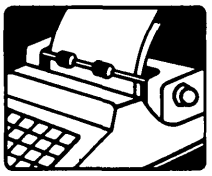
Editorial



Type II Diabetes: Toward Improved Understanding and Rational Therapy

Still not clearly defined is the fundamental defect or defects involved in the pathogenesis of type II non-insulin-dependent diabetes mellitus. Abnormalities in both insulin secretion and insulin action have been demonstrated, and there has been considerable debate as to which is the predominant lesion. During the 1970s, with the evolution of the concept of two major types of diabetes—type I and type II—a simplistic view developed that type I diabetes involved islet B-cell deficiency and a marked impairment in insulin secretion, while type II diabetes involved an impairment in insulin action, generally attributable to diminished insulin receptors on target cells.[1] This view gained credence by virtue of the observations that insulin receptor concentration increased and insulin action improved in association with the use of many of the therapeutic modalities common in the treatment of type II diabetes: calorie restriction,[2] physical training,[3] and sulfonylurea therapy.[4–6] Nevertheless, numerous studies have established that patients with type II diabetes have impaired islet B-cell function as well.[7,8] Indeed, since simple obesity is associated with impairment of insulin action and diminished insulin receptors in the absence of glucose intolerance, it would seem that impaired islet B-cell function is a universal feature of type II diabetes. Thus, type II diabetes is characterized by defects both in islet B-cell function and in insulin action.

Impaired islet B-cell function in type II diabetes is manifested in at least three ways: (1) absence of first phase insulin response to glucose, resulting in an overall *delayed* insulin secretory response to glucose;[9,10] in most circumstances, however, second phase insulin response is sufficient to control postprandial glucose excursions, restoring plasma glucose to basal (preprandial) levels before the next meal, albeit with prolonged postprandial glucose elevations;[11,12] (2) decreased sensitivity of insulin response to glucose, such that insulin response to glucose is attenuated,[13,14] and that the islet B-cell shows a relative "blindness" to hyperglycemia;[7,11] (3) decreased overall insulin secretory capacity, particularly in more severe type II diabetes.[15,16] It is important to note that impaired islet B-cell function may not be easily appreciated, since simple measurement of fasting or postprandial plasma insulin will not necessarily identify the impairment.[7] Circulating insulin levels must be related to simultaneous glycemia and to degree of obesity to be interpreted appropriately.[17] Careful quantification of islet B-cell function requires use of more sophisticated techniques.[9,18,19] Nevertheless, it can be generalized that patients with the most severe degrees of type II diabetes, evidenced by significant fasting hyperglycemia (i.e., fasting plasma glucose > 200 mg/dl), have the greatest impairment of islet B-cell function[9,18,19] and are relatively insulin deficient.[9,15,16,20]

Impaired insulin action in type II diabetes, i.e., insulin resistance, can be demonstrated in terms of both decreased insulin-mediated glucose disposal and subnormal suppression of hepatic glucose output.[21,22] The insulin resistance in type II diabetes is due to an impairment of insulin action at target cells. Although there is variability in the degree and nature of insulin resistance among different individuals and among different tissues within an individual, two categories of insulin resistance have been identified: (1) decreased insulin binding to cellular receptors as a consequence of reduced numbers of receptors;[1,21,23] and (2) defective insulin action as a consequence of defects in the effector system beyond the level of insulin binding to cellular receptors, collectively referred to as "postreceptor defects."[22,24] In patients with impaired glucose tolerance or mild type II diabetes, the degree of postreceptor defect is minimal, whereas in patients with more severe degrees of type II diabetes, evidenced by significant fasting hyperglycemia (i.e., fasting plasma glucose > 200 mg/dl), the degree of postreceptor defect is marked, resulting in the greatest degree of insulin resistance.[22]

Given that the patients with the most severe degree of impairment in islet B-cell function are also the patients with the most severe degree of impairment in insulin action, it is reasonable to hypothesize that the postreceptor insulin resistance is a consequence of impaired islet B-cell function and insulin deficiency. Elsewhere in this issue of DIABETES CARE, Scarlett et al. report their findings in which this hypothesis

was tested by treating six type II diabetic patients with exogenous insulin and measuring the effects of such treatment on in vivo insulin action.[25] Insulin therapy significantly ameliorated the postreceptor defect in insulin action in their patients, thus supporting the contention that the postreceptor defect in insulin action is an abnormality secondary to some aspect of the insulin-deficient state. This also may explain the clinical aphorism that it is much easier to maintain glucose control than it is to attain glucose control. Furthermore, these observations suggest that insulin therapy may be the treatment of choice, at least for initial therapy, in patients with severe type II diabetes, i.e., those with significant fasting hyperglycemia (fasting plasma glucose > 200 mg/dl). Correction of the postreceptor defect may then permit glycemic control to be more easily maintained even in the absence of continued insulin therapy. This thesis needs to be tested.

The article by Scarlett et al. provides the first evidence in man that postreceptor defects in insulin action may be a consequence of some aspect of the insulin-deficient state. (An earlier study by Ginsberg and Rayfield demonstrated that some type II patients show correction of insulin resistance after insulin therapy.[26]) There has been accumulating evidence in experimental animals that the induction of insulin deficiency begets insulin resistance,[27,28] particularly localized to a postreceptor site, at the level of glucose transport.[28] Recent evidence suggests that this may be due to depletion of the intracellular pool of glucose transport units,[29] which are translocated to the plasma membrane in response to insulin stimulation.[30]

A number of studies have demonstrated that re-regulation of plasma glucose in type II diabetes, as a consequence of insulin treatment, results in improvement in endogenous insulin response to a meal challenge,[31,32] and presumably improved islet B-cell function. Since insulin receptors have been identified on pancreatic islets[33] and since insulin is an important growth factor for pancreatic B-cell cultures,[34] insulin may exert important biologic actions on pancreatic islet cells just as it does on other cells. Since the most severe defects in islet B-cell function and in insulin action are present in the same patients, and since both defects are ameliorated by intensive therapy, these may very well be two manifestations of a common defect involving glucose metabolism. If the differentiated function of a cell is to release insulin, i.e., an islet B-cell, then the defect is manifested by a reduction in insulin secretion. If the differentiated function of a cell is to dispose of glucose, i.e., a target cell for insulin action, then the defect is manifested by a postreceptor defect in insulin action.

The improvement of both manifestations of the defect, that in islet B-cell function and that in insulin action, concomitant with intensive therapy with insulin and correction of hyperglycemia, is consistent with the defect being a consequence of insulin deficiency or hyperglycemia. The nature of such a defect is not yet known, but it could arise from deficient generation of an intracellular mediator responsible for transduction of insulin action within cells after insulin binding to its receptor.[35–37] It is possible that adequate chronic insulinization is necessary for maintenance of a critical basal level of insulin mediator (or mediator precursor protein) within cells, or to maintain synthesis of a critical level of glucose transporter units, as discussed above.[29,30] Alternatively, hyperglycemia may serve to alter cellular function, perhaps via nonenzymatic glycosylation of a crucial membrane protein,[38,39] resulting in blocking of insulin action. Thus, either chronic insulin deficiency or glucose toxicity could result in an alteration of cellular function such as that seen in type II diabetes. Correction of the metabolic state would lead to improvement of cellular function in terms of both islet B-cell function and insulin action, making maintenance of the improved metabolic state easier. Such control then could be maintained until some intercurrent stress (e.g., illness) results in decompensation of the regulated state.

Although the above scheme contains considerable speculation, the hypotheses generated should be testable, particularly as progress is made in identification of the family of intracellular mediators of insulin action.[35–37] Mediator generation would seem a logical control step in the metabolic pathway of insulin action, and thus a point of potential mischief in the pathogenesis of type II diabetes. Whether intracellular mediators are involved in either the stimulation of synthesis of glucose transporter units or their translocation to plasma membrane is not known. Whether mediator precursor protein (a membrane protein) could be altered by nonenzymatic glycosylation is also unknown. It can be seen, however, that the several candidate abnormalities mentioned above may even be interrelated.

It is interesting, too, that the Colorado group, in a recent abstract, have demonstrated that sulfonylurea therapy may also result in correction of the postreceptor defect in insulin action seen in type II diabetes.[40] There is in vitro evidence that sulfonylureas potentiate insulin action at a postreceptor site, namely, that of glucose transport.[41] Sulfonylureas also are well known to improve islet B-cell function.[18,42,43] Thus, this represents another example of an agent that results in concomitant improvement in both islet B-cell function and insulin action, again perhaps by a common mechanism.

Our understanding of the pathogenesis of type II non-insulin-dependent diabetes mellitus remains incomplete. The article by Scarlett et al.[25] in this issue of DIABETES CARE represents an important contribution to our knowledge of the nature of the disease, in terms of both conceptualization of mechanisms and design of rational therapy. Intensive insulin therapy may be a logical therapeutic choice to correct hyperglycemia and overcome altered cellular function, improving both insulin secretion and insulin action, thus breaking a vicious cycle and facilitating maintenance of glycemic control.

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