Addressing the Insulin Secretion Defect: A Logical First-Line Approach

John E. Gerich

The pathogenesis of type 2 diabetes has been an area of intense investigation, considerable controversy, and continuing discovery. It is now clear that this is a heterogeneous condition both phenotypically and genotypically, and that acquired reversible abnormalities/risk factors also play an important role. Currently, type 2 diabetes can be viewed as developing in genetically susceptible individuals, who, because of impaired β-cell function, are incapable of increasing their insulin release appropriately to compensate for reduced insulin sensitivity which is acquired through life for various reasons (eg, obesity, aging, physical inactivity, drug use, or diet). As our knowledge of the interplay of these elements increases, there will be important consequences regarding the choice of the most appropriate therapeutic approach for individual patients. This review will analyze issues pertaining to the interaction of reduced insulin sensitivity and impaired β-cell function in type 2 diabetes, specifically: which is the primary genetic factor, which is more important in determining hyperglycemia, what is the most important site affected by impaired β-cell function and insulin sensitivity, and which, if any, should be the preferential target for therapeutic intervention.

TYPE 2 DIABETES mellitus is a heterogeneous disorder due to a combination of inherited and acquired factors that adversely affect glucose metabolism.[1] It is thought that these factors lead to diabetes mainly by affecting β-cell function and tissue insulin sensitivity. For the last decade at least, the relative contributions of impaired β-cell function and insulin sensitivity in type 2 diabetes have been controversial, especially with respect to which is the primary genetic factor; which is more important in determining hyperglycemia; what is the most important site affected by impaired β-cell function and insulin sensitivity; and which, if any, should be the preferential target for therapeutic intervention. This brief review will deal with these issues.

WHICH IS THE PRIMARY GENETIC DEFECT?

This subject has recently been reviewed.[2] Although the issue is not entirely resolved, current evidence favors β-cell dysfunction as the first demonstrable defect. The strongest data come from studies of monozygotic twins, which found that there is impaired β-cell function in the discordant twin who still has normal glucose tolerance but whose insulin sensitivity is not yet reduced.[3] Most, but not all, studies indicate that normoglucose-tolerant first-degree relatives of type 2 diabetic individuals have reduced β-cell function and normal insulin sensitivity if one carefully matches groups for gender, age, obesity, and physical fitness.[2] Finally, several studies have actually shown that weight reduction in obese patients with type 2 diabetes, who constitute more than 80% of all type 2 diabetics, can completely restore normal insulin sensitivity, but cannot reverse β-cell dysfunction.[4-6]

Taken together, these observations suggest that β-cell dysfunction is likely to be the primary genetic factor. One must bear in mind, however, that the genetics of type 2 diabetes in its most common type encountered in clinical practice are complex; it is a polygenic disorder,[1] except for similar phenotypes in maturity-onset diabetes of the young (MODY),[7] an autosomal dominant disorder, the rare genetic defects in insulin receptors,[8] and the late onset type 1 diabetes patients,[9] all of which probably account for only about 15% of phenotypic type 2 diabetes. One may question whether there are specific diabetogenic genes as opposed to genetically determined risk factors. In theory, there may be 5 to 10 genetic polymorphisms that act as risk factors for the development of type 2 diabetes but only cause the disease if a certain number are simultaneously present in combination with certain acquired risk factors.

Some of these risk factors may cause abnormal appetite and energy expenditure. These could lead to obesity and insulin resistance. Since obesity has a significant genetic component,[10] insulin resistance occurring as a result of it could be considered genetic. A similar argument could be made for body fat distribution. Nevertheless, most obese individuals who are insulin-resistant are not diabetic. What distinguishes these individuals from those who are diabetic is their plasma insulin levels, ie, the ability of their pancreatic β-cells to compensate for their insulin resistance. Therefore, in simplistic terms, one may ascribe the pathogenesis of type 2 diabetes to a genetically determined inability to compensate for decreased tissue insulin sensitivity.[11,12]

WHICH IS MORE IMPORTANT IN DETERMINING HYPERGLYCEMIA?

This question has been examined in a most sophisticated manner by determining the relative contribution of impaired β-cell function and insulin resistance to the risk of developing diabetes. Also, multivariate analysis was used to determine the relative contributions of variation in β-cell function and insulin sensitivity to variations in fasting and 2-hour plasma glucose during oral glucose tolerance tests (OGTTs). As an example of the former, Lillioja et al[13] found that impaired β-cell function, as assessed by the acute insulin response to intravenous glucose, conveyed a relative risk of 2.2 for developing type 2 diabetes, and insulin resistance a relative risk of 5.0, based on glucose clamp experiments. Two problems with such analyses are that only first-phase insulin release was examined, and that β-cell response and insulin resistance are inversely related.[14] In other

From the Department of Medicine, University of Rochester, Rochester, NY.

Supported in part by NIH/DRR/GCRC Grants No. 5M01-RR00044 and NIDDK-20411.

Address reprint requests to John E. Gerich, MD, University of Rochester School of Medicine, 601 Elmwood Ave, Box MED/CRC, Rochester, NY 14642.

0026-0495/00/4910-2004$10.00/0
doi:10.1053/meta.2000.17824

words, a reduction in insulin sensitivity usually results in a compensatory increase in insulin secretion, such as occurs in pregnancy. The foregoing analysis fails to take into consideration this relationship and would tend to underestimate the impact of an insulin secretory defect which did not permit an appropriate compensatory increase in insulin secretion in the presence of insulin resistance.

As an example of the multivariate approach, Van Haeften et al[15] used the hyperglycemic glucose clamp to examine insulin secretion and insulin sensitivity in 320 subjects: 185 with normal glucose tolerance, 98 with impaired glucose tolerance, and 37 with mild type 2 diabetes (glycated hemoglobin [HbA_{1C}] 6.4%). Multiple linear regression was then used to determine to what extent variation in β-cell function and insulin sensitivity contributed to the variations in fasting and 2-hour plasma glucose concentrations during OGTT.

As shown in Table 1, for fasting plasma glucose, the partial correlation coefficient for insulin sensitivity was comparable to that for insulin release. Similarly, for the 2-hour plasma glucose concentration during OGTT, which is a reasonable indicator of glucose tolerance, the partial correlation coefficients were comparable. These data thus provide evidence that insulin resistance and β-cell function are approximately equally important factors in determining hyperglycemia.

Another approach to these issues is the relative influence of changes in β-cell function and insulin sensitivity in determining responses to therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), there was a reduction in the ability of all monotherapies (sulfonylureas, metformin, diet, and once-daily ultralente insulin) to maintain satisfactory glycemic control ($HbA_{1C} < 7.0\%$)[16]: the newly diagnosed diabetic subjects had an approximately 50% reduction in β-cell function and a 40% reduction in insulin sensitivity. Over the course of the study, β-cell function progressively deteriorated, whereas insulin sensitivity did not change. It was concluded that progressive deterioration in β-cell function, which had started before the diagnosis of diabetes, was responsible at least in part for the loss of treatment efficacy. Similar results were obtained in the Belfast study,[17] a 10-year prospective trial in which the loss of effectiveness of diet therapy (as determined by changes in HbA_{1C} levels) was solely due to deterioration in β-cell function since insulin sensitivity did not change over the observation period.

Table 1. Multiple Linear Regression of Fasting and 2-Hour Plasma Glucose Concentrations Versus Insulin Secretion and Insulin Sensitivity

	Partial Correlation Coefficient
Fasting plasma glucose*	
Insulin release	−0.48
Insulin sensitivity	−0.31
2-h plasma glucose†	
Insulin release	−0.70
Insulin sensitivity	−0.65

*Overall correlation coefficient −0.58, $P < .0001$.
†Overall correlation coefficient −0.74, $P < .0001$.
Data from Van Haeften et al.[15]

ABNORMALITIES OF β-CELL FUNCTION

Pancreatic β cells secrete insulin in a pulsatile fashion and, in response to a square-wave increase in interstitial glucose concentration, release insulin in a biphasic manner, characterized by a "spike" lasting approximately 10 minutes (first-phase release) and followed by gradually increasing release (second-phase release). It has been suggested that these different phases of insulin release represent 2 different intraislet pools[18]: one—a rapidly releasable pool accounting for about 5% of islet insulin—represents granules close to the cell membrane and is thought to be responsible for first-phase insulin release. The second is a reserve pool, the release of which requires adenosine triphosphate–dependent mobilization of insulin-containing granules into the rapidly releasable pool for subsequent exocytosis.

Both phases of insulin release are important for maintaining normal glucose homeostasis.[19] However, considerably more emphasis has been placed on the importance of first-phase insulin, assuming that this is the major determinant of "early" insulin release, ie, the increase in plasma insulin levels observed during the initial 30 minutes following glucose or meal ingestion. Experimental attenuation of this early increase in plasma insulin by the use of somatostatin has been shown to cause glucose intolerance and late hyperinsulinemia in normal volunteers.[20]

Pulsatile insulin release in humans is characterized by small increments having a period of about 10 to 14 minutes.[21] It has been variously proposed that this pulsatility reflects intrinsic electrical activity of β cells, oscillatory fluxes in β-cell glycolysis, a negative-feedback system reflecting fluctuations in extracellular glucose concentrations, or the influence of the central nervous system mediated through intrapancreatic ganglia. Several studies have shown that pulsatile insulin release is more effective than sustained release in promoting suppression of glucose production and stimulation of glucose utilization.[22,23]

Abnormalities in both pulsatile insulin release and first-phase or early insulin release occur in people with type 2 diabetes or impaired glucose tolerance[24-26] and have been observed in healthy first-degree relatives of patients with type 2 diabetes,[26-30] as well as in glucose-tolerant monozygotic twins of type 2 diabetics.[3] Both of these abnormalities have been correlated with abnormalities in either insulin-stimulated glucose disposal[29] or insulin suppression of glucose release.[25]

The molecular basis for these abnormalities of β-cell function is unclear. Dose-response experiments suggest that the capacity to secrete insulin rather than β-cell sensitivity to glucose is involved.[24,31] However, considering that type 2 diabetes is a polygenic disorder,[2] one would expect a combination of molecular defects. Indeed, in a study of normoglucose-tolerant first-degree relatives of type 2 diabetics, Pimenta et al[27] found some individuals to have defects in only first- or only second-phase insulin release and some with defects in both phases. Hosker et al have reported similar decrements in first- and second-phase insulin release in subjects with type 2 diabetes.[32]

As recently reviewed by DeFronzo[33] and Lebovitz,[34] sulfonylureas and meglitinides are the only agents that directly act on the β cell to improve impaired insulin secretion. Both groups of drugs bind to a "sulfonylurea" receptor associated with the potassium channel, causing its closure and release of insulin.

The nonsulfonylureas apparently also have additional binding sites associated with the potassium channel, which is thought to account for their more rapid and less prolonged stimulation of insulin release.

It is presently unclear whether these insulin secretagogues preferentially affect the different phases of insulin release. In normal volunteers, glyburide and glipizide have been reported to augment both phases of insulin release in hyperglycemic clamp experiments, whereas in patients with type 2 diabetes, both agents have only improved second-phase insulin release.[35] In contrast, gliclazide has been reported to augment both phases of insulin release in patients with type 2 diabetes.[32,36] No comparable studies have been reported concerning the nonsulfonylurea agents repaglinide and nateglinide, which produce more rapid and short-lived insulin release that might be attributable to preferential enhancement of first-phase secretion.

WHAT IS THE MAJOR SITE OF INSULIN RESISTANCE?

Hyperglycemia develops when rates of glucose release into the circulation exceed rates of tissue glucose uptake. This may occur because release is increased, because uptake is reduced, or due to a combination of factors such as increased release with a lesser increase in uptake.

For many years, skeletal muscle was considered the major site of insulin resistance.[37] This concept has been challenged recently as information has accrued regarding the relative importance of skeletal muscle in glucose homeostasis.[38] In the postabsorptive state, the majority of tissue glucose uptake occurs in tissues independent of insulin[39]; brain alone accounts for about 50%. Skeletal muscle has been estimated to account for only 20% to 25%,[38] and probably half of this is simply the result of the mass action of glucose because postabsorptive circulating insulin levels are low. On the other hand, all release of glucose into the circulation by liver and kidney is sensitive to insulin and small changes in plasma insulin can alter glucose release without affecting tissue glucose uptake.[40] From these physiologic considerations, it would therefore appear that, in the postabsorptive state, release of glucose would be more likely than tissue glucose uptake to be affected by alterations in insulin availability and insulin sensitivity.

It is well established that both the liver (which is responsible for 75% to 85% of postabsorptive glucose release)[41] and skeletal muscle are insulin-resistant in type 2 diabetes.[38] During euglycemic hyperinsulinemic clamp experiments, reduced skeletal muscle glucose uptake has been convincingly demonstrated.[42] This observation has been mistakenly interpreted to indicate that in everyday life, skeletal muscle glucose uptake is reduced in people with type 2 diabetes; actually, virtually all studies to date measuring postabsorptive skeletal muscle glucose uptake have found it to be normal or increased.[43-48] The clamp experiments merely demonstrated that skeletal muscle took up glucose less efficiently in type 2 diabetics; fasting hyperglycemia and the often accompanying fasting hyperinsulinemia are able to overcome this inefficiency. In fact, the reduced systemic glucose clearance found in postabsorptive patients with type 2 diabetes can be explained by reduced glucose clearance in the brain, rather than in muscle.[49]

On the other hand, despite hyperglycemia and hyperinsulinemia—both of which should be suppressive—abnormally increased rates of glucose release are universally found in hyperglycemic patients with type 2 diabetes.[38] Thus, in an absolute sense, the liver is a more important site of insulin resistance in the postabsorptive state than skeletal muscle.

Similar arguments can be made regarding the postprandial state. Of an ingested glucose load, about 30% is immediately extracted by splanchnic tissues, presumably due to hepatic glycogen repletion.[46,50] Of the remaining glucose that enters the systemic circulation, about 15% is extracted by splanchnic tissues.[51] Skeletal muscle takes up about 30%, with brain, adipose tissue, kidney, and blood cells accounting for the remainder.[50] Thus, in terms of disposal of ingested glucose, the liver is responsible for a greater proportion than skeletal muscle (~45% *v* ~30%). In addition, the liver plays an important role in postprandial glucose homeostasis by decreasing its release of glucose into the circulation by 60% to 80%.[46,50]

Thus, the liver plays a much more important role than skeletal muscle in postprandial glucose homeostasis, and alterations in insulin availability and insulin sensitivity would be more likely to affect postprandial glucose homeostasis through changes in hepatic glucose metabolism. Studies of hepatic and skeletal muscle glucose metabolism after glucose/meal ingestion corroborate this prediction. Most studies measuring postprandial forearm or leg muscle glucose uptake in patients with type 2 diabetes have found it not to be significantly different from that of nondiabetic individuals,[43-48] whereas all studies have found reduced suppression of hepatic glucose release[44-47,52,53] and some have found reduced splanchnic glucose extraction.[46,51] Thus it appears that postprandially the liver is the most important site affected by abnormalities of insulin secretion and insulin sensitivity in type 2 diabetes.

THERAPEUTIC IMPLICATIONS

Based on the foregoing considerations, one may ask which should be the preferential target for therapeutic intervention: abnormal insulin secretion or insulin resistance?

A first attempt to answer this question may be to examine the relative efficacy of various treatment modalities. Agents currently available include sulfonylureas, which work by improving β-cell function,[54] metformin, which acts primarily by reducing excessive glucose production,[55] insulin itself, which obviously supplements endogenous insulin secretion and, in appropriate doses, overcomes insulin resistance, intestinal alpha glucosidase inhibitors,[54] which delay absorption of ingested carbohydrate and thus compensate to some degree for delayed early insulin release, and thiazolidinediones, which reduce hepatic and peripheral insulin resistance.[33] Most studies have compared their efficacy versus placebo rather than against each other and for relatively short periods, ie, less than 5 years and usually less than 1 year. In the typical obese patient with type 2 diabetes, oral agents such as sulfonylureas and nonsulfonylurea insulin secretagogues, metformin, and the thiazolidinediones rosiglitazone and proglitazone have lowered HbA_{1C} levels the most and to roughly comparable degrees (~1.0% to 1.5%), whereas other oral agents, such as the alpha glucosidase inhibitors, have lowered HbA_{1C} levels somewhat less (~0.5% to 1.0%).[33] The results with insulin have been highly dependent

on the insulin regimen employed and the aggressiveness with which targets have been pursued, but HbA_{1C} levels have been reduced in some studies by greater than 2.0% to values below 7.0%.[56] The best data available regarding this question come from the UKPDS,[9] where approximately 5,000 newly diagnosed patients with type 2 diabetes were randomized to diet, sulfonylurea, metformin, or insulin initial monotherapy. A recent publication[9] summarized the ability of each of these agents to achieve an HbA_{1C} level below 7.0% and some of the variables associated with achievement of this goal (Table 2). In the typical obese patient at the 9-year follow-up, diet, sulfonylurea, and metformin as monotherapy were able to maintain HbA_{1C} levels below 7.0% in 11%, 21%, and 13%, respectively, of patients initially randomized to that form of monotherapy. These results suggest that agents which enhance β-cell function may be superior as monotherapy to agents which reduce insulin demands (ie, improve insulin sensitivity). Nevertheless, thiazolidinediones were not included in this study and, curiously, insulin itself was effective in maintaining HbA_{1C} levels below 7.0% in only 24% of patients, and it is possible that β-cell function and glucose tolerance may have been preserved if treatment had been started earlier before the onset of overt diabetes. Indeed, it has been reported that treatment of subjects with impaired glucose tolerance with a thiazolidinedione can restore normal glucose tolerance and improve β-cell function.[57]

Table 2. Percentage of Patients in the UKPDS on Monotherapy Achieving an HbA_{1C} of Less Than 7.0% at 9 Years

Monotherapy	Lean and Obese	Obese
Diet	9	11
Sulfonylurea	24	21
Metformin	—	13
Insulin	28	24

Data from Turner et al.[9]

CONCLUSIONS

In summary, present evidence indicates that, although impaired β-cell function appears to be the major genetic component contributing to the development of type 2 diabetes, insulin resistance—largely the consequence of obesity, especially intra-abdominal obesity, physical inactivity, and glucose toxicity—is equally important as a risk factor for developing diabetes and in explaining variation in glucose tolerance. However, once diabetes has occurred, further deterioration in β-cell function appears to be a major factor in determining responses to therapeutic interventions.

REFERENCES

1. Hamman R: Genetic and environmental determinants of noninsulin dependent diabetes mellitus (NIDDM). Diabetes Metab Rev 8:287-338, 1992
2. Gerich J: The genetic basis of type 2 diabetes mellitus: Impaired insulin secretion versus impaired insulin sensitivity. Endocr Rev 19:491-503, 1998
3. Vaag A, Henriksen J, Madsbad S, et al: Insulin secretion, insulin action, and hepatic glucose production in identical twins discordant for non-insulin-dependent diabetes mellitus. J Clin Invest 95:690-698, 1995
4. Bak J, Moller N, Schmitz O, et al: In vivo action and muscle glycogen synthase activity in type II (noninsulin dependent) diabetes mellitus: Effects of diet treatment. Diabetologia 35:777-784, 1992
5. Beck-Nielsen H, Pedersen O, Lindskov H: Normalization of the insulin sensitivity and the cellular insulin binding during treatment of obese diabetics for one year. Acta Endocrinol (Copenh) 90:103-112, 1979
6. Freidenberg G, Reichart D, Olefsky J, et al: Reversibility of defective adipocyte insulin receptor kinase activity in non-insulin-dependent diabetes mellitus: Effect of weight loss. J Clin Invest 82:1398-1406, 1988
7. Fajans S: Maturity-onset diabetes of the young (MODY). Diabetes Metab Rev 5:579-606, 1989
8. Taylor S: Insulin resistance: Lessons from patients with mutations in the insulin-receptor gene. Diabetes 41:1473-1490, 1992
9. Turner R, Cull C, Frighi V, et al: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement for multiple therapies (UKPDS 49). JAMA 281:2005-2012, 1999
10. Bouchard C: Genetics and the metabolic syndrome. Int J Obesity 19:S52-S59, 1995 (suppl 1)
11. Polonsky K, Sturis J, Bell G: Noninsulin-dependent diabetes mellitus—A genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 334:777-783, 1996
12. Reaven G: Pathophysiology of insulin resistance in human disease. Physiol Rev 75:473-486, 1995
13. Lillioja S, Mott D, Spraul M, et al: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: Prospective studies of Pima Indians. N Engl J Med 329:1988-1992, 1993
14. Bergman R, Phillips J, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: Measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 68:1456-1467, 1981
15. Van Haeften T, Pimenta W, Mitrakou A, et al: Different factors regulate glucose tolerance and insulinemia in NGT and IGT subjects. Diabetes 48:A436-A437, 1999 (suppl 1, abstr)
16. UK Prospective Diabetes Study Group: U.K. prospective diabetes study 16: Overview of 6 years' therapy of type II diabetes: A progressive disease. Diabetes 44:1249-1258, 1995
17. Levy J, Atkinson A, Bell P, et al: Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: The 10-year follow-up of the Belfast Diet Study. Diabetic Med 15:290-296, 1998
18. Rorsman P, Eliasson L, Renström E, et al: The cell physiology of biphasic insulin secretion. News Physiol Sci 15:72-77, 2000
19. Gerich J: Is insulin resistance the principal cause of type 2 diabetes? Diabetes Obesity Metab 1:1-7, 1999
20. Calles-Escandon J, Robbins D: Loss of early phase of insulin release in humans impairs glucose tolerance and blunts thermic effect of glucose. Diabetes 36:1167-1172, 1987
21. Weigle D: Pulsatile secretion of fuel-regulatory hormones. Diabetes 36:764-775, 1987
22. Bratusch-Marrain P, Komjati M, Waldhausel W: Efficacy of pulsatile versus continuous insulin administration on hepatic glucose production and glucose utilization in type I diabetic humans. Diabetes 35:922-926, 1986
23. Paolisso G, Scheen A, Albert A, et al: Effects of pulsatile delivery of insulin and glucagon in humans. Am J Physiol 257:E686-E696, 1989
24. VanHaeften T, Van Maarschalkerveerd W, Gerich J, et al: Decreased insulin secretory capacity and normal pancreatic B-cell

glucose sensitivity in nonobese patients with NIDDM. Eur J Clin Invest 21:168-174, 1991

25. Mitrakou A, Kelley D, Mokan M, et al: Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med 326:22-29, 1992

26. Byrne M, Sturgis J, Sobel R, et al: Elevated plasma glucose 2h postchallenge predicts defects in B-cell function. Am J Physiol 270:E572-E579, 1996

27. Pimenta W, Kortytkowski M, Mitrakou A, et al: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. JAMA 273:1855-1861, 1995

28. O'Rahilly S, Turner R, Matthews D: Impaired pulsatile secretion of insulin in relatives of patients with noninsulin-dependent diabetes. N Engl J Med 318:1225-1230, 1988

29. Boden G, Chen X, Polansky M: Disruption of circadian insulin secretion is associated with reduced glucose uptake in first-degree relatives of patients with type 2 diabetes. Diabetes 48:2182-2188, 1999

30. Schmitz O, Porksen N, Nyholm B, et al: Disorderly and nonstationary insulin secretion in relatives of patients with NIDDM. Am J Physiol 272:E218-E226, 1997

31. Ward W, Bolgiano D, McKnight B, et al: Diminished β-cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. J Clin Invest 74:1318-1328, 1984

32. Hosker J, Rudenski A, Burnett M, et al: Similar reduction of first- and second-phase B-cell responses at three different glucose levels in type II diabetes and the effect of gliclazide therapy. Metabolism 38:767-772, 1989

33. DeFronzo R: Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 131:281-303, 1999

34. Lebovitz H: Insulin secretogogues: Old and new. Diabetes Rev 7:139-153, 1999

35. Groop L, Luzi L, Melander A, et al: Different effects of glyburide and glipizide on insulin secretion and hepatic glucose production in normal and NIDDM subjects. Diabetes 36:1320-1328, 1987

36. Della Casa L, Del Rio G, Glaser B, et al: Effect of 6-month gliclazide treatment on insulin release and sensitivity to endogenous insulin in NIDDM: Role of initial continuous subcutaneous insulin infusion-induced normoglycemia. Am J Med 90:37S-45S, 1991 (suppl)

37. DeFronzo R, Ferrannini E, Simonson D: Fasting hyperglycemia in noninsulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism 38:387-395, 1989

38. Gerich J: Is muscle the major site of insulin resistance in type 2 (noninsulin-dependent) diabetes mellitus? Diabetologia 34:607-610, 1991

39. Gerich J: Control of glycaemia. Baillieres Clin Endocrinol Metab 7:551-586, 1993

40. Hother-Nielsen O, Henriksen J, Holst J, et al: Effects of insulin on glucose turnover rates in vivo: isotope dilution versus constant specific activity technique. Metabolism 45:82-91, 1996

41. Stumvoll M, Meyer C, Mitrakou A, et al: Renal glucose production and utilization: new aspects in humans. Diabetologia 40:749-757, 1997

42. DeFronzo R, Gunnarsson R, Bjorkman O, et al: Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (Type II) diabetes mellitus. J Clin Invest 76:149-155, 1985

43. Jackson R, Perry G, Rogers J, et al: Relationship between the basal glucose concentration, glucose tolerance, and forearm glucose uptake in maturity-onset diabetes. Diabetes 22:751-761, 1973

44. Firth R, Bell P, Marsh H, et al: Postprandial hyperglycemia in patients with noninsulin-dependent diabetes mellitus. Role of hepatic and extrahepatic tissues. J Clin Invest 77:1525-1532, 1986

45. McMahon M, Marsh H, Rizza R: Effects of basal insulin supplementation on disposition of a mixed meal in obese patients with NIDDM. Diabetes 38:291-303, 1989

46. Mitrakou A, Kelley D, Veneman T, et al: Contribution of abnormal muscle and liver glucose metabolism in postprandial hyperglycemia in noninsulin-dependent diabetes mellitus. Diabetes 39:1381-1390, 1990

47. Kelley D, Mokan M, Veneman T: Impaired postprandial glucose utilization in non–insulin-dependent diabetes mellitus. Metabolism 43:1549-1557, 1994

48. Kelley D, Simoneau J: Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. J Clin Invest 94:2349-2356, 1994

49. Gerich J, Mitrakou A, Kelley D, et al: Contribution of impaired muscle glucose clearance to reduced postabsorptive systemic glucose clearance in NIDDM. Diabetes 39:211-216, 1990

50. Kelley D, Mitrakou A, Marsh H, et al: Skeletal muscle glycolysis, oxidation, and storage of an oral glucose load. J Clin Invest 81:1563-1571, 1988

51. Ferrannini E, Wahren J, Felig P, et al: The role of fractional glucose extraction in the regulation of splanchnic glucose metabolism in normal and diabetic man. Metabolism 29:28-35, 1980

52. Ferrannini E, Simonson D, Katz L, et al: The disposal of an oral glucose load in patients with noninsulin-dependent diabetes. Metabolism 37:79-85, 1988

53. Bell P, Firth R, Rizza R: Assessment of the postprandial pattern of glucose metabolism in nondiabetic subjects and patients with noninsulin-dependent diabetes mellitus using a simultaneous infusion of [2-^{3}H] and [3-^{3}H]-glucose. Metabolism 38:38-45, 1989

54. Gerich J: Oral hypoglycemic agents. N Engl J Med 321:1231-1245, 1989

55. Stumvoll M, Nurjhan N, Perriello G, et al: Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 333:550-554, 1995

56. Abraira C, Colwell J, Nuttall F, et al: Veterans affairs cooperative study on glycemic control and complications in type II diabetes (VA CSDM): Results of the feasibility trial. Diabetes Care 18:1113-1123, 1995

57. Cavaghan M, Ehrmann D, Byrne M, et al: Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. J Clin Invest 100:530-537, 1997