Review

EARLY INSULIN THERAPY IN TYPE 2 DIABETES

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Diabetes is a group of metabolic disease characterised by hyperglycemia resulting from defect in insulin secretion, insulin action or both. Impairment of insulin secretion and defects in insulin action frequently coexists in the same patient and it is often unclear which abnormality is the primary cause of the hyperglycemia. It is widely accepted that insulin resistance is an early finding, evident before the onset of hyperglycemia and predictive of the development of diabetes. However, recent studies clearly indicate that early phase insulin secretory defect may be the initial abnormality in the development of type 2 diabetes (1-2). Further insulin secretory dysfunction in type 2 diabetes is both quantitative and qualitative. In addition to the relative impairment in the amount of insulin released, the pattern of insulin secretion is abnormal (3-4). This article is focused on the critical role of impaired early insulin secretion in the pathogenesis of type 2 diabetes and the strategies to enhance insulin secretion and to improve the glucose tolerance.

NORMAL INSULIN SECRETION

Insulin Secretion is Phasic

Intravenous infusion of glucose in a non-diabetic results in an immediate increase in the plasma insulin secretion, which peaks three to five minutes after the start of infusion and is completed within ten minutes. Continuing the infusion of glucose leads to a second phase of insulin secretion that can be sustained for several hours.

The peak insulin response or the acute insulin secretory response (AIR) to glucose is an index of first phase insulin secretion and is calculated as the mean incremental in plasma insulin concentration in samples obtained 3,4 and 5 minutes after the glucose bolus.

Because the AIR is measured in response to an unphysiologic beta-cell stimulus (an intravenous glucose bolus), the relevance of this measure to normal physiology has been questioned. The fact that the AIR is correlated to early insulin responses during a mixed meal or an OGTT supports the hypothesis that first phase insulin secretion is physiologically relevant (5).

The Role of Early Insulin Secretion

The early first phase of insulin secretion is an important physiological response to rapidly shift the metabolic process from the fasting to the prandial (fed) state. During fasting, tissue insulin concentration is low, lipolysis and circulating non-esterified fatty acids are high and the glucose requirements of the brain and the other tissues are met through the endogenous glucose production. The initial increase in plasma glucose upon the ingestion of a meal stimulates rapid increase in insulin secretion. The antilipolytic action of insulin causes rapid decrease in non-esterified fatty acids and inhibition of endogenous glucose production. The early insulin secretion also primes the insulin sensitive tissues to increase the efficiency of glucose disposal. Thus within minutes, the metabolic state is efficiently shifted from glucose production towards glucose disposal.

Loss of first phase insulin secretion may alter the signalling capacity of hormones. It may be one of the factors implicated in the genesis of insulin resistance (6). In the absence of first phase insulin secretion, the stimulatory effect of glucagons on gluconeogenesis is enhanced (7).

Marked impairment in the first phase insulin secretory response occurs to intravenous glucose at a very early stage in the development of hyperglycemia. This becomes evident as by the time fasting plasma glucose concentration exceeded 109 mgs/dl (6.1 mmol/L), the first phase insulin response was found to be mostly absent (8).

Since early phase insulin secretion plays a key role in the normal suppression of endogenous glucose production in response to a meal, the loss of normal insulin secretory response could contribute to post prandial hyperglycemia in patients with diabetes. In non-diabetic subject, endogenous

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glucose production was promptly suppressed by more than 50% within thirty minutes of the meal (9). In contrast, in patients with diabetes, endogenous glucose production was approximately 50% higher at baseline and was not suppressed until 2 hours after the ingestion of a meal. Thus the inadequate suppression of endogenous glucose production resulting from impaired or absent early phase insulin secretion results in postprandial hyperglycemia. Further it has also been observed that the acute insulin response (AIR) is lower in subjects with impaired glucose tolerance (IGT), who progress to diabetes than in those revert to normal glucose tolerance (10). In subjects with IGT prandial hyperglycemia results primarily from reduced suppression of hepatic glucose production secondary to inadequate early β-cell response (11).

RESTORATION OF FIRST PHASE INSULIN SECRETION

Loss of early insulin secretion is apparently the critical event in the development of glucose intolerance. The early rise in plasma insulin concentration ensures a smoother prandial glucose profile; it may relieve the stress on the β-cell and reduce the prevalent hyperinsulinemia of the late phase after the ingestion of a meal (12). The strategy is to look for the potential therapeutic agents that augment early insulin secretion.

A. Rationale for Insulin Administration as First Line Therapy

It has already been alluded to that the acute insulin response is lost if the fasting plasma glucose level exceeds 109 mg/dl and is associated with a progressively greater risk of developing micro and macrovascular complications (8). The physiological therapeutic approach should be to restore the defective early phase insulin secretion by insulin and not by drugs to stimulate insulin secretion that are likely to cause beta cells apoptosis in the future.

i. Intravenous Insulin Infusion

Intravenous insulin infusion given during the first 30 minutes of an oral glucose tolerance test to mimic normal insulin secretory responses markedly improved the glucose tolerance and lessened late hyperinsulinemic response (12). The improvement in glucose tolerance was not simply due to the additional insulin, as a continuous infusion of identical amount of insulin has no effect on the glycemic response. This study also showed that the timing of insulin was critical, as delaying the infusion by 30 minutes did not improve the glucose tolerance. This study not only showed the critical importance of early insulin responses in determining the glycemic response to the meal but also established the therapeutic potential of augmenting early insulin secretion.

ii. Rapid Acting Insulin Preparation

Obviously intravenous insulin infusion is not a practical clinical intervention. The recently introduced rapidly acting insulin analogs (Lispro and Aspart) have been found to have therapeutic effect similar to intravenous infusion in replacing early insulin secretion. The effects of rapid acting lispro insulin and regular insulin administration before an oral glucose challenge in type 2 diabetes have been compared (12).The plasma insulin concentration peaked earlier with lispro (60 versus 120 minutes). The glucose area under the curve was 46% lower with lispro than with regular insulin. The difference was attributed to rapid and complete suppression of endogenous glucose production with lispro than with regular insulin, as rates of appearance of ingested glucose did not differ between treatments.

iii. Pulmonary Insuin-Nasal Insulin

Pulmonary insulin-nasal insulin, which are yet to be introduced, have a pharmacodynamic profile suggesting that they could have utility in replacing the early insulin response and thus controlling post prandial hyperglycemia.

B. Other Modes of Therapy

a) GLP-1

GLP-1 is a potent naturally occuring hormone that increases insulin secretion in a glucose dependent manner. Subcutaneous injection of GLP 1 improved insulin responses during the 30 minutes immediately after the ingestion of a standard test meal compared to placebo (13). This resulted in a 58% decrease in the glucose area under the curve. Drugs targeting the glucagon like peptide (GLP 1) receptors might also prove efficacious in augmenting the endogenous early insulin secretion and thus controlling the post prandial hyperglycemia.

b) Sulfonylureas

Several studies have shown that sulfonylurea augment first phase of insulin secretion. This effect does not appear specific for first phase insulin secretion as basal and second phase secretion is

increased as well. The current treatment of type 2 diabetes extensively uses sulfonylurea compounds that stimulate insulin secretion through a glucose like effect on the K^+-ATP channel (14). It seems possible that long term treatment with sulfonylurea could over stimulate β-cells, resulting in negative consequences. The frequency of hypoglycemic episodes, weight gain and loss of clinical efficacy in the long term are some of the drawbacks with them.

Yet another undesirable action of sulfonylurea is their ability to stimulate amyloid formation. Amylin and insulin are co-located in the beta cells. Any stimulus that induces the secretion of insulin also stimulates the co-secretion of amylin. Amylin (Islet Amyloid Peptide) is a constituent peptide of amyloid deposits. The amyloid deposits form between islet cells and capillaries. Accumulations of these deposits destroy islet endocrine cells and results in progressive worsening of beta cell function.

Therapy with sulfonylureas by increasing the concentration of constituent peptides of islet amyloid may lead to a greater deposition of islet amyloid and faster decline in beta cell function in type 2 diabetes than therapy with diet or insulin (15). If one is compelled to use oral agent, probably the safe choice should be insulin sparing sulfonylureas (glimipride) or non-sulfonylureas secretagogues (repaglinide or netaglinide).

HOW EARLY TO USE INSULIN?

In the natural history of diabetes, the blood glucose levels at which the insulin secretion declines could be an indicator of early insulin intervention. Very few persons with a fasting plasma glucose concentration above 109 mg/dl, the lower cut off for the recently defined category of impaired fasting glucose are able to mount even a minimal response to IV glucose challenge (16). With fasting plasma glucose of more than 140 mg., 75% of beta cell function is lost (3) and the acute insulin response is totally lost with the fasting plasma glucose above 180 mgs./dl. Similarly, insulin secretion starts to become impaired with 2-hour plasma glucose value during OGTT exceeding 200 mg/dl (17). If the beta cell secretion is declining, the attempt should be to replace insulin which is deficient, instead of stimulating the beta cell which is bound to fail over time. A reduced need for insulin production will reduce the production of amyloid peptide. This is achieved by early insulin therapy in the course of type 2 diabetes (15). One should consider insulin when fasting plasma glucose is more than 140 mg, as at this level more than 75% of beta cells are lost. Controlling plasma glucose does not mean correcting the underlying pathogenesis, which has caused hyperglycemia. Treating by any other means, other than insulin amounts to whipping the surviving 25% of beta cells to compensate for the loss of 75% of beta cell function. This approach is unphysiological as the aim is to preserve the beta cell function.

Inducing better control by intensive insulin treatment in type 2 diabetic patients has repeatedly been shown to improve insulin secretion (18). Cerasi et al (19) induced long-term glycemic control in newly diagnosed type 2 diabetics by a short-term intensive insulin treatment. According to standard practice when diet fails oral agents and/or insulin are added. In their study, they observed that normalisation of blood glucose using transient intensive insulin treatment, re-established diet responsiveness for several years. The amount of total daily insulin needed was 0.6 units/kg, which was less than the endogenous insulin production in non-diabetics. Hence, the concern of treatment-induced hyperinsulinemia is unwarranted. Further, the transient nature of the treatment should alleviate such fears. A similar observation was made by Sahay et al. (personal communication) from Hyderabad. These findings suggest that the present approach of using oral hypoglycemic agents in the management of newly diagnosed type 2 diabetes may need revision.

The metabolic disturbance in the natural history of type 2 diabetes does not occur in sequential events. The insulin secretory dysfunction and resistance to the action of insulin occurs in every stage of the disease as it progresses from normal glucose tolerance to frank diabetes and thus both these abnormalities are to be addressed in the prevention and manaement (20). A logical approach to correct the pathogenesis of hyperglycemia is to restore insulin deficiency and to rectify resistance to the action of insulin. This is possible in persons who fail to respond to a meal plan with oral anti diabetic drugs or insulin, but the later mode of therapy has a distinct advantage (18,19). With the normalisation of blood sugar, by using insulin, the glucotoxicity declines and the insulin secretion and action improves. After the correction of glucotoxicity, further management could be insulin or insulin sparing secretogogues with or without combination of insulin sensitizers. Probably by practicing evidence-based medicine to protect and preserve the beta cells, the life of diabetics will be a lot more better in the future.

REFERENCES

1. Kim DJ, Lee MS, Kim KW, Lee MK: Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metab Clin Exp 2001; 50(5): 590-3.

2. Pimenta, W. Kortykowski, A. Mitrakou, T. Jenssen, H. Yki Jarvinen, W. Evron, G. Dailey, J. Gerich: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM JAMA 1995; 273: 1855-61.

3. Porte D Jr. Banting Lecture 1990. Beta-cells in type II diabetes mellitus. Diabetes 1991; 40: 165-80.

4. Byrne MM, Sturis J, Cavaghan M, O'Meara NM, Polonsky KS. Insulin secretion in humans. Physiological regulations and alterations in disease states. *In:* Le Roith D, Taylor SI *(eds)* Diabetes mellitus: a fundamental and clinical text 2000. Lippincott, Philadelphia, pp 105-14.

5. Partley RE, Weyer C. The role of impaired early insulin secretion in the pathogenesis of type II diabetes mellitus. Diabetologia 2001; 44: 929-45.

6. Luzi L, De Fronzo RA. Effect of loss of first phase insulin secretion on hepatic glucose production and tissue glucose disposal in humans. Amer Jour Physiol 1989; 257:E 241-6.

7. Steiner KE, Mounton SM, Williams PE, Bowles CR, Cherrington AD: The relative importance of first and second-phase insulin secretion in countering the action of glucagon on glucose turnover in the conscious dog. Diabetes 1982; 31: 964-72.

8. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensink JW, Bierman EL, Porte D Jr Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976; 42: 222-9.

9. Kelley D, Mokan M Veneman T. Impaired postprandial glucose utilization in non-insulin-dependent diabetes mellitus. Metabolism 1994; 43: 1549-57.

10. Weyer C, Bogardus C, Mott Dm, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104: 787-94.

11. Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, Gerich J. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med 1992; 326: 22-9.

12. Bruttomesso D, Pianta A, Mari A et al. Restoration of early rise in plasma insulin levels improves the glucose tolerance in type 2 diabetic patients. Diabetes 1999; 48: 99-105.

13. Todd JF, Edwards CM, Ghatei MA, Mather HM, Bloom SR. Subcutaneous glucagons-like peptide-1 improves postprandial glycemic control over a 3-week period in patients with early type 2 diabetes. Clin Sci (Colch) 1998; 95: 325-9.

14. Grill Valdemar and Bjorklund Anneli. Overstimulation and β-cell function. Diabetes 2001; 50, (supplement 1) S122-S124.

15. Rachman J, Levy JC, Barrow BA, Payne MJ, Turner RC, Holman RR: Changes in Amylin and amylin-like peptide concentrations and b-cell function in response to sulfonylurea or insulin therapy in NIDDM. Diabetes Care 1998; 21: 810-6.

16. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of Diabetes mellitus. Diabetes Care 1999; 22: S5-S19.

17. DeFronzo, F. The triumvirate: β-cell, muscle and liver: a collusion responsible for NIDDM. Diabetes 1988; 347: 667-87.

18. Kosaka K, Kuzuya T, Akanuma Y, Hagura R. Increase in insulin response after treatment of overt maturity-onset diabetes independent of the mode of treatment. Diabetologia 1980; 18: 735-40.

19. Ilkova Hasan, Glaser Benjamin, Tunckale Aydin, Bagriacik Nazif, Cerasi Erol: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin teatment. Diabetes Care 1997; 20: 1353-6.

20. Weyer C, Bogardus C, Mott Dm, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care 2001; 24: 89-94.