Glucose Regulation in Non-Insulin-Dependent Diabetes Mellitus

Interaction between Pancreatic Islets and the Liver

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The degree of fasting hyperglycemia in patients with non-insulin-dependent diabetes mellitus is dependent on the rate of hepatic glucose production. The basal rate of hepatic glucose production is increased in patients with non-insulin-dependent diabetes mellitus, and there is a positive correlation between hepatic glucose production and fasting glucose levels. Diminished secretion of insulin, impaired hepatic sensitivity to insulin's effects, or a combination of these factors could contribute to the elevated hepatic glucose production in patients with non-insulin-dependent diabetes mellitus. The relationship between insulin secretion and hepatic glucose production is regulated by a closed feedback loop operating between glucose levels and pancreatic beta cells. Although fasting insulin levels are usually comparable between patients with non-insulin-dependent diabetes mellitus and normal subjects, insulin secretion is markedly impaired in non-insulin-dependent diabetes mellitus in relation to the degree of hyperglycemia present. In fact, the degree of fasting hyperglycemia in a given patient with non-insulin-dependent diabetes mellitus is closely related to the degree of impaired pancreatic beta-cell responsiveness to glucose. Such findings suggest that impaired insulin secretion leads to increased hepatic glucose production, which raises the plasma glucose level. The resulting hyperglycemia helps to maintain relatively normal basal insulin output. Chronic sulfonylurea drug therapy of patients with non-insulin-dependent diabetes mellitus enhances pancreatic islet sensitivity to glucose, leading to increased insulin secretion, suppression of hepatic glucose production, and a decline in the steady-state fasting glucose level.

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The presence of hyperglycemia during the fasting state is a characteristic finding in patients with non-insulin-dependent diabetes mellitus and is currently a major diagnostic criterion for the disease [1]. The degree to which circulating glucose levels are elevated in the post-absorptive state depends on the balance between the rate of endogenous glucose production and the rate of removal of glucose from the circulation. Abnormalities in glucose disposal have been demonstrated in patients with non-insulin-dependent diabetes mellitus when circulating insulin levels are increased experimentally by infusion of insulin [2–5]. These abnormalities may be relevant to the post-prandial hyperglycemia that also occurs in patients with non-insulin-dependent diabetes mellitus. However, the relevance of these findings to the circulating glucose levels in the fasting state, when insulin levels are low, is unclear. This article reviews recent

findings that strongly suggest that altered regulation of endogenous glucose production is a key feature in the pathogenesis of fasting hyperglycemia in type II diabetes mellitus.

ROLE OF THE LIVER IN GLUCOSE HOMEOSTASIS

After an overnight fast, the liver is the major site of glucose production. This glucose is derived from both breakdown of glycogen and gluconeogenesis, although the former process is more important. Among the factors determining the rate of hepatic glucose production is the availability of glycogen and of gluconeogenic precursors. The availability of other fuel sources may also influence glucose production. For example, recent evidence suggests that increased availability of free fatty acids and increased lipid oxidation may directly stimulate hepatic gluconeogenesis [6]. In the presence of an adequate amount of insulin, the glucose level itself can exert an inhibitory influence on hepatic glucose production [7]. A number of hormones and neural influences also contribute to the regulation of glucose production by the liver. Physiologically important short-term regulators include insulin, glucagon, and adrenergic agonists. Other hormones such as glucocorticoids, growth hormone, and thyroid hormone have more of a long-term influence on hepatic glucose production.

Hormones secreted by the pancreatic islets drain directly into the liver, so they are ideally suited to regulate hepatic glucose production. The liver is, in fact, extremely sensitive to changes in insulin or glucagon levels. An example of this sensitivity can be seen in the increased hepatic glucose production exhibited by normal subjects whose basal insulin levels were slightly suppressed during a two-day infusion of somatostatin with glucagon replacement [8]. Although mean insulin levels only declined from 8 to 6 μU/ml, hepatic glucose production increased in all subjects. This increase in hepatic glucose production was sufficient to cause the mean fasting glucose level to increase from 89 to 114 mg/dl. Thus, even a very modest suppression of basal insulin secretion in normal humans leads to increased glucose production by the liver and fasting hyperglycemia.

An important feature of the interaction between pancreatic islet hormones and the liver is the closed-loop feedback system illustrated in **Figure 1**. An increase in hepatic glucose production leading to increased plasma glucose levels will result in stimulation of insulin secretion, which tends to inhibit hepatic glucose production and reset plasma glucose levels. For example, a change in hepatic responsiveness to insulin will not result in significant fasting hyperglycemia due to overproduction of glucose if insulin and glucagon secretion are regulated appropriately by a normally functioning hepatic-pancreatic islet feedback loop. It is also clear that in the presence of such a closed-loop feedback system, it is impossible to interpret one aspect of the system (e.g., plasma insulin levels) in a meaningful way without taking into account the other regulated variables. In particular, a comparison of circulating insulin levels in groups of individuals studied at different plasma glucose levels can lead to a gross misinterpretation of the status of pancreatic islet function.

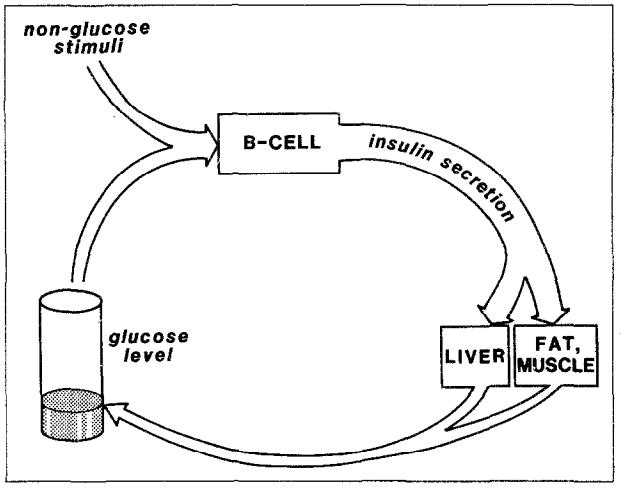

Figure 1. *Normal basal feedback loop for insulin and glucose. Insulin secretion, through effects on liver, fat, and muscle, modulates the plasma glucose level by suppressing glucose production by the liver and enhancing utilization of glucose in fat and muscle. The blood glucose level, via interaction with non-glucose stimuli, feeds back to the islet to maintain insulin output. (Adapted from [17] with permission.)*

ROLE OF HEPATIC GLUCOSE PRODUCTION IN THE FASTING HYPERGLYCEMIA OF NON-INSULIN-DEPENDENT DIABETES MELLITUS

The positive correlation between fasting plasma glucose level and the basal rate of hepatic glucose production that we have observed in patients with non-insulin-dependent diabetes mellitus is illustrated in **Figure 2** [9] and has been confirmed by several other recent studies [5,10–12]. This positive relationship is even more impressive considering the previously mentioned suppressive effect of hyperglycemia per se on hepatic glucose production, an effect that can also be demonstrated in patients with non-insulin-dependent diabetes mellitus [12]. These findings strongly suggest that increased hepatic glucose production contributes to the fasting hyperglycemia of patients with type II diabetes. Further support for the importance of the rate of hepatic glucose production as a determinant of fasting plasma glucose levels in non-insulin-dependent diabetes mellitus comes from studies of the effects of various treatment regimens to lower these levels. Dietary regimens, exercise training, and sulfonylurea drug therapy, which result in lower fasting plasma glucose levels, are also associated with a reduction in glucose production by the liver [9–11,13]. Furthermore, the

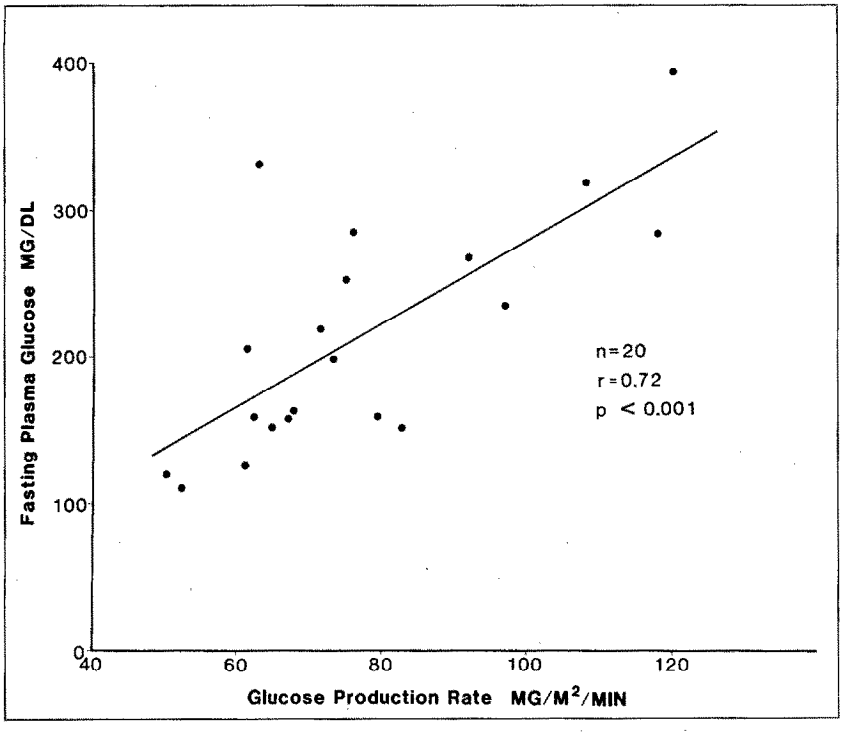

Figure 2. *Correlation between fasting plasma glucose level and glucose production rate in 20 patients with untreated non-insulin-dependent diabetes mellitus. Despite the suppressive effect of hyperglycemia on glucose production, those patients with the highest glucose levels had the highest production rates. (Adapted from [9] with permission.)*

degree to which glucose production by the liver is reduced has been correlated with the magnitude of the decline in the rate of hepatic glucose production [9–11].

The mechanism for the increased glucose production by the liver in non-insulin-dependent diabetes mellitus has received considerable attention. Although basal glucagon levels are not elevated in patients with non-insulin-dependent diabetes mellitus, glucagon responses to stimulation may be increased [14,15]. In addition, there is evidence that glucose-level suppression of glucagon secretion is impaired in patients with non-insulin-dependent diabetes mellitus, which may contribute to abnormal functioning of the glucose-pancreatic islet feedback loop [15,16]. The recent demonstration of a positive correlation between free fatty acid levels, lipid oxidation rate, and basal hepatic glucose production in Pima Indians with non-insulin-dependent diabetes mellitus [5] has suggested a role for increased mobilization of free fatty acids from fat tissue (perhaps as a result of insufficient peripheral insulin availability) to stimulate hepatic glucose pro-

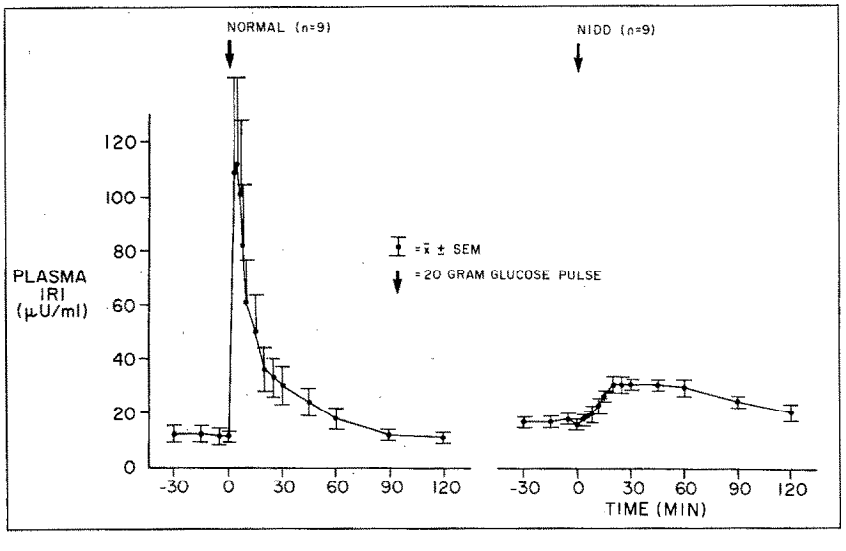

Figure 3. *Insulin responses to intravenous glucose stimulation in normal subjects and in patients with non-insulin-dependent diabetes mellitus. The average fasting plasma glucose level for the normal individuals was 85 ± 3 mg/dl; for the patients with non-insulin-dependent diabetes mellitus, the level was 166 ± 10 mg/dl. Glucose-induced first-phase insulin secretion did not occur in patients with non-insulin-dependent diabetes mellitus, but glucose-induced second-phase insulin secretion was preserved. (Adapted from [28] with permission).*

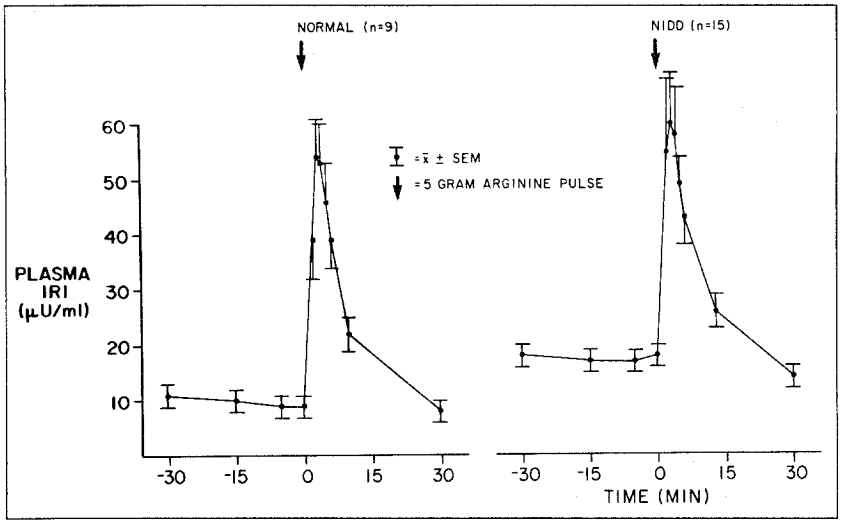

Figure 4. *Insulin response to intravenous arginine stimulation in normal subjects and in patients with non-insulin-dependent diabetes mellitus. The normal or near-normal glucose-induced second-phase (Figure 3) and arginine-induced insulin release in the diabetic subjects is partially maintained by their elevated plasma glucose levels. (Adapted from [28] with permission.)*

duction. However, the major emphasis in studies of hepatic glucose production regulation in type II diabetes has been on the roles of impaired insulin secretion and diminished hepatic sensitivity to insulin.

REGULATION OF INSULIN SECRETION IN NON-INSULIN-DEPENDENT DIABETES MELLITUS

Impaired pancreatic beta-cell sensitivity to glucose is characteristic of non-insulin-dependent diabetes mellitus and is an important contributing factor to the increased hepatic glucose production and fasting hyperglycemia in this disease. The acute stimulating effect of glucose on insulin secretion is markedly impaired in all patients with fasting hyperglycemia. A somewhat more subtle, but equally important, abnormality in beta-cell function in non-insulin-dependent diabetes mellitus involves the effect of glucose in potentiating the insulin-secretory response to a variety of non-glucose neural, substrate, and hormonal secretagogues, which contributes to the maintenance of both basal and post-prandial insulin levels [17]. As illustrated in **Figures 3** and **4**, basal insulin levels and insulin secretory responses to non-glucose secretagogues measured at the basal glucose level are not below normal values in many patients with non-insulin-dependent diabetes mellitus. However, the ability of glucose levels to potentiate the insulin-secretory response to non-glucose secretagogues is markedly impaired in these patients. This impairment has been demonstrated by studying the dose-response relationship between glucose levels and the insulin-secretory responses to intravenous administration of isoproterenol or arginine [15,18]. As shown in **Figure 5,** patients with non-insulin-dependent diabetes mellitus have lower insulin responses to arginine than do normal subjects at any matched plasma glucose level. Mathematical analysis of these dose-response curves has demonstrated a defect in islet responsiveness to maximal glucose levels, suggesting that an impaired beta-cell secretory capacity is characteristic of non-insulin-dependent diabetes mellitus [15].

The impairment in pancreatic beta-cell responsiveness to glucose can be expressed as the slope of the relationship between plasma glucose level and acute insulin re-

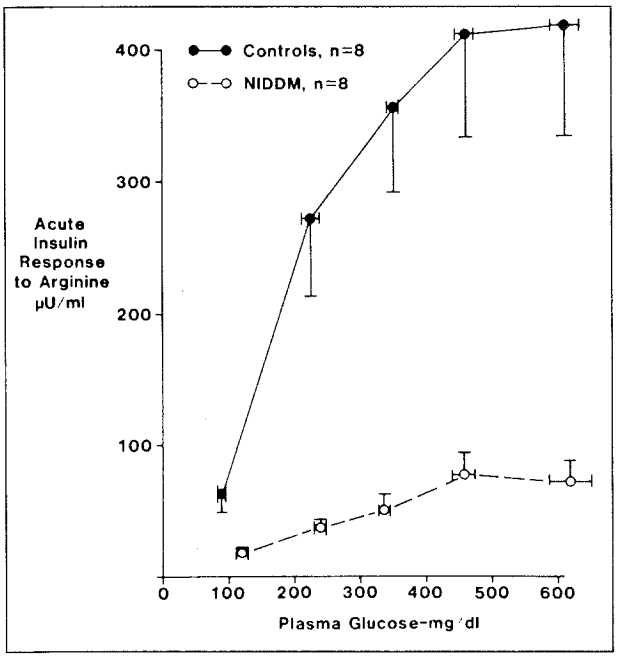

Figure 5. *Comparison of acute insulin responses (mean ± SEM) to a 5 g intravenous bolus of arginine at five plasma glucose levels in eight patients with non-insulin-dependent diabetes mellitus and eight control subjects. The insulin responses to arginine stimulation were greater in the control group than in the diabetic group at all matched glucose levels ($p < 0.001$ at all levels). (Adapted from [15] with permission.)*

sponse to a non-glucose secretagogue over the linear portion of the dose-response curve. This value correlates closely with the value of the acute insulin response to the maximal glucose level, the measure of beta-cell secretory capacity. We have found that this measure of beta-cell responsiveness to glucose is closely related to the fasting plasma glucose level over a wide range of glycemia [18]. Thus, the most severely hyperglycemic subjects have the most impaired beta-cell responsiveness to glucose.

These findings led us to postulate that basal hyperglycemia in non-insulin-dependent diabetes mellitus helps to maintain basal insulin levels and insulin responses to non-glucose secretagogues. This hypothesis is illustrated in **Figure 6**. We suggest that as beta-cell function declines, insulin levels tend to fall, and hepatic glucose production increases. Plasma glucose levels then rise until there is a sufficient potentiating effect on beta-cell function to re-establish a new steady state in which basal insulin secretion is restored toward normal levels. In this way, the increased hepatic glucose production and resulting hyperglycemia compensate for the impaired beta-cell function in non-insulin-dependent diabetes mellitus. However, because of the obligate loss of glucose via the kidneys as hyperglycemia develops, some patients with more severe beta-cell failure may not be able to maintain a sufficiently high plasma glucose level to compensate for the degree of impaired beta-cell sensitivity to glucose. These patients have low basal insulin levels and subnormal responses to both glucose and non-glucose stimuli [18].

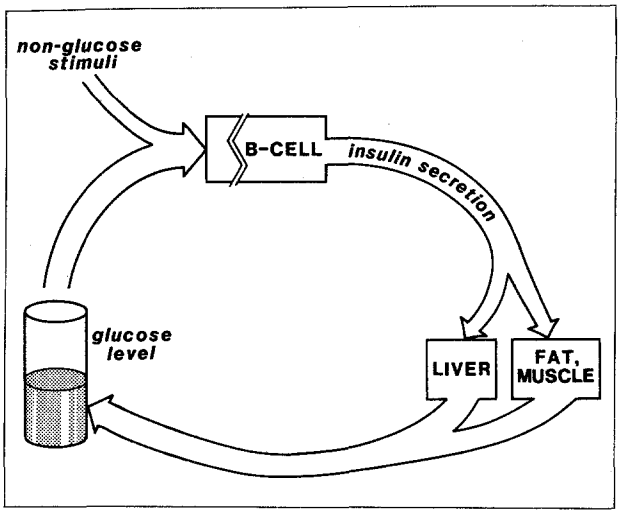

Figure 6. *Schematic illustrating how hyperglycemia compensates for beta-cell dysfunction in patients with non-insulin-dependent diabetes mellitus. Insulin deficiency from an initial islet lesion leads to increased hepatic glucose production and increased hyperglycemia that, in turn, provides increased stimulation of insulin secretion. Thus, resulting basal insulin output is restored toward normal levels. (Adapted from [17] with permission.)*

INTERACTION OF IMPAIRED BETA-CELL FUNCTION AND INSULIN RESISTANCE IN NON-INSULIN-DEPENDENT DIABETES MELLITUS

A number of studies have addressed the role of the decreased sensitivity of the liver to insulin's suppressive effect on hepatic glucose production in non-insulin-dependent diabetes mellitus. Hyperinsulinemic insulin-clamp studies in patients with type II diabetes have demonstrated a shift to the right of the dose-response curve for suppression of hepatic glucose production by insulin, with total suppression of hepatic glucose production at high insulin levels [2,5,19]. Such a decrease in hepatic sensitivity to insulin in patients with non-insulin-dependent diabetes mellitus would tend to lead to an increased rate of hepatic glucose production. However, because of the feedback loop between plasma glucose levels and beta-cell function, increased hepatic glucose production leading to increased plasma glucose levels would normally result in increased insulin secretion, which would tend to overcome the hepatic insensitivity. The net result would be the development of hyperinsulinemia, but the maintenance of relatively normal rates of hepatic glucose production as well as normal levels of plasma glucose.

Since patients with non-insulin-dependent diabetes mellitus have impaired beta-cell functioning, they are not able to compensate for the increased insulin resistance. Because of beta-cell insensitivity to glucose, the plasma glucose level may have to increase considerably in order to augment insulin secretion sufficiently to compensate for the insulin resistance. Thus, in non-insulin-dependent diabetes mellitus, the plasma glucose level and the rate of hepatic glucose production are determined by both the degree of impaired beta-cell functioning and the degree of hepatic insensitivity to insulin. A theoretic model to predict the interaction of impaired beta-cell functioning and insulin resistance in determining the level of fasting hyperglycemia has been described [20]. However, the application of such a model has been limited by the lack of a validated approach allowing quantitative comparison of the insulin resistance in individual subjects.

IMPLICATIONS FOR TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS

The important contribution of increased hepatic glucose production to fasting plasma glucose levels in non-insulin-dependent diabetes mellitus and the interaction of impaired beta-cell functioning and insulin resistance in the control of hepatic glucose production have important implications for the management of hyperglycemia in non-insulin-dependent diabetes mellitus. It is apparent that efforts to improve beta-cell functioning and to reduce hepatic unresponsiveness to insulin can both have therapeutic efficiency. Insulin therapy can substitute for the beta-cell defect and can theoretically overcome hepatic insulin resistance. However, large doses of insulin

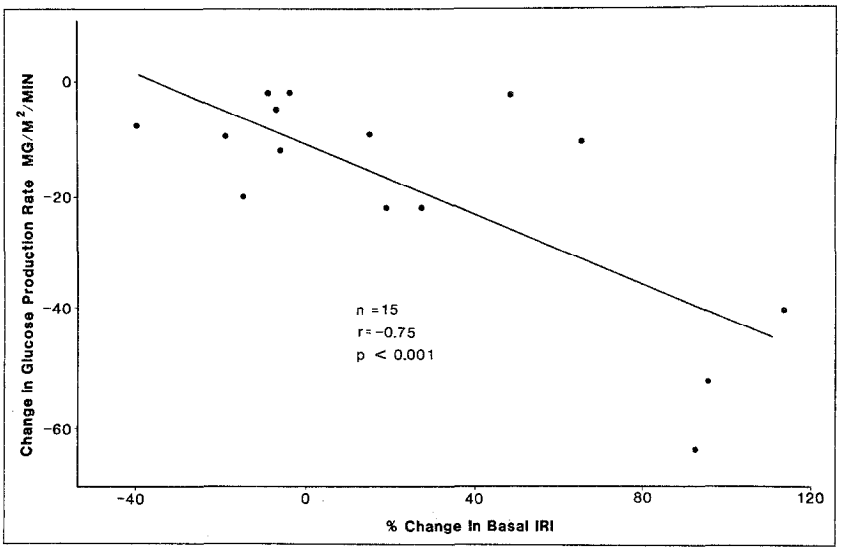

Figure 7. *Relationship between the percent change in basal insulin level and the change in glucose production rate in patients with non-insulin-dependent diabetes mellitus during three to six months of chlorpropamide therapy. Patients who had the greatest relative increase in basal insulin level had the greatest decline in glucose production rate during treatment. (Adapted from [9] with permission.)*

may be needed to achieve euglycemia [21–23], both because of the insulin resistance and because endogenous insulin secretion will be suppressed as plasma glucose levels fall as a result of the feedback loop and as a result of the direct suppression of beta-cell functioning by insulin [24–26]. It is also noteworthy that insulin treatment appears to improve the insulin resistance of patients with non-insulin-dependent diabetes mellitus [19, 21–23].

Sulfonylurea drugs have been reported to improve beta-cell functioning and to reduce insulin resistance, although the latter effect may apply to peripheral rather than hepatic insulin action [27]. Long-term sulfonylurea therapy clearly leads to increased circulating insulin levels in many patients with non-insulin-dependent diabetes mellitus [28]. The greatest absolute increases in insulin levels are observed in those patients who are the most hyperglycemic [29] and whose pre-treatment insulin levels were the lowest because of inadequately compensated beta-cell functioning. In fact, changes in insulin levels during sulfonylurea therapy are rather poor indicators of the effect of these drugs on beta-cell function, since insulin levels reflect the negative influence of the decline of glucose level on beta-cells as well as the positive influence of the drugs. When changes in glucose levels are taken into account, it is clearly evident that there is a marked enhancement of beta-cell sensitivity to glucose during sulfonylurea therapy in patients with non-insulin-dependent diabetes mellitus [29].

A number of studies have demonstrated that hepatic glucose production decreases in response to sulfonylurea therapy. As illustrated in **Figure 7**, there is a significant relationship between the magnitude of the fall in hepatic glucose production and the degree to which basal insulin levels increase [9]. This finding, plus the marked enhancement of beta-cell sensitivity to glucose, clearly link the decline in hepatic glucose production and the plasma glucose-lowering effect of sulfonylureas to the improvement in beta-cell functioning. In contrast, because of conflicting findings [9–11], the role of a possible improvement of hepatic sensitivity to insulin in the fall of hepatic glucose production and fasting plasma glucose during sulfonylurea therapy remains to be determined.

REFERENCES

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28: 1039–1057.
2. Kolterman OG, Gray RS, Griffin J, et al: Receptor and post-receptor defects contribute to the insulin resistance in non-insulin-dependent diabetes mellitus. J Clin Invest 1981; 68: 957–969.
3. Rizza RA, Mandarino LJ, Gerich JE: Mechanism and significance of insulin resistance in non-insulin-dependent diabetes mellitus. Diabetes 1981; 30: 990–995.
4. DeFronzo RA, Simonson D, Ferrannini E: Hepatic and peripheral insulin resistance: a common feature of type II (non-insulin-dependent) and type I (insulin-dependent) diabetes mellitus. Diabetologia 1982; 23: 313–319.
5. Bogardus C, Lillioja S, Howard VV, Reaven G, Mott D: Relationships between insulin secretion, insulin action, and fasting plasma glucose concentration in non-diabetic and non-insulin-dependent diabetic subjects. J Clin Invest 1984; 74: 1238–1246.
6. Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA: Effect of fatty acids on glucose production and utilization in man. J Clin Invest 1983; 72: 1737–1747.
7. Sacca L, Hendler R, Sherwin RS: Hyperglycemia inhibits glucose production in man independent of changes in glucoregulatory hormones. J Clin Endocrinol Metab 1978; 47: 1160–1163.
8. Ward WK, Best JD, Halter JB, Porte D Jr: Prolonged infusion of somatostatin with glucagon replacement increases plasma

glucose and glucose turnover in man. J Clin Endocrinol Metab 1984; 58: 449–454.
9. Best JD, Judzewitsch RG, Pfeifer MA, Beard JC, Halter JB, Porte D Jr: The effect of chronic sulfonylurea therapy on hepatic glucose production in non-insulin-dependent diabetes. Diabetes 1982; 31: 333–338.
10. Kolterman OG, Gray RS, Shapiro G, Scarlett JA, Griffin J, Olefsky JM: The acute and chronic effects of sulfonylurea therapy on type II diabetic subjects. Diabetes 1984; 33: 346–354.
11. Simonson DC, Ferrannini E, Bevilacqua S, et al: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. Diabetes 1984; 33: 838–845.
12. Revers RR, Fink R, Griffin J, Olefsky JM, Kolterman OG: Influence of hyperglycemia on insulin's in vivo effects in type II diabetes. J Clin Invest 1984; 73: 664–672.
13. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH: The effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. Diabetes 1984; 33: 311–318.
14. Palmer JP, Benson JW, Walter RM, Ensinck JW: Arginine-stimulated acute phase of insulin and glucagon secretion in diabetic subjects. J Clin Invest 1976; 58: 565–570.
15. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte D Jr: Diminished beta-cell secretory capacity in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1984; 74: 1318–1328.
16. Hollander PM, Asplin CM, Palmer JP: Glucose modulation of insulin and glucagon secretion in non-diabetic and diabetic men. Diabetes 1982; 31: 489–495.
17. Ward WK, Beard JC, Halter JB, Pfeifer MA, Porte D Jr: Pathophysiology of insulin secretion in non-insulin-dependent diabetes mellitus. Diabetes Care 1984; 7: 491–502.
18. Halter JB, Graf RJ, Porte D Jr: Regulation of insulin-secretory responses by plasma glucose levels in man: evidence that hyperglycemia in diabetes compensates for impaired insulin release. J Clin Endocrinol Metab 1979; 48: 946–954.
19. Nankervis A, Proietto J, Aitken P, Harewood M, Alford F: Differential effects of insulin therapy on hepatic and peripheral insulin sensitivity in type II (non-insulin-dependent) diabetes. Diabetologia 1982; 23: 320–325.
20. Turner RC, Holman RR, Matthews D, Hockaday RDR, Peto J: Insulin deficiency and insulin resistance interaction in diabetes: estimation of the relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism 1979; 28: 1086–1096.
21. Foley JE, Kashiwagi A, Verso MA, Reaven G, Andrews J: Improvement in in vitro insulin action after one month of insulin therapy in obese non-insulin-dependent diabetics: measurements of glucose transport and metabolism, insulin binding, and lipolysis in isolated adipocytes. J Clin Invest 1983; 72: 1901–1909.
22. Garvey TW, Olefsky JM, Griffin J, Hamman RF, Kolterman OG: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222–234.
23. Andrews WJ, Vasquez B, Nagulesparan M, Klimes I, Foley J, Unger R, Reaven GM: Insulin therapy in obese, non-insulin-dependent diabetes induces improvements in insulin action and secretion that are maintained for two weeks after insulin withdrawal. Diabetes 1984; 33: 634–642.
24. Service FJ, Nelson RL, Rubenstein AH, GO VLW: Direct effect of insulin on secretion of insulin, glucagon, gastric inhibitory polypeptide, and gastrin during maintenance of normoglycemia. J Clin Endocrinol Metab 1978; 47: 488–493.
25. DeFronzo RA, Binder C, Wahren J, Felig P, Ferrannini E, Faber OK: Sensitivity of insulin secretion to feedback inhibition by hyperinsulinemia. Acta Endocrinol (Copenh) 1981; 98: 81–86.
26. Waldhausl WK, Gasic S, Bratusch-Marrain P, Korn A, Nowotny P: Feedback inhibition by biosynthetic human insulin of insulin release in healthy human subjects. Am J Physiol 1982; 243: E476–E482.
27. Putnam WS, Andersen DK, Jones RS, Lebovitz AG: Selective potentiation of insulin-mediated glucose disposal in normal dogs by the sulfonylurea glipizide. J Clin Invest 1981; 67: 1016–1023.
28. Pfeifer MA, Halter JB, Judzewitsch RG, et al: Acute and chronic effects of sulfonylurea drugs on pancreatic islet function in man. Diabetes Care 1984; 7 (suppl 1): 25–34.
29. Judzewitsch RG, Pfeifer MA, Best JD, Beard JC, Halter JB, Porte D Jr: Chronic chlorpropamide therapy of non-insulin-dependent diabetes augments basal and stimulated insulin secretion by increasing islet sensitivity to glucose. J Clin Endocrinol Metab 1982; 55: 321–328.