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Annotations

Diabetes in puberty

Successful treatment of type I insulin-dependent diabetes (IDDM) is of particular importance during puberty for the achievement of normal growth and sexual maturation and to reduce the risk of long term microvascular complications. Yet, with the onset of puberty, glycaemic control as judged by serial glycated haemoglobin (HbA_1) concentrations, may deteriorate.[1–3] This deterioration is often attributed to the psychological problems of adolescence and poor compliance with diet and insulin dosage.[4 5] However, over the last few years it has become clear that this is not the complete explanation and that the endocrine changes of puberty may also contribute to the poor glycaemic control, disordered growth and sexual maturation in IDDM.

Insulin resistance during puberty

Normal pubertal development is associated with dramatic changes in insulin sensitivity and fasting insulin concentrations rise during puberty reaching a peak in both sexes at stage 3 and 4 before declining and returning to prepubertal values during early adult life.[6] Furthermore, during puberty the plasma insulin responses to both oral and intravenous glucose are greater than those observed in younger children or adults.[7 8] Using the hyperinsulinaemic clamp technique Amiel *et al* [9] showed an appreciable reduction in insulin stimulated glucose metabolism in pubertal compared with prepubertal and adult subjects which resulted from decreased glucose uptake in muscle rather than any change in hepatic glucose production rates.[10] Similar changes of insulin sensitivity can be demonstrated in adolescents with IDDM. As in normal subjects, insulin resistance is maximal in late puberty but at every stage of puberty diabetics are more insulin resistant than controls.

Growth hormone

In their studies, Amiel *et al* demonstrated a correlation between changes in insulin sensitivity and mean growth hormone concentrations.[9] Puberty is characterised by an increase in growth hormone pulse amplitude,[11] and mean overnight growth hormone concentrations rise during puberty being maximal in mid to late puberty corresponding to the changes in insulin sensitivity.[12] Some authors have noted an earlier rise in growth hormone concentrations in girls[13] corresponding to the earlier pubertal growth spurt whereas sex differences in the timing of changes in insulin sensitivity have not been consistently demonstrated.[14 15]

In adolescents with IDDM, plasma growth hormone profiles are characterised by an increase in both pulse amplitude and baseline concentrations.[13] Growth hormone excess has been shown to impair the ability of insulin to suppress hepatic glucose production and to stimulate peripheral glucose uptake.[16 17] Direct evidence that these high growth hormone concentrations are responsible for the increased insulin resistance during puberty in IDDM has largely been gathered from studies of the dawn phenomenon. In subjects with IDDM insulin requirements increase overnight and are maximal between 8.00–9.00 am. The extent of this overnight change in insulin sensitivity can be correlated with mean growth hormone concentrations and it is reversed after suppression of growth hormone secretion.[18 19] The dawn phenomenon is maximal at puberty stage 3–4 in both sexes,[18] but there is considerable variation between and within individuals which leads to major problems targeting insulin treatment during puberty.

Failure of current insulin regimens

Although it has long been recognised that insulin requirements in IDDM rise during puberty, increases of insulin doses of up to 1·5 units/kg/day only lead to marginal improvements in HbA_1 concentrations.[20] It could be argued that greater increases are necessary but current insulin regimens do not permit appropriate insulin delivery overnight.[21] Even where the long acting insulin is given late at night as part of a multiple injection treatment, free insulin concentrations tend to be high during the early part of the night and then wane as the night proceeds. The over insulinisation during the early part of the night can lead to a high incidence of unrecognised hypoglycaemia,[22] and the low concentrations of insulin during the latter part of the night often fail to control the dawn rise in blood glucose concentrations.

The failure to achieve appropriate insulin concentrations overnight may also lead to an increase in growth hormone secretion. Hyperinsulinaemia during the early part of the night may stimulate growth hormone secretion directly[23] or as part of a counter-regulatory response to hypoglycaemia.[24] Low concentrations of insulin during the latter part of the night lead to a decrease in insulin-like growth factor I (IGF-I) bioactivity with a resulting feedback drive for further growth hormone secretion. The role of insulin in the regulation of the growth hormone/IGF-I axis in IDDM has only recently been elaborated. Despite high growth hormone concentrations, serum concentrations of IGF-I tend to be low in IDDM. This growth hormone resistance may be

the result of inadequate portal delivery of insulin as insulin has a permissive role in growth hormone receptor function. The major IGF-I binding proteins (IGFBP-3, IGFBP-1) are also altered in IDDM.[25] IGFBP-1 appears to be an inhibitor of IGF-I bioactivity and its concentrations are reciprocally regulated by insulin.[26] Inadequate insulin concentrations overnight lead to a rise in IGFBP-1 and a fall in IGF-I bioactivity: the degree of abnormality in IGFBP-1 can be directly correlated with HbA_1 values.[25 27]

Increasing insulin doses to achieve concentrations necessary for suppression of IGFBP-1 may only lead to unacceptable hypoglycaemia without necessarily suppressing growth hormone secretion. During puberty the very high growth hormone concentrations may also lead to accelerated ketogenesis and contribute to the rapid decompensation and diabetic ketoacidosis which result from poor compliance.

Growth and pubertal development

Low circulating IGF-I concentrations and reduced bioactivity in IDDM could lead to abnormalities of pubertal growth. Severe abnormalities are now infrequent but the pubertal growth spurt may be blunted particularly in girls.[28] In early studies, sexual maturation was also delayed in many children with IDDM, but this is now rare although a dissociation between pubarche and adrenarche has been reported.[29] Menstrual irregularities appear to be more common in adolescents with IDDM and may be related to low concentrations of sex hormone binding globulin.[30]

Growth problems are often more severe in adolescent girls with IDDM and other sex differences can be demonstrated. Glycaemic control as judged by HbA_1 is often worse in boys during early puberty and in girls during later puberty.[1] The tendency to put on excessive weight is also more common in late adolescent girls and cannot entirely be explained by disordered eating habits and differences in exercise patterns.[31] Further studies of the endocrinology of puberty are needed to explain these sex differences and to understand the well documented effects of puberty on the rate of development of diabetic microangiopathic complications.

Conclusions

Pubertal development is accompanied by rapid growth and an almost doubling of lean body mass. The provision of adequate nutrition and appropriate insulin requirements in adolescents with IDDM is therefore a major challenge. The insulin dose should be increased, either in line with pubertal development or growth,[32] and requirements may reach 1·5–2·0 units/kg/day. It is important, however, to be aware of the risks of over insulinisation overnight and it must be remembered that insulin requirements fall back to prepubertal concentrations at the end of the teenage years. Failure to reduce insulin requirements in the late adolescent girls may aggravate weight gain.

Multiple injection treatment not only offers greater advantages for the adolescent but also provides a logical way of delivering basal insulin requirements during puberty. However, treatment with pen injectors will not necessarily improve glycaemic control and overnight insulin profiles may be far from satisfactory.[21] Continuous subcutaneous insulin delivery has not proved acceptable in adolescents with IDDM and the development by the pharmaceutical industry of more stable long acting insulins should be encouraged. Finally direct attempts to reduce growth hormone secretion without compromising growth might have a place in the treatment of the adolescent with IDDM. Poor compliance during adolescence should not be unexpected, given the rigours of the diabetic regimen. It is therefore important that good compliance is rewarded by an improvement in glycaemic control, normal growth and development and a reduction in the risks of diabetic complications.

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