

### Background

Type 2 diabetes is achieving notoriety as one of the scourges of the developed and developing world. Since 1996, the number of people in the UK alone who have been diagnosed with diabetes has risen from 1.4 million to 2.8 million. It is estimated that by 2025, this number will have risen to more than 4 million ([www.diabetes.org.uk](http://www.diabetes.org.uk)). Moreover, it is estimated that a further 1.1 million of the population have the disease but remain, as yet, undiagnosed. Type 2 diabetes is predominantly a disease of the elderly and, given the UK's steadily aging population, it is difficult to envisage any future improvement in the disease statistics. Furthermore, the last ten years have seen the emergence of an alarming trend, with the occurrence of type 2 diabetes in children, adolescents and adults of normal weight. A recent survey carried out on behalf of the WHO has estimated the number of people with diabetes worldwide to be 347 million.

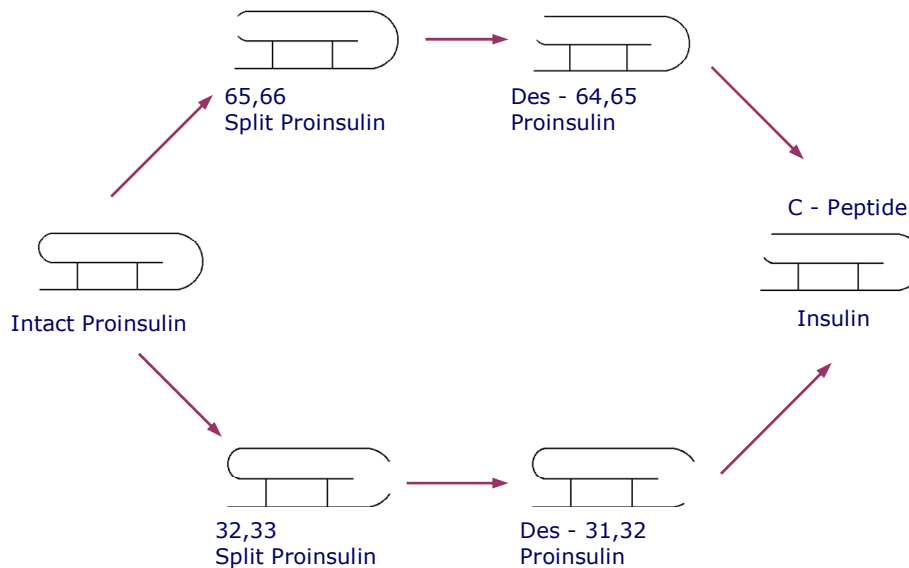
A formal diagnosis of type 2 diabetes relies primarily on the demonstration of glucose intolerance. However, in many patients, the disease may be well advanced at the time the diagnosis is made. Such patients are already at an increased risk of cardiovascular disease and may require therapeutic intervention. Early detection of the disease is desirable since this provides an opportunity to initiate changes in lifestyle (eg diet and exercise) that can prevent or delay the onset of disease symptoms and in doing so impact significantly on the life quality for many as well as reducing treatment costs.

This situation poses challenges at many levels, including diagnosis, monitoring and therapy. Better diagnosis can lead to earlier intervention. More rigorous monitoring can delay the onset of symptoms, while new treatments may offer better glycaemic control. The hallmark of type 2 diabetes is insulin resistance. Additionally and, possibly as a consequence of this, significant changes in pancreatic  $\beta$ -cell function occur from an early stage. Such changes can be assessed by measuring the release of insulin and its molecular precursors in the fasting state and in response to a glucose challenge.

### Insulin Processing

Insulin is released from the  $\beta$ -cells of the Islets of Langerhans in the pancreas in response to the rise in blood glucose that follows a carbohydrate containing meal. It is synthesised initially as a high molecular weight precursor, proinsulin. This molecule is cleaved at two specific sites to yield two short polypeptide chains linked by two disulphide bridges (Figure 1). Under normal circumstances, only trace amounts of "intact" proinsulin or the intermediate metabolites of processing ("split" proinsulins) survive to be released into peripheral blood. When the pancreas is subjected to repeated or increased stimulation by glucose, as occurs in insulin resistance, this molecular processing becomes less efficient and increasing proportions of intact and split proinsulins appear in peripheral blood.

Figure 1: Insulin Formation in the Pancreatic B-cell



### Early Detection of Type 2 Diabetes

While the risk of becoming diabetic risk can be calculated on the basis of lifestyle markers, it has not yet been possible to identify at-risk subjects on the basis of biochemical abnormalities. Classically, a diagnosis of diabetes is made on the basis of a fasting plasma glucose >7.0 mmol/l and/or a plasma glucose >11.1 mmol/l two hours after a 75g oral glucose load.

Early in 2010, the American Diabetes Association (ADA) recommended the use of glycosylated haemoglobin measurement (HbA1c) both for the diagnosis of type 2 diabetes (HbA1c ≥ 6.5%) and also as a potential screening test for the early diabetic subject (HbA1c 5.7-6.4%). Data produced within the subsequent year have done little to support this latter proposal, one study reporting that an HbA1c within the range 5.7-6.4% detected only 23% of at-risk individuals whereas 59% were found to have impaired glucose tolerance (1). The main attraction of HbA1c as a screening test is that it precludes the inconvenience of obtaining fasting blood samples.

In the last 20 years, several studies have suggested that changes in pancreatic β-cell function may indicate a pre-diabetic situation. In 1999, Wareham et al (2) published data on a 4.5 year population-based longitudinal study in which they demonstrated an association between elevated fasting proinsulin concentrations at the beginning of the study and a subsequent progression to diabetes. This predictive value of proinsulin measurement has been confirmed in other studies (3, 4).

## Insulin Resistance

A quantitative measure of insulin resistance can be helpful in designing appropriate therapy and predicting outcome in patients with type 2 diabetes. The accepted methods for determining insulin resistance, such as the euglycaemic clamp or intravenous glucose tolerance test are expensive and time consuming and so inappropriate for routine investigation. A homeostatic model analysis (HOMA), based on the relationship between fasting insulin and fasting glucose, has been widely used in epidemiological studies as an index of insulin resistance. Overall, the HOMA score correlates well with euglycaemic clamp results, though it is recognised to be of relatively little value in the individual subject because of its low specificity (5).

Recent studies have confirmed that circulating proinsulin is a highly specific marker of insulin resistance (6). Earlier work in Japan had demonstrated that while the sulphonylurea glyclazide was effective in improving glycaemic control in diabetics, a thiazolidinedione (pioglitazone) was equally effective but, in addition, produced a significant reduction in proinsulin levels (7). It is logical to conclude that proinsulin measurement in individual diabetic patients provides a reliable index of insulin resistance. In addition to its role as an early indicator of the disease, it may also provide an important marker for selecting and monitoring an appropriate therapeutic regime.

## References

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