Islet Cell Function – Its Role in the Onset and Progression of Type 2 Diabetes

a report by
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Studies of the natural history of type 2 diabetes have transformed views on the nature of the condition in the last two decades. The Belfast Study is one of the earliest and most complete studies to observe the change in blood glucose control during six years of best possible management by dietary means.[1] After the rapid initial fall from presenting blood glucose levels over 11mM, mean fasting blood glucose was maintained around 8mM for only two years before an inexorable rise occurred. By six years after diagnosis mean plasma glucose was over 10mM. This work is all the more impressive as no oral agent therapy was used during the course of the study which truly observed natural history modified only by consistent and expert dietary advice. Calculated beta cell function revealed a fall from around 30% of normal function at diagnosis to around 22% after six years.[2] Immediately these data raise questions:

- How much loss of islet cell function can be tolerated without elevation of blood glucose levels?

- What was happening in the islets during and beyond the phase leading up to diabetes?

- Are these processes modifiable?

- Did the process really commence at the time suggested by extrapolating backwards the rate of decline – around nine years before diagnosis?

Subsequently, the UK Prospective Diabetes Study confirmed the fact that type 2 diabetes is a moving target, requiring successive addition of oral hypoglycaemic agents and eventually insulin therapy.[3] Extrapolation suggested a prodromal phase of islet cell decline of around 12 years. Minds became concentrated on unravelling the mysteries of the subclinical phase of type 2 diabetes in order to understand the progressive nature of the condition.

Histological Studies

Most of the studies of cellular composition of the pancreas in type 2 diabetes have demonstrated a decreased beta cell mass. Such studies are complicated by post-mortem autolysis and lack of full clinical details. These confounders were minimised in a recent study from the Mayo clinic.[4] This study observed a 63% decrease in beta cell mass in an obese type 2 diabetic group compared with an obese non-diabetic group. Remarkably, they also observed a 40% decrease in beta cell mass in subjects who had had impaired fasting glucose. Given that it is established that a 50% pancreatectomy in humans causes loss of normal glucose regulation[5] the degree of beta cell loss observed in post-mortem studies of type 2 diabetes is sufficient to account for at least some part of the hyperglycaemia.

Beta cell number will be determined by initial attained number and the subsequent rate of turnover. It is clear that a steady rate of neogenesis co-exists with a steady rate of apoptosis.[6] Butler and colleagues observed that the frequency of beta-cell apoptosis was increased 10-fold in lean and three-fold in obese cases of type 2 diabetes compared with their respective nondiabetic control group.[4] This is important as the dynamic nature of this process may be susceptible to therapeutic intervention. In this respect it is important to note that fatty acid accumulation can increase rates of apoptosis.[7,8]

Amyloid accumulation in the islet remains a contentious matter. Butler observed amyloid plaques in 81% of type 2 pancreas compared with 10% in non-diabetic pancreas. Despite intensive work on the secretion of islet associated polypeptide the pathogenic significance of amyloid accumulation, and any potential for its modification, is uncertain.

Fewer studies have examined change in alpha cell number in the pancreas of people with type 2 diabetes. A doubling of alpha cell number has been reported.[9] A more recent study observed a ratio of alpha to beta cell areas of 0.30 in non-diabetic compared with 0.83 in type 2 diabetic pancreas.[10] The published literature is less extensive than on beta cell number, but it appears that alpha cell number is increased in type 2 diabetes.

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Change in Beta Cell Function

The earliest detectable change in beta cell function is loss of first phase insulin secretion. Although this is an artificial phenomenon relating to the intravenous glucose tolerance test, it has a day to day correlate in the normal brisk increase in insulin secretion over the first 15 minutes or so after eating. This is already blunted in impaired glucose tolerance. Although hyperinsulinaemia has been said to be the earliest abnormality in the development of type 2 diabetes, it has to be considered that this is merely the physiological response to obesity and not strictly part of the pathogenesis of diabetes. The main characteristic of insulin secretion in type 2 diabetes is that it is inadequate to control postprandial blood glucose levels. As each individual goes through the process of requiring ever higher doses of ever more oral hypoglycaemic agents, and ultimately requiring insulin, the apparent beta cell defect worsens.

Change in Alpha Cell Function

Hyperglucagonaemia is typical of both type 2 diabetic subjects and their offspring.[13] Furthermore, it is present in impaired glucose tolerance at the same time as the earliest detectable beta cell deficit.[14] After meals plasma glucagon levels decrease in normal subjects. However, in type 2 diabetes plasma glucagon exhibits a paradoxical rise.[15] When the molar ratio of glucagon to insulin is plotted it is found to parallel the time course of HGP suppression and recovery although the continued high glucagon levels will also inhibit hepatic glycogen synthesis.[16]

The effect of such hyperglucagonaemia was investigated by mimicking the glucose and insulin response to a glucose load whilst either maintaining plasma glucagon levels or allowing the normal suppression.[17] This was achieved by somatostatin suppression of both insulin and glucagon and intravenous infusion of hormones and glucose in

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The situation is complicated by the fact that the set-point for insulin secretion can be acutely modified in normal individuals. When glucose is infused to create a small increase in blood glucose, a subsequent glucose challenge will elicit a lower insulin response.[11] A similar phenomenon is observed when hyperglycaemia in diabetes is controlled, for instance, by short term insulin treatment. For a period of days insulin secretion and blood glucose control remains reasonable once the treatment is withdrawn. Interpretation of information on the level of beta cell competence at any one time must take into account recent change in blood glucose itself.

The inexorable decline in islet cell function which occurs in the later stages of type 2 diabetes is likely to represent a summation of several adverse factors. Chronic hyperglycaemia itself will blunt insulin secretion. Triglyceride accumulation in th islets induces enzyme changes similar to models of beta cell dysfunction.[12] Both of these factors may accelerate beta cell apoptosis. Amyloid plaque formation may further impair function. However, there is little firm evidence on the pathophysiology of end-stage type 2 diabetes.

appropriate patterns. Importantly, insulin infusions were given to one group of subjects to mimic the normal, rapid insulin response and to the other group to mimic the slowly rising insulin response of type 2 diabetes. The results showed clearly that failure to suppress glucagon in the presence of a subnormal insulin response caused a 3mM difference in achieved blood glucose. This was associated with failure to suppress hepatic glucose production. However, if the insulin response was normal only a small difference in blood glucose was observed. There can be no doubt about the deleterious effect of high glucagon levels when the insulin response is subnormal.

Intervening in the Rate of Decline of Islet Function

Several studies have shown a major effect of exercise on the prevention of progression of IGT to type 2 diabetes. Although the major immediate effect is on change in insulin sensitivity, there must be an effect of preservation of islet cell function given its central role in the onset of diabetes. The Da Qing six-year randomised study on IGT subjects demonstrated that increased physical exercise decreased the incidence of diabetes by 47% (8.3 vs 15.7 per 100 patient years).[18]

The exercise advised was aerobic and individually suited to each subject. Randomisation was by clinic, raising the possibility of a group reinforcing effect. The results have been confirmed in two other large prospective studies randomised on an individual basis. The Diabetes Prevention Program showed that combined exercise (150 minutes of moderate exercise per week) and dietary advice decreased the incidence of diabetes from 11.0 to 4.8 per 100 patient years.[19] The Finnish Diabetes Prevention Study aimed to achieve 30 minutes of moderate to vigorous exercise per day together with a low fat diet and reported decrease in diabetes incidence from 6.8 to 4.0 per 100 patient years.[20] These studies provide dramatically clear evidence that increased levels of physical activity will delay the development of type 2 diabetes and this implies an effect upon the natural history of change of islet function.

It is noteworthy that studies of exercise therapy in established type 2 diabetes have not yielded consistent results. Most studies have combined exercise with a programme of weight loss, and it is likely that beneficial effects relate mainly to the latter.[21-24] Some aerobic exercise programmes have failed to achieve a clinically significant change in blood glucose control and those which have tend to attribute the change to exercise rather than to the evident weight loss. No relationship of achieved exercise level to observed change in HbA1c has been noted in some studies. Overall, there is little evidence upon which to judge whether life-style interventions will change the underlying natural history of established type 2 diabetes even though improvements in ambient blood glucose control are certainly possible by such means.

Thiazolidinediones have been shown to slow the rate of development of diabetes in high risk women. Hispanic women who developed gestationa diabetes were recruited to a study of troglitazone, an agent now withdrawn. Whereas those taking placebo developed diabetes at the expected rate (over 10% per year), those on active treatment had stable beta cell function for 5 years.[25] A recently reported follow study has demonstrated that those women who had received placebo and then received pioglitazone in the second study showed a marked slowing in the rate of development of diabetes. On placebo a decline of beta cell function of 33% occurred over 4.6 years, whereas on pioglitazone for three years there was a stablisation of beta cell function and the rate of development of diabetes was

approximately 5% per year.[26] These data require to be confirmed in other patient groups, but suggest that this class of drug does change the natural history of islet function in the pre-diabetes phase.

The new GLP-1 agonists may also protect the islet. Current information indicates the existence of potential protective mechanisms including decreased rate of beta cell apoptosis.[27,28] Clinical studies are awaited to determine whether such mechanisms can bring about in vivo slowing of the rate of decline of islet function and hence prevent the steady worsening of diabetes control.

Conclusion

Both decreased beta cell number and increased alpha cell number are present at the time of presentation of type 2 diabetes. These changes correspond with decreased early insulin secretion and failure to suppress glucagon secretion in response to eating. The subsequent changes which dictate the deterioration in blood glucose control are not clear, but beta cell apoptosis, perhaps speeded by excess fatty acid supply, and amyloid plaque formation may both be relevant. Increased physical exercise and decreased weight can modify the rate of decline in islet cell function prior to the onset of type 2 diabetes, but a genuine effect upon natural history in established diabetes is not clear. Therapy with thiazolidinediones can modify at least the pre-diagnosis stage of islet cell function, and further information is awaited on the clinical effects of GLP-1 agonists which can change the rate of beta cell apoptosis.

When Elliot Joslin visited the Pima Indians at the end of the 19th century, he commented that it was remarkable that there was not one case of diabetes amongst these people, who at the time were subsistence farmers. The vulnerability of the islet to modifiable environment can be seen by considering the current 40% incidence of type 2 diabetes in Pima Indians. The external factors include lack of physical exertion and plentiful high fat food. Unlocking the secrets of how the micro-environment of the islet brings about functional failure could lead to effective prevention of islet cell deterioration in type 2 diabetes. ■

A version of this article containing additional figures can be found in the Reference Section on the website supporting this briefing (www.touchbriefings.com).

References

1. Hadden D R, Blair A L T, Wilson E A et al., "Natural history of diabetes presenting age 40-69 years: a prospective study of the influence of intensive dietary therapy", Quarterly Journal of Medicine (1986);230: pp. 579–598.

2. Rudenski A S, Hadden D R, Atkinson A B et al., "Natural history of pancreatic islet B-cell function in type 2 diabetes mellitus studied over six years by homeostasis model assessment", Diabetic Medicine (1988);5: pp. 36–41.

3. UKPDS, "Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)", Lancet (1998);352: pp. 837–852.

4. Butler A E, Janson J, Bonner-Weir S, Ritzel R, Rizza R A, Butler P C, "Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes", Diabetes (2003);52: pp. 102–110.

5. Seaquist E R, Robertson R P, "Effects of hemipancreatectomy on pancreatic alpha and beta cell function in healthy human donors", J. Clin. Invest. (1992);89: pp. 1,761–1,766.

6. Rhodes C J, "Type 2 diabetes-a matter of beta-cell life and death?", Science (2005);307: pp. 380–384.

7. Unger R H, Orci L, "Diseases of liporegulation: new perspective on obesity and related disorders", Faseb J. (2001);15: pp. 312–321.

8. Wrede C E, Dickson L M, Lingohr M K, Briaud I, Rhodes C J, "Fatty acid and phorbol ester-mediated interference of mitogenic signaling via novel protein kinase C isoforms in pancreatic beta-cells (INS-1)", J. Mol. Endocrinol. (2003);30: pp. 271–286.

9. Rahier J, Godbbels R M, Henquin J C, "Cellular composition of the human diabetic pancreas. Diabetologia (1983);24: pp. 366–371.

10. Yoon K H, Ko S H, Cho J H et al., "Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea", J. Clin. Endocrinol. Metab. (2003);88: pp. 2,300–2,308.

11. Ferner R E, Ashworth L, Tronier B, Alberti K G M M, "Effects of short-term hyperglycaemia on insulin secretion in normal humans", American Journal of Physiology (1986);250:E655–E661.

12. Busch A K, Cordery D, Denyer G S, Biden T J, "Expression profiling of palmitate- and oleate-regulated genes provides novel insights into the effects of chronic lipid exposure on pancreatic beta-cell function", Diabetes (2002);51: pp. 977–987.

13. Shah P, Vella A, Basu A, Basu R, Schwenk W F, Rizza R A, "Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes", Journal of Clinical Endocrinology and Metabolism (2000);85: pp. 4,053–4,059.

14. Larsson H, Ahren B, "Islet dysfunction in insulin resistance involves impaired insulin secretion and increased glucagon secretion in postmenopausal women with impaired glucose tolerance", Diabetes Care (2000);23: pp. 650–657.

15. Singhal P, Caumo A, Carey P E, Cobelli C, Taylor R, "Regulation of endogenous glucose production after a mixed meal in type 2 diabetes", Am. J. Physiol. Endocrinol. Metab. (2002);283:E275–E283.

16. Jiang G, Zhang B B, "Glucagon and regulation of glucose metabolism", Am. J. Physiol. Endocrinol. Metab. (2003);284:E671-678.

17. Shah P, Vella A, Basu A et al., "Effects of Free Fatty Acids and Glycerol on Splanchnic Glucose Metabolism and Insulin Extraction in Nondiabetic Humans", Diabetes (2002);51: pp. 301–310.

18. Pan X R, Li G W, Hu Y H et al., "Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study", Diabetes Care (1997);20: pp. 537–544.

19. Knowler W C, Barrett-Connor E, Fowler S E et al., "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin", New England Journal of Medicine (2002);346: pp. 393–403.

20. Laaksonen D E, Lindstrom J, Lakka T A et al., "Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study", Diabetes (2005);54: pp. 158–165.

21. Kirk A F, Higgins L A, Hughes A R et al., "A randomized, controlled trial to study the effect of exercise consultation on the promotion of physical activity in people with Type 2 diabetes: a pilot study", Diabet. Med. (2001);18: pp. 877–882.

22. Kirk A, Mutrie N, MacIntyre P, Fisher M, "Effects of a 12-month physical activity counselling intervention on glycaemic control and on the status of cardiovascular risk factors in people with Type 2 diabetes", Diabetologia (2004);47: pp. 821–832.

23. Dunstan D W, Daly R M, Owen N et al., "Home-based resistance training is not sufficient to maintain improved glycemic control following supervised training in older individuals with type 2 diabetes", Diabetes Care (2005);28: pp. 3–9.

24. Cauza E, Hanusch-Enserer U, Strasser B et al., "The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus", Arch. Phys. Med. Rehabil. (2005);86: pp. 1,527–1,533.

25. Buchanan T A, Xiang A H, Peters R K et al., "Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women", Diabetes (2002);51: pp. 2,796–2,803.

26. Xiang A H, Peters R K, Kjos S L et al., "Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes", Diabetes (2006);55: pp. 517–522.

27. Ranta F, Avram D, Berchtold S et al., "Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4", Diabetes (2006);55: pp. 1,380–1,390.

28. Gallwitz B, "Glucagon-like peptide-1 as a treatment option for type 2 diabetes and its role in restoring beta-cell mass", Diabetes Technol Ther (2005);7: pp. 651–657.