

## Glucose tolerance and ageing

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### Summary

Hyperglycaemia, impaired glucose tolerance and non-insulin dependent diabetes become progressively more common with advancing age. The mechanism is insensitivity to the actions of insulin at the postreceptor level. Inadequate secretion of insulin and decreased hepatic sensitivity to insulin's action in suppressing glucose output also occur. The age-related changes may be made worse by obesity, renal failure or the ingestion of certain drugs, or may be lessened by increased physical activity.

### Introduction

Diabetes, particularly non-insulin dependent diabetes, becomes increasingly common with advancing age and impaired glucose tolerance is also common in older people<sup>1</sup>. Diabetes remains a serious condition in older people and mortality and morbidity from conditions such as cardiovascular disease, neurological and visual disease is higher in elderly diabetic subjects than in non-diabetic people of the same age<sup>2</sup>. This may be related to a high frequency of undiagnosed diabetes in older people<sup>3</sup>. Of the risk factors for diabetes in older people, obesity appears to be the commonest<sup>4</sup>. Severe uncontrolled diabetes in elderly people also has a high mortality, often because it tends to present for medical attention rather late<sup>5</sup>.

### Mechanisms for glucose intolerance in elderly people

There are a number of possible mechanisms for glucose intolerance in elderly people: (1) impaired insulin secretion; (2) peripheral insulin insensitivity (insulin receptor; postreceptor); or (3) changes in other hormones.

#### *Insulin secretion*

Deficient insulin secretion as a cause of glucose intolerance in old age has not been described and insulin levels are either the same as those in younger people, or in some cases higher<sup>6</sup>. While it may be argued that insulin secretion is inadequate in comparison with the co-existing hyperglycaemia, the common finding in elderly people of high glucose levels accompanied by normal or high insulin levels is evidence of insulin resistance.

#### *Insulin resistance*

Insulin resistance occurs when a normal amount of insulin produces a subnormal biological response<sup>7</sup>. Insulin resistance may be measured by a number of techniques. One of the most common of these is the clamp technique, where glucose disposal is measured

at constant levels of glucose and insulin. Studies using clamp techniques show that glucose disposal in elderly people is defective, suggesting a state of peripheral insulin resistance<sup>8,9</sup>. Two pieces of evidence suggest that the insensitivity to insulin is not at the insulin receptor but at postreceptor level. The first is that studies of insulin binding to cell membranes of different types of cells, including circulating monocytes and isolated fat cells, have found no abnormality in insulin binding affinity or in receptor number in cells from older people<sup>6</sup>. Experiments using the clamp techniques to study dose-response curves at different levels of insulin confirm a postreceptor defect<sup>8</sup>. The high levels of insulin, which are often found in older people, are thought to be a compensatory mechanism for co-existing insulin resistance and hyperglycaemia, but there is also evidence of decreased metabolic clearance of insulin in older people<sup>10</sup>. As well as peripheral insensitivity to insulin's action, there is evidence that insulin's effect on the suppression of hepatic glucose output is also defective in old age<sup>8</sup>. In general, insulin's actions on lipid and amino acid metabolism are not impaired in older people. It has recently been suggested that some of the insulin resistance in old age may be related to increased production of free radicals<sup>11</sup>.

The other commonly used technique for studying insulin secretion and action is the frequently sampled intravenous glucose tolerance test with the results analysed by computer modelling (the minimal model). Studies using this technique have found both deficient insulin secretion and insulin resistance in older people<sup>12</sup>. Other more direct methods of measuring insulin activity have confirmed resistance to the effect of insulin in older people<sup>13</sup>.

Overall, therefore, the evidence suggests that the major defect in old age is decreased insulin sensitivity in the peripheral tissues at postreceptor level. There are no age related differences in the number of insulin receptors or the affinity with which insulin binds to peripheral cells. There is also a decrease or delay in insulin induced suppression of hepatic glucose uptake. Although insulin levels are higher in older than younger people, there seems to be an abnormality in insulin secretion from the pancreas and this is possibly compensated for by decreased metabolic clearance of insulin in the peripheral tissues.

#### *Counter regulatory hormones*

A number of hormones increase glucose levels or interact with, modify or oppose the action of insulin. These include glucagon<sup>14</sup>, growth hormone<sup>15</sup>, gastric inhibitory polypeptide<sup>14</sup>, catecholamines<sup>16</sup> and human pancreatic polypeptide<sup>14</sup>. Apart from the latter, whose biological significance is unclear, there are no significant differences in the levels or actions of these hormones in older compared with younger people.

### Other factors affecting glucose intolerance in older people

A number of other factors which may occur in old age may affect glucose tolerance: obesity; physical inactivity; reduced dietary carbohydrate; impaired renal function; hypokalaemia; increased sympathetic NS activity; and drugs.

#### *Body weight*

As people get older there is a tendency to both an increase in total body weight and an increase in the distribution of adipose tissue in the abdomen.

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Although these influence glucose tolerance by causing insulin resistance, the evidence suggests that they do not fully account for all the changes that occur in ageing<sup>17</sup>.

#### Physical activity

There is a tendency for a decreased amount of physical activity with increasing age<sup>18</sup>, partly because of a change in habits but also influenced by disabling conditions such as arthritis and neurological disease. With decreased physical activity and decreased physical fitness, there is a tendency to insulin resistance and hyperglycaemia<sup>19</sup>. While these occur in older people, they do not appear to account for all of the glucose intolerance of ageing and indeed physical inactivity is probably less important in this regard than increased body weight<sup>20</sup>.

#### Other factors

While changes in diet, impaired renal function, electrolyte abnormalities, increased sympathetic nervous system activity and the ingestion of drugs such as thiazide diuretics<sup>21</sup> may influence glucose homeostasis in old age, these do not account for the occurrence of glucose intolerance in older people.

#### Conclusion

In older people a metabolic disorder consisting of glucose intolerance, peripheral insulin insensitivity at the postreceptor level, inappropriate insulin secretion and decreased hepatic insulin sensitivity occurs. The metabolic changes may be decreased by increasing physical activity and may be made worse by increased body weight and abdominal adiposity, impaired renal function and the ingestion of diuretic drugs. In the management of diabetes in older people, avoidance of these factors would be the first approach but there will still remain a group of subjects who have hyperglycaemia and diabetes.

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## Diabetes in the elderly: epidemiology

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#### Introduction

Until recently, the elderly were a very much neglected group amongst people with diabetes. Kelly West, in his monograph on the epidemiology of diabetes, noted

that different studies produced wildly different estimates of its relative prevalence in the elderly and the young; he commented that lack of interest in the aged could explain these discrepancies and argued the need for more surveys<sup>1</sup>. This short article will describe what progress has been made and consider how our present knowledge should affect the planning of health care delivery and individual case management. For a fuller review, the reader is referred to the reviews by Tattersall and Kerr<sup>2,3</sup>.

#### Prevalence, incidence and type of diabetes

Data on *incidence* in the elderly are scarce but *prevalence* figures have been published from many countries and different ethnic groups<sup>4-12</sup>. Almost all studies have found a progressive increase with age,

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