin-sensitive tissue in the human body. It appears that in healthy nondiabetic humans, an insulin level of $\sim 50 \mu$U/ml results in half maximal stimulation of peripheral (muscle) glucose uptake. It is interesting that doubling the insulin secretion inhibits hepatic glucose output by 80%, while it increases peripheral glucose uptake by only 20%. On the other hand, while the insulin effect on glucose production is virtually complete when insulin secretion rises threefold its basal levels, its effect on peripheral glucose uptake does not saturate even with the highest physiologic insulin levels. It takes a pharmacological arterial insulin concentration in excess of 500 $\mu$U/ml to saturate glucose uptake under euglycemic conditions. Thus, the sensitivity of glucose production to insulin is far greater than glucose utilization, but the capacity of the glucose utilization response is much greater than that of glucose production. Glucose transport through the low $K_m$ glut-4 transporters is rate-limiting for muscle. While part of the glucose is stored as glycogen (nonoxidative pathway), the rest is metabolized through the oxidative pathway for energy production. Since muscle does not have the key gluconeogenic enzyme glucose-6-phosphatase, it cannot release glucose into the circulation. Glucose can only leave the muscle cell as lactate to be taken up by liver for gluconeogenesis. While in the fasting state, 70% of total glucose uptake occurs in insulin-insensitive tissues like the nervous system, in the fed state 50–67% of the total glucose uptake occurs in the insulin-sensitive tissues like muscle [30].

There have been numerous studies that have clearly shown that whole body and regional glucose uptake is significantly reduced in individuals with insulin resistance. While the main defect in muscle glucose uptake in these
individuals is that of reduced glucose transport across the muscle cells, this results in reduced nonoxidative metabolism, and hence glycogen storage. Nuclear magnetic resonance studies have confirmed this observation. It has also been shown that the defect in peripheral glucose uptake contributes to fasting and postprandial hyperglycemia in those with mild and severe diabetes mellitus [31]. During clamp conditions of physiological hyperglycemia and hyperinsulinemia [14], the impaired glucose uptake in individuals with type-2 diabetes, in muscle and liver accounted almost entirely (~85%) for the decrease in total body glucose uptake, with a defect in the former making an approximately twofold greater contribution than the latter. With higher insulin concentrations, the defect in muscle glucose uptake in those with type-2 diabetes accounted for a greater contribution to the decrease in whole body glucose uptake seen in these individuals [14, 27]. These data indicate that as insulin concentrations increase, muscle makes a proportionately larger contribution to glucose disposal than the splanchnic bed in both nondiabetic and diabetic individuals both during euglycemia and hyperglycemia. Therefore, agents that selectively increase insulin action in muscle may have a greater impact than agents that selectively increase insulin action in the liver.

The relative contribution of defects in insulin action and secretion was recently demonstrated in lean nondiabetic, obese nondiabetic and matched obese diabetic individuals [32]. Whereas, obese diabetic and nondiabetic individuals had comparable defects in glucose clearance, those with type-2 diabetes also had defects in hepatic glucose production. It appears from these experiments that an isolated defect in insulin action has a more pronounced and prolonged effect than does an isolated change in the pattern of insulin secretion. Hepatic and extrahepatic insulin resistance results in marked and sustained hyperglycemia.

References

Discussion

Dr. Marette: I am quite convinced that splanchnic glucose uptake plays an important role in diabetics. However, in trying to relate your talk with those of this morning's session, I wanted to know if splanchnic glucose uptake is also regulated negatively or downregulated by cytokines which are known to be increased in the diabetic state. Since glucose seems to be an important stimulator as splanchnic glucose uptake, I was wondering if this type of regulation was also downregulated by inflammatory cytokines?

Dr. Basu: That is a very interesting question. I don’t think we know the answer to that yet because studies investigating splanchnic glucose uptake are difficult to do. As you saw we have to place catheters in various places. Certain groups have looked at splanchnic glucose uptake using diverse other techniques including PET scanning as well as the OG clamp, but I have my doubts with those techniques. Certainly Iozzo et al. [1] in Italy have looked at liver glucose uptake with PET scanning. Now one of the assumptions of PET scanning is that fluorodeoxyglucose (FDG) is given which is taken up by the liver but not metabolized or released. Unfortunately, FDG can also be easily released by the hepatocytes, hence transport is not unidirectional as is assumed by this technique, therefore the doubt. Now as I illustrated, we have to remember in splanchnic glucose metabolism or hepatic glucose metabolism that the process is different than muscle glucose uptake. There is an influx as well as an efflux of glucose. The efflux of glucose does not occur in the muscle because the muscle doesn’t have glucose-6-phosphatase. So I have my doubts about those studies using the PET technique because I don’t think they fully explain or fully account for glucose efflux from the liver although they have done fancy mathematical calculations and models to account for that. Clearly, this technique has to be validated. But basically they have suggested that elevated free fatty acid levels could alter splanchnic glucose uptake or could diminish splanchnic glucose uptake. Now they didn’t look at cytokines, but free fatty acids are possibly mediators of hepatic glucose uptake. When we looked at hepatic glucose uptake by elevated free fatty acid levels in the scenarios of splanchnic catheterization, we did not see a reduction in splanchnic glucose uptake although a reduction in muscle glucose uptake was seen. We in fact saw an elevation in splanchnic glucose uptake or a tendency for splanchnic glucose uptake to rise due to free fatty acids, but I don’t think the cytokines have been looked at as far as their effect on splanchnic glucose uptake is concerned. But as a corollary I showed the data looking at splanchnic glucose uptake during intravenous glucose infusion. In a further series of studies [2], published a couple of years back, using the same experimental technique in which our study participants also had a feeding tube, we added glucose through the nasal duodenal tube in people with diabetes and in non-diabetic individuals while they had catheters in the hepatic vein. We found that even in the presence of nasal duodenal glucose infusion, splanchnic glucose uptake was reduced by about

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50% in individuals with type-2 diabetes. So it doesn’t matter whether you take glucose intravenously or through the gut, the splanchnic glucose uptake is reduced, but you must remember that all of these were done on the somatostatin clamp. When one eats, not only the insulin levels and the glucose levels alter, but we have to take into account the incretin effect of the gastric inhibitory polypeptide, glucagon-like peptide-1 (GLP1), and we haven’t accounted for that. So clearly it is not as simple as it sounds, there are lots of complexities here.

**Dr. Go:** Basically in all your experiments you have to use somatostatin to inhibit endogenous C peptide release. The problem I have, and I have read all your papers and have tried to figure out what somatostatin is doing, giving somatostatin does have some other effects. Have you monitored some of these other effects? You already mentioned the free fatty acid level, does it change the free fatty acid level? Have you measured leptin, and can leptin be affected in this issue? In relation to what we discussed this morning about the stress situation, have you also had additional blockade in your studies, αβ blockade, to see what happened to glucose production in the liver?

**Dr. Basu:** Those are fascinating ideas. Certainly we did not measure leptin. We measured free fatty acid levels in those studies and clearly with the insulin levels going up, both in diabetic and non-diabetic individuals, the free fatty acid levels plummeted significantly, but throughout the study the free fatty acid levels were slightly higher in the diabetic than in the non-diabetic population, but they plummeted. As far as αβ blockade is concerned, that is the next step in the experiments that should logically lead from this. But yes, the reason that we have to give somatostatin is because we have to match the insulin and the glucose concentrations, otherwise there would be too many confounders and variables that would cloud interpretation of the study.

**Dr. Tan:** As a clinician your talk was very interesting in the sense that we know that home glucose monitoring is very important in the therapy and management of diabetes. Based on my practice, I measure fasting blood glucose in terms of home glucose monitoring, but I also ask my patients to check their glucose 2 h after lunch, which has been shown to be more predictive of hemoglobin A1C than a bad glucose level before a meal. The recent expert committee report on a new diagnosis for diabetes [3], Dr. Rizza is one of them, does not recommend 2 h postprandial when in fact we know that epidemiologically there is an increased risk of cardiovascular disease. What was the consensus and what do you do clinically? Do you consider or do you monitor glucose 2h after lunch or dinner to be able to get a very good hemoglobin A1C? Based on our clinical study, if we were able to get the fasting blood sugar below 140 or 2 h postprandial below 160 and 50%, we were able to get hemoglobin A1C plus 7.

**Dr. Basu:** Those are excellent points, there is no question about that. As far as I know the American Diabetes Association has not yet come up with a firm statement for monitoring postprandial glucose levels. I know Dr. Rizza is involved in a meeting to discuss that in Copenhagen. But at least in clinical practice at the Mayo Clinic we do not measure postprandial glucose levels except during pregnancy, that is the only exception. Otherwise the patients are monitored preprandially and at bed time. So there is plenty of epidemiological evidence that the postprandial glucose concentration is related to cardiovascular morbidity and mortality, but we haven’t made that transition yet in clinical practice. But clearly that is coming, postprandial glucose metabolism is going to be a major concern.

**Dr. Tantibhaedhyangkul:** Between the non-diabetic and the diabetic is there a different partition of glucose metabolism between the glycolytic pathway and free fatty acid and very low-density lipoprotein triglyceride? When you have increased free fatty acid is the hepatic production of ketone bodies also increased?

**Dr. Basu:** Those are very good questions. As far as very low-density lipoprotein triglycerides and the glycolytic pathway are concerned, I am not very sure. I know that
certainly non-oxidated glucose disposal is significantly altering in individuals with type-2 diabetes. What was the second question?

Dr. Tantibhaedhyangkul: When free fatty acid production is increased, theoretically the production of ketone bodies is also increased and these ketone bodies can be utilized by the brain, therefore ketone production is increased by the liver and disposal is also increased by the brain, and the net blood level more or less remains constant. Now when the ketone bodies utilized by the brain are increased, glucose utilization is reduced by the brain and this would contribute to the increase in blood glucose.

Dr. Basu: We did not measure ketone bodies, since the insulin concentrations were hopefully adequate to prevent ketogenesis. We did studies looking at splanchnic glucose metabolism during elevated free fatty acid levels. In those we measured ketone bodies and we did not see a rise in ketone bodies in the blood, but that of course is because the insulin concentrations were higher and insulin we know suppresses ketogenesis.

Dr. Kopelman: Can I press you a bit on glinides because when they were first introduced there was great interest on the basis of improving first-phase insulin release, but the reality in clinical practice and, as far as I am aware, in the trials is disappointing. They don’t seem to improve or enhance glucose control in type-2 diabetes. Is this simply a timing of the introduction of the drug or alternatively, if one used it earlier would it have an added effect? My concern is of course that it may enhance already established hyperinsulinemia.

Dr. Basu: Correct, I don’t know the answer to that and, then again, the other side of the coin is that with type-2 diabetes there is the story about the islet amyloid polypeptide (IAPP), and as we know IAPP is co-secreted with insulin so there is the theoretical risk that if you give insulin secretagogues to people with type-2 diabetes and stimulate insulin it could also stimulate IAPP and that could cause β-cell death. We don’t know the answer to that but I know some of our colleagues are looking at that question. They are intriguing questions and I don’t know the answers to them. Certainly, as far as insulin sensitizers are concerned, metformin through the Diabetes Prevention Program trial [4] and then Troglitazone (TZD) through the Tripod studies have shown that the earlier introduction of insulin sensitizers, whether TZD or metformin, seems to delay the progression into frank type-2 diabetes from impaired glucose tolerance. At the Mayo Clinic we are even now attempting to introduce at least metformin earlier on in people who already have an impaired fasting glucose and perhaps a bit of diabetic dyslipidemia. We start them on metformin apart from therapeutic lifestyle changes (TLC).

Dr. Bunnag: What about GLP1 and the effect on the β-cell function?

Dr. Basu: GLP1, there are a lot of studies and we have done a few studies on GLP1 too. In many ways GLP1 is a perfect antidote for type-2 diabetes, it stimulates insulin secretion in a glucose-dependent fashion, hence the risk of hypoglycemia is low, it inhibits glucagon secretion, it delays gastric emptying, so it does a lot of things that would be beneficial in an individual with type-2 diabetes. We have used GLP1 in the experimental setting; most of the volunteers in the studies vomit so that is the problem. Certainly there are studies that have looked at using exendin and the dipeptidylpeptidase-4 antagonist that increase endogenous GLP1 levels which have been shown to have fewer side effects and be beneficial in type-2 diabetes. Another point about GLP1, which is also not appreciated, is that GLP1 receptors are present in the vascular endothelium. There have been studies in animals that have shown that infusing GLP1 can increase heart rate and blood pressure. So that is a concern, and I don’t think these studies have been done yet in humans as such to see whether GLP1 has any independent vascular effect. It certainly seems to have independent effects on cardiac output, cardiac function and vascular endothelium in animals, no question about that.
Dr. Sudomo: In the case you showed, was treatment given simultaneously or one by one, step by step? Should insulin resistance be distinguished between pre- and post-receptor, for instance the role of the glucose transporter?

Dr. Basu: I will answer the second question first. Insulin resistance is a broad term, a black box. There are obviously multiple areas that could be a problem, it could be an enzymatic problem, it could be a glucose transport problem, there are many candidates or candidate genes that could be involved in so-called insulin-resistance because type-2 diabetes is clearly not a simple disease. It is a many headed beast and there is no question that there won't be one solution for type-2 diabetes to combat insulin resistance whether it is pre- or post-receptor or whatever. What was the first question?

Dr. Sudomo: In the case you showed, what kind of treatment did you chose?

Dr. Basu: Initially most individuals with type-2 diabetes are overweight, about 9 of 10 type-2 diabetics are overweight I should say. We usually start with insulin sensitizers like metformin because that is perhaps the only weight-lowering anti-diabetic agent that we know of. So we start with insulin sensitizers and then add insulin, secretagogues, metformin or TZD depending on the situation. If the fasting glucose is already high, by high I mean over 200 mg/dl, it usually signifies absolute insulin deficiency or reduced insulin reserve by the pancreas, hence we add secretagogues at that point. But for most individuals we start with the sensitizers like metformin, because it is cheaper than the TZDs.

Dr. Tappy: I would like to get back to the decreased splanchnic glucose uptake you observed in diabetic patients. I think it is an important issue because conceptually an increased glucose uptake may contribute to some of the metabolic complications of diabetes. As you mentioned glucose uptake in the liver is essentially regulated by glucokinase, and glucokinase is not acutely regulated by insulin but the expression of the gene in the liver is. Now there is this very nice work from Shimomura et al. [5] showing dual signaling of insulin at the liver cell level. As a consequence, you can get a decreased insulin action with regard to suppression of gluconeogenesis, but yet retain a full insulin effect to stimulate glucokinase expression and lipogenic enzyme activity. So my question is, is the decreased glucose uptake you observe in type-2 diabetes related to insulin deficiency during the days preceding the study?

Dr. Basu: Yes, actually I didn’t have the time to show the data. We actually recently did an insulin dose-response curve in people with type-2 diabetes and without diabetes, looking at splanchnic glucose uptake, using hepatic catheterization [6]. We have shown that people with type-2 diabetes for the same glucose levels and the same insulin levels have lower splanchnic glucose uptake at every insulin level. We looked at insulin levels of 150, 350 and 700 pmol/l, and found that for all 3 levels of insulin, given that glucose levels are constant at 165, splanchnic glucose uptake in diabetic individuals was reduced by 50% at all 3 insulin concentrations.

Dr. Tappy: But the possibility remains that the diabetic patients were hypoinsulinemic in the days before, and hence had less glucokinase expressed in their livers.

Dr. Basu: That is always a possibility because for all these laboratory studies our diabetic patients are taken off their antidiabetic medications for about 3 weeks prior to the study to avoid any confounding effect, but that is a clear possibility.

Dr. Rock: Before we get too far away from treatment, and this is more of a comment than a question. I am sure you will agree with me that in fact the lifestyle interventions that you are talking about are really the first step before metformin.

Dr. Basu: Yes, I absolutely agree, and TLC are a given, no question about it.

Dr. Rock: What we learn from the diabetes prevention trials is that even a body weight loss of only 7% is far superior to any of these drugs.

Dr. Basu: 58% for lifestyle, so TLC, which is not only tender loving care but therapeutic lifestyle changes, is a given, no questions.

Dr. Rock: It is far more effective than any of the other things.
**Dr. Go:** I was fascinated by your hepatic studies in which there is a steady state when the tracer is infused. I assume this is a glucose tracer.

**Dr. Basu:** Yes.

**Dr. Go:** So if there is a steady state, there is a glucose tracer. Did you analyze the glucose tracer itself? Did you use the tracer study to calculate some other metabolites in the liver? What is the outcome with regard to the trichloroacetic acid cycle, pentose cycle, fatty acid synthesis and all those things?

**Dr. Basu:** We didn’t look. We infused $^{14}$C-palmitate as well to look at free fatty acid metabolism and, although I did not go into that clearly, we showed that people with type-2 diabetes have increased rates of lipolysis, not only whole body lipolysis but increased splanchnic lipolysis too. But perhaps surprisingly, we found that the major contributor of whole body lipolysis was not the splanchnic tissues, it was the non-splanchnic upper body tissues that were clearly the 75% contributor to whole body lipolysis, both in diabetic and in non-diabetic individuals. Another important point that I need to make with regard to whole body lipolysis is that when we looked at the various correlates we clearly found that people with the highest levels of visceral fat have higher levels of whole body non-splanchnic upper body lipolysis. So the heavier you are not only in visceral fat but also in upper body obesity, the worse off you are.

**Dr. Go:** So in a sense what you are basically saying is that if these data can be proven, then losing weight, losing your fat mass, is one of the best solutions to your problem because the liver abnormality may not be the primary liver abnormality in diabetes, the fat mass may be the primary abnormality the way you said it.

**Dr. Basu:** As some of our predecessors have pointed out, I think if Minkowsky had been ajeusic perhaps diabetes would have been a fatty acid metabolism problem, not a glucose metabolism problem, I don’t know.

**Dr. Biolo:** Extremely elegant studies, thank you very much. Now we know all the mechanisms of hyperglycemic type-2 diabetes and we can target the drugs. I have a technical question. You of course measured the blood flow across the splanchnic area. Did you find any difference there between normal subjects and diabetics in different situations regarding blood flow?

**Dr. Basu:** Not really. Generally somatostatin was given to all subjects, diabetics and non-diabetics. Somatostatin reduces blood flow, but that was a constant confounder, and we found that blood flow tended to be a bit higher in the diabetic than the non-diabetic subjects; not significantly, but it tended to be higher, it did not reach statistical significance. But at all levels of insulin and glucose the blood flow was slightly higher in the diabetic splanchnic tissues than the non-diabetic splanchnic tissues although splanchnic glucose uptake was reduced by 50%. So it was a conservative error if at all.

**Dr. Komindr:** What is your view on the role of low-glycemic index carbohydrate in insulin sensitivity?

**Dr. Basu:** I think I had best defer that to other people who are probably much more conversant with that than I am. I stick to my glucose insulin physiology.

**Dr. Komindr:** We are talking about TLC and this is one of the things that we need to look at.

**Dr. Basu:** I am sure there are others in this room who are much more qualified than I am.

**Dr. Komindr:** We did a study published by the General Medical Association in Thailand about the use of a low-glycemic index diet for the treatment of diabetics, and we found that by giving this kind of diet for 4 weeks we can improve the insulin tolerance test response in type-2 diabetic patients [7].

**Dr. Rock:** If I can answer that. The literature on modulating the glycemic index of different sources of carbohydrate goes back probably about 20 years at this point, and what is clear is that total carbohydrate is the main issue. There are some differences
in digestibility across carbohydrate sources, but basically you have to look at the total amount of carbohydrate in addition to that score. The actual post-feeding response is heavily influenced by other factors in the meal, and so really I would like to refer you to the last good documentation from the nutrition guidelines group of the American Diabetes Association [8] in which they reviewed all the studies, but it is really simplifying to just say it is glycemic index factors.

Dr. Komindr: In our study we controlled the calories so that they have isocaloric and isocarbohydrate amounts. We also give a fiber load, so I have to give credit to the carbohydrate itself.

Dr. Rock: Then you weren’t really testing the original Jenkins glycemic index because what they tested was 50-gram carbohydrate portions (the equivalent food amounts that would provide 50 g of carbohydrate). For example carrots, there would be several cups of carrots which were compared to a couple of teaspoons of sugar. So in the context of the meal, if you control for the total amount of carbohydrate there would be one thing but the actual volume of food that the people receive would be very different according to the circumstances. So as in epidemiologic research, what has been done is to actually link this glycemic index to glycemic load. That sounds like what you are dealing with, you look at the glycemic index number but then you actually modify the amount eaten based on these other influencing factors.

Dr. Komindr: No, the glycemic index itself. We did that by giving them 50 g of each kind of carbohydrate, divided into different kinds of glycemic index carbohydrate. After we had determined that, we gave all these people the same amount of carbohydrate according to a maintaining diet. After 4 weeks we repeated the trials, and it turned out that by giving them the same amount of insulin as their glucose response, the rate of glucose decrease is faster on the lower glycemic index diet, which means the mung bean noodles given at lunch. I think these are very good trials.

References