MANAGEMENT OF INSULIN-DEPENDENT DIABETES: HYPOGLYCAEMIA AND THE EYE

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The treatment of type 1 (ketosis-prone) or insulin-dependent diabetes has not changed radically since the introduction of insulin into clinical practice in the 1920s. Modifications and improvements in the purity, supply, formulations and regimens of insulin have provided significant progress in diabetic management, but the presently available range of insulins and methods of delivery are still far removed from simulating the normal physiology of insulin secretion and action. The loss of the normal homeostatic mechanisms which maintain blood glucose within a narrow physiological range, render the diabetic individual susceptible to wide excursions in blood glucose and the intermittent hazard of metabolic extremes. This occurs with chronic hyperglycaemia and diabetic ketoacidosis, which is fortunately now relatively infrequent, and acute hypoglycaemia which is an exceedingly common therapeutic side effect of insulin. Hypoglycaemia will be addressed in more detail here because of its potential effects on the diabetic eye.

AIMS OF TREATMENT OF DIABETES

It was recognised at an early stage that insulin replacement by injection represented only a method of treatment and was not a cure for diabetes.[1] The principal aim of therapeutic management is to restore the deranged metabolism of the insulin-deficient state to as near normal as possible and to maintain this situation indefinitely. Treatment has to be modified and adjusted to cope with intercurrent illness such as infection, other stress including surgical procedures, and acute vascular events such as a stroke or myocardial infarction.

A longer-term aim of therapy is to prevent the development, or at least delay the progression, of the microvascular complications of diabetes, which include retinopathy and nephropathy, neuropathy and also macrovascular disease. The efficacy of insulin treatment in type 1 diabetes and the role of quality of glycaemic control is currently being investigated prospectively in a large multicentre study in North America, called the Diabetes Control and Complications Trial (DCCT).[2]

A fundamental aspect of the modern treatment of diabetes is the active participation of the patient in self-management, with regular home monitoring of glycaemic control and appropriate adjustment of therapy including the timing and dosage of insulin administration. To this end much emphasis is now placed on continuing patient education and motivation, with the development of a team approach (incorporating physician, nurse specialist, dietitian and others) to diabetic care and encouragement of the patient's active involvement.

INDICATIONS FOR INSULIN THERAPY

Insulin is essential for all patients with true type 1 diabetes resulting from the autoimmune destruction of pancreatic beta cells and consequent failure of insulin secretion. The dose of insulin may be reduced considerably, or even temporarily discontinued, in specific situations such as the period of remission which often occurs after treating newly diagnosed patients, or immediately after delivery in diabetic pregnancy, but life-long treatment is essential. Patients with secondary diabetes caused by chronic pancreatitis or pancreatic resection often require insulin, and insulin may also be required on a temporary basis during gestational diabetes.

The other major group who may require insulin are patients with type 2 (non-insulin-dependent) diabetes who develop secondary failure to oral hypoglycaemic agents, normally after several years of treatment. Such patients sometimes need insulin for peri-operative management during surgery or in association with the stress of acute medical problems such as septicaemia or acute myocardial infarction. Because type 2 patients often retain the capacity to secrete some endogenous insulin, their insulin requirement is often lower than that of patients with type 1 diabetes and they are less susceptible to severe hypoglycaemia.

INSULIN TREATMENT

A detailed account of the nuances of insulin therapy is

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Table I. Insulin regimens for insulin-treated diabetic patients

(*a*) *Frequency of administration*	
	Type of insulin by time–action profile
Once daily	Long-acting, intermediate-acting
Twice daily	Short-acting, intermediate-acting
Multiple	Short-acting
(*b*) *Principal insulin formulations*	
	Duration of action (hours)
Short-acting: Soluble	1–4
Intermediate acting: Isophane	4–12
Lente	2–16
Long-acting: Ultralente	8–24

beyond the scope of this article, and the reader is referred to review articles.[3–5] Human insulin is less immunogenic and is now generally prescribed in preference to animal insulins, although few other biological benefits are apparent. Differing insulin formulations are used which have either a short, intermediate or long duration of action, and can be given in various combinations and times of administration. These are summarised in Table I and are tailored to the needs of the individual patient.

A schematic representation of the time–action profiles produced by different insulin regimens is given in Fig. 1. Many elderly patients are adequately controlled with a single daily injection of insulin, particularly where strict glycaemic control is not desirable and the main aim is to maintain them free of osmotic symptoms of hyperglycaemia. Most patients are treated with conventional twice-daily insulin regimens, combining unmodified soluble insulin (1–4 hours) with isophane insulin which has an intermediate range of action (4–12 hours). Fixed mixtures of insulins are popular (e.g. 30% soluble combined with 70% isophane), but have the disadvantage of limiting flexibility of adjustment of dosage of the individual components.

Multiple injections of short-acting (soluble) insulin before meals, supplemented by an evening dose of intermediate or long-acting insulin, a so-called basal-bolus insulin regimen, has increased in usage and popularity in recent years. This was stimulated by the development of pen devices containing cartridges of insulin for insulin administration, although these devices are simply a more sophisticated means of insulin delivery. Disposable pen and cartridge units are now being introduced. This regimen is considered to provide a plasma insulin profile which is most similar to the pattern of insulin secretion in the non-diabetic person. However, none of the present methods and routes of administering insulin mimic normal physiology whereby insulin is secreted into the portal circulation and is transported directly to the liver. The systemic administration of insulin results in peripheral hyperinsulinaemia with relatively low plasma concentrations in the portal blood.

Although the introduction of pen devices for administration of insulin has been a simple but significant improvement in the method of insulin delivery, the use of continuous subcutaneous insulin infusion (CSII) using mechanical pumps has been much less successful. This technique was widely tested in the 1980s but insulin pump therapy is expensive, presents considerable practical problems and technical difficulties with maintenance, and requires much expenditure of staff time on patient education. CSII has never been applied on any large scale for patient management, and apart from the use of intravenous insulin infusion in specific cases such as patients with severe insulin resistance, pump therapy has largely been abandoned as a feasible method of treatment. Trials of insulin analogues, pro-insulin and monomeric insulins may produce active insulin preparations with more effective pharmacokinetic properties, but while these may improve present therapy, they will not radically change diabetic management. Future treatment may be possible with implantation of pancreatic islets if these can be protected from autoimmune destruction, and research is being pursued in this direction.

Home Monitoring of Glycaemic Control

An important aspect of patient self-management is the regular monitoring of blood glucose to ensure good glycaemic control. The advent of dry biochemical technology with blood glucose strips which depend on colour change and can be read visually, has revolutionised the treatment of insulin-treated diabetes. This has enabled much more objective analysis of glycaemic control and identified the extent of problems such as nocturnal hypoglycaemia, allowing appropriate and logical modification of insulin

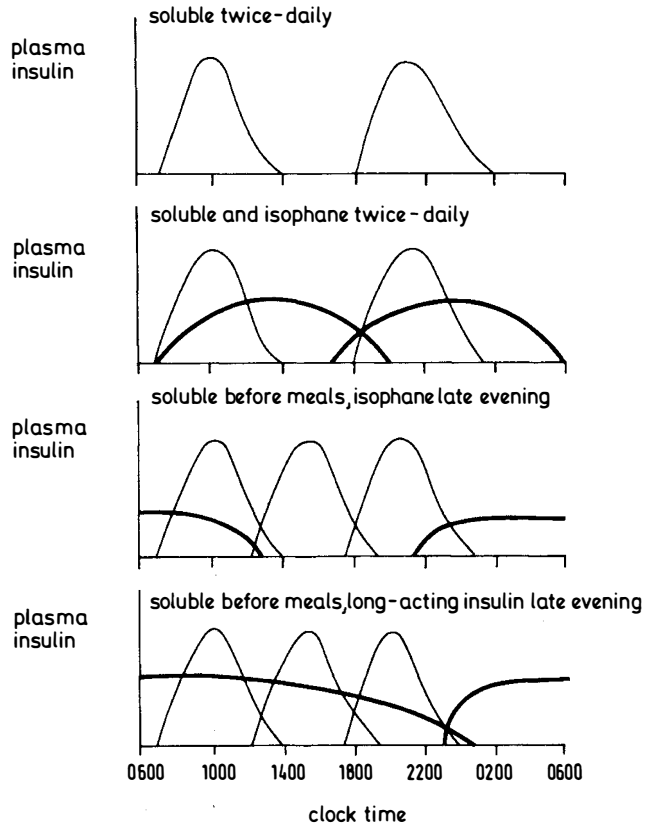

Fig. 1. *A diagrammatic representation of the theoretical profiles of plasma insulin concentrations associated with various insulin regimens, illustrating the potential range of insulin pharmacokinetics.*

therapy. A range of blood glucose meters is available which give a digital reading of blood glucose estimated with considerable precision.

Acute Hypoglycaemia

The commonest and most feared side effect of treatment with insulin is the development of acute hypoglycaemia. While in most instances this may be relatively minor and simply constitutes a therapeutic nuisance, severe hypoglycaemia is potentially life-threatening and has a substantial morbidity and mortality. It can be very disruptive to a patient's normal lifestyle. In the diabetic patient treated with insulin, various acquired syndromes occur with increasing duration of diabetes which exacerbate the severity of hypoglycaemia by interfering with the normal warning symptoms (loss of hypoglycaemia awareness) and impairing normal recovery of blood glucose (counter-regulatory hormonal deficiencies). Both of these problems are also associated with strict glycaemic control, although they will disappear if intensive treatment is stopped and strict control is relaxed. These syndromes have been reviewed elsewhere.[6–8]

Severe hypoglycaemia, requiring the assistance of another person to effect recovery, is relatively common, occurring annually in 10–20% of all insulin-treated patients. A small group (3%) suffer recurrent severe hypoglycaemia with its attendant problems of coma, convulsions and injury. The DCCT group have confirmed that the major risk factors for severe hypoglycaemia include intensive insulin therapy (producing a reduction in glycosylated haemoglobin), duration of diabetes and the age of the patient, a history of previous severe hypoglycaemia, hypoglycaemia unawareness and sleep.[9]

Hypoglycaemia promotes acute activation of the sympatho-adrenal system with secretion of catecholamines, and also stimulates the release of several other hormones such as angiotensin II and vasopressin. These hormones and autonomic activity have profound haemodynamic and haemostatic effects which may have important pathological sequelae in the diabetic patient. The morbidity of acute hypoglycaemia in diabetic patients has been reviewed recently,[10] and potential effects on various organs are summarised in Table II. The specific physiological effects of hypoglycaemia on the normal healthy eye are described below, and the implications for aggravating diabetic eye disease are discussed.

BLOOD GLUCOSE CHANGES AND THE EYE

Hyperglycaemia

Following the initiation of insulin therapy in diabetic patients, blurring of vision is a well-recognised consequence of rapid restoration of blood glucose towards normal, without induction of hypoglycaemia. Changes in refraction are a recognised feature of hyperglycaemia; there is a tendency towards myopia, although hyperglycaemia has in fact been shown to precede hyperopia.[11] Controversy surrounds the mechanism of altered refractive power of the lens; this may result from osmotic hydration of the lens resulting from salt and water retention, although an alternative mechanism has been invoked to suggest that intralenticular osmotic pressure is increased by accumulation of glucose and its metabolic products within the lens. Irrespective of the precise mechanism, refractive changes with blurring of vision certainly occur or increase when blood glucose is lowered by initiation or intensification of treatment, especially if this is effected rapidly.

Hypoglycaemia

Hypoglycaemia is associated with symptoms of blurring of vision and diplopia. An assessment of symptoms of hypoglycaemia in insulin-treated diabetic patients using factor analysis has indicated that blurring of vision segregates with neuroglycopenic symptoms.[12] However, while diplopia is probably a direct effect of neuroglycopenia, blurring of vision may be caused by a combination of autonomic and neuroglycopenic effects on visual function.

In both normal and diabetic humans acute hypoglycaemia causes a sudden and significant fall in intraocular pressure, which is related temporally to the onset of the acute autonomic reaction.[13] The fall precedes the maximal increment in plasma catecholamines and is probably a direct effect of autonomic neural stimulation; it is not caused by circulating adrenaline. Studies in normal humans using different forms of pharmacological blockade have indicated that this is mediated via an alpha-adrenoceptor mechanism.[14] The changes in systolic and diastolic blood pressure which occur during hypoglycaemia do not alter mean arterial pressure, and are unlikely to have a contributory role.

Acute hypoglycaemia has also been shown to alter the dimensions of the anterior chamber of the eye in normal human subjects, with an acute shallowing occurring at the time of acute autonomic stimulation.[15] The volume of the anterior chamber decreased by approximately 8% and peripheral anterior chamber depth declined by 9%, with a return to normal around 45 minutes after the autonomic reaction. These rapid and transient changes in volume of the anterior chamber may be associated with the fall in intraocular pressure. Consistent changes in pupillary size in response to a similar degree of hypoglycaemia were not shown previously in normal subjects,[16] but constriction of the pupil has been demonstrated recently using a different

Table II. Morbidity of acute hypoglycaemia in diabetic patients treated with insulin

Target organ	Clinical presentation
Brain	Coma
	Convulsions
	Brain damage (acute; chronic)
	Transient ischaemic attack; stroke
	Cognitive impairment
Heart	Myocardial ischaemia/infarction
	Cardiac arrhythmias
Eye	Vitreous haemorrhage
	? Worsens retinopathy

technique.[17] This would suggest that parasympathetic neural stimulation may contribute to the observed reduction in depth of the anterior chamber of the eye by causing contraction of the ciliary muscle and by altering the size of the pupil.

Studies of controlled hypoglycaemia in normal and diabetic subjects have shown no change in corrected visual acuity for distance or near vision in the eye,[18] but did demonstrate a deterioration in colour discriminative ability which correlated with the fall in blood glucose. The colour vision changes were generalised and were not selectively limited to any one section of the visible spectrum. The effects of hypoglycaemia on retinal blood flow in humans have not been reported, but a study in anaesthetised minipigs has shown an increase in retinal blood flow by 44% during hypoglycaemia compared with the basal resting state.[19]

Neurophysiological changes can be demonstrated during hypoglycaemia by measurement of event-related brain potentials, which reflect the timing of sensory and cognitive processes. The P300 cortical brain potential is easily recorded and is related to decision time. Visual stimuli can be used to examine the latency of the P300 response during visual evoked potentials (VEPs). Alternatively the P100 (a single wave VEP) can be measured using a shift or reversal of a chequerboard pattern. In general the latency of VEPs is prolonged during hypoglycaemia in normal and diabetic humans,[18,20] although Tamburrano *et al.*[21] found no change in latency of the P100 wave during hypoglycaemia. The effect of acute hypoglycaemia in prolonging reaction times following visual stimuli has recently been reviewed.[22]

It is not clear from these studies whether hypoglycaemia affects predominantly retinal generation of impulses, conduction in the neurovisual pathways or the response of the visual cortex. These effects may have implications for visual reaction times and rapid decision-making during tasks such as driving.

Hypoglycaemia and the Diabetic Eye

Anecdotal reports have appeared of vitreous haemorrhage occuring after severe (particularly nocturnal) hypoglycaemia causing sudden loss of vision.[23] These might result from either a relative rise in perfusion pressure or the mechanical stress imposed by sudden changes in intraocular pressure on vulnerable capillaries in areas of neovascularisation. Alternatively, trauma associated with hypoglycaemia-induced coma or convulsions (particularly head injury) may precipitate rupture of new vessels in the eye. The effects on the retinal vasculature are more speculative, but it seems credible that sudden perturbations in haemodynamic and haemostatic parameters such as viscosity and coagulability could influence microvascular flow in an already diseased microvasculature affected by diabetic retinopathy. It has been proposed that recurrent acute hypoglycaemia may aggravate the severity of diabetic microangiopathy.[24] This may take the form of progression of the histopathological lesions affecting capillaries, or the promotion of adverse functional effects (such as ischaemia) on the tissues supplied by these vessels.

Circumstantial support for this premise is provided by observations reported by the Kroc, Steno and Oslo studies in the 1980s which examined the effects of strict glycaemic control using intensive insulin therapy on established diabetic retinopathy. A period of strict glycaemic control caused a dramatic, and unexpected, deterioration in the appearance of the retinae with progression of background retinopathy to pre-proliferative changes and overt retinal ischaemia.[25] The retinal ischaemia gradually resolved despite persistence of the intensive insulin therapy, so this phenomenon is reversible. Although the principal explanation was that the reduction in blood glucose causes retinal hypoperfusion and tissue hypoxia, the strict glycaemic control was associated with an increased frequency of acute hypoglycaemia. It is possible that the putative effects of hypoglycaemia on microvascular flow precipitated localised capillary closure and promoted retinal ischaemia. It is evident that rapid 'normoglycaemic re-entry' is detrimental to established microvascular disease and should be avoided when attempting to improve glycaemic control. A similar phenomenon has also been observed in patients with type 2 diabetes.[26]

A non-selective spatial-frequency loss with contrast sensitivity testing has been described in patients with type 1 diabetes of short duration who had no detectable evidence of diabetic retinopathy.[27] The authors have suggested that repetitive hypoglycaemic insults may contribute to the underlying mechanism causing damage to the optic nerve.

Diabetic Eye Disease and Driving

In a review of the management of type 1 diabetes with respect to the diabetic eye, it is important to include some mention of the potential problems of diabetic eye disease to the diabetic driver. Hypoglycaemia is once again the most serious hazard to diabetic patients treated with insulin and has been reviewed previously[10,28] – with the additional caveat that hypoglycaemia can cause blurring of vision and diplopia (see above).

Table III. Factors affecting visibility when driving

Human	Environmental
Visual acuity	Adverse weather: fog, snow, rain
Peripheral vision	Darkness
Depth perception	Surrounding topography
Eye coordination	Vehicle design
Light/dark adaptation	Headlight glare
Colour vision	Road lighting, signs, marking

Table IV. Driving and diabetes: impaired vision

	Visual function		
Type of diabetic eye disease	Visual acuity	Visual fields	Dark adaptation
Cataract	↓	↓	—
Maculopathy	↓	—	—
Proliferative retinopathy	↓	↓	↓

Monocular vision is accepted for driving in the United Kingdom and the statutory requirement is the ability to read a car number plate with letters 3.5 in. (8.9 cm) high from a distance of 75 feet (22.9 m), corrected with spectacles if necessary. This corresponds approximately to 6/10 on the Snellen chart. The inadequacy of this number plate test for assessing vision for driving becomes evident when the multiple factors which can affect visibility are noted (Table III). It examines static vision alone, is difficult to perform under clinical conditions and does not assess the ability to see moving objects or night vision (relevant for diabetic retinopathy). The potential of extensive photocoagulation to reduce visual fields has been recognised by the Driver and Vehicle Licensing Agency, as assessment of visual fields by perimetry is now requested for some patients as part of their medical report.

The effects of different forms of diabetic eye disease on visual function are summarised in Table IV. Cataract formation may accentuate glare from headlights and affected patients should avoid driving when it is dark. Fortunately, surveys of diabetic drivers have shown that most stop driving voluntarily when their eyesight deteriorates,[29–31] so that few would fail the current eyesight tests. However, more practical and relevant tests of vision are required for routine assessment of the diabetic driver.

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Key words: Diabetes, Diabetic retinopathy, Driving, Hypoglycaemia, Insulin, Intraocular pressure.

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