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Metabolic Syndrome Linked to Kidney Disease

Metabolic syndrome (MetS) and its components are linked to the development of chronic kidney disease (CKD).

The investigators searched MEDLINE (1966 to October 2010), SCOPUS, and the Web of Science for relevant studies. There were 11 studies identified, enrolling a total of 30,146 participants, that met inclusion criteria. The meta-analysis showed a significant association between MetS and the development of an eGFR of less than 60 mL/minute/1.73 m².

Primary care physicians may need to consider using metabolic syndrome as a marker to identify patients at higher risk of developing kidney disease.

For individual components of MetS, the ORs for the development of an eGFR of less than 60 mL/minute/1.73 m² in patients with MetS were 1.61 for elevated blood pressure, 1.27 for elevated triglycerides, 1.23 for low high-density lipoprotein (HDL) cholesterol levels, 1.19 for abdominal obesity, and 1.14 for impaired fasting glucose levels. There were 3 studies showing that MetS was associated with increased risks for the development of microalbuminuria or overt proteinuria.

MetS and its components are associated with the development of eGFR <60 ml/min per 1.73 m² and microalbuminuria or overt proteinuria.

Limitations of this analysis include significant clinical heterogeneity; inability to perform subgroup analyses by race and sex; and observational design of the individual studies, with the potential for unknown confounding factors, selection bias, and attrition bias.

Clin J Am Soc Nephrol. August 18, 2011.

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Better Way to Predict Weight Loss?

The 3,500-calorie rule: Since there are 3,500 calories in a pound of fat, one have to eat 500 fewer calories a day to lose a pound a week.

But researchers now say the formula is wrong because it fails to account for a slowing metabolism, the fact that dieters lose muscle as well as fat, and other factors that influence weight loss. The 3,500-calorie rule leads to unrealistic expectations and may undermine people's efforts to lose extra pounds.

Hall and colleagues with the World Health Organization, Columbia University, and the Harvard School of Public Health have developed a web-based model that they say more accurately predicts a dieter's expected weight loss over time. The body weight simulator, which can be found on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) web site.

Weight loss actually occurs more gradually than is thought. A better guide for the typical overweight adult is that cutting 10 calories a day from their diet will lead to the loss of a pound over three years. So reducing calorie intake by 250 calories a day will eventually lead to a 25-pound weight loss, but it will take three years for most overweight or obese adults to get 95% of the way there. About half the weight will be lost in the first year of dieting, with weight loss slowing after this.

Based on their model, the researchers conclude that to achieve average weight levels similar to those seen in the 1970s, moderately obese people would have to cut 500 calories out of their diet a day for several years. We really should be focusing more on preventing weight gain in the first place, especially among children.

Hall, K. The Lancet, Aug. 27, 2011; vol 378: pp 826-837.

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From the Flight Deck: Diabetics, Watch Your Insulin

Changes in cabin pressure during flights may cause insulin pumps to deliver too much or too little of the medication.

After learning of a 10-year-old girl with type 1 diabetes whose blood sugar got too low an hour after take-off, Bruce King of John Hunter Children's Hospital in Newcastle, Australia, and colleagues found cases of other insulin-pump-using diabetics who reported the same problem during flight.

To see what was going on, they put ten insulin pumps on a commercial flight. Sure enough, during takeoff (when air pressure was decreasing), the pumps delivered about 1 to 1.4 extra units of insulin, on average. And during descent, when pressure was increasing, some insulin was sucked back into the pumps -- causing them to give out too little insulin, by less than 1 unit.

Dr. Cohen said he expected those types of changes to be more of a problem for kids and people who use low doses of insulin to begin with.

To prevent any danger to flyers, the researchers set out a list of recommendations, including that insulin cartridges should only contain 1.5 mL of insulin.

Diabetics should disconnect the pump before takeoff, remove air bubbles and reconnect at cruising altitude, then disconnect again and prime the line with 2 insulin units after landing before reconnecting for good. They should also disconnect the pump during flight emergencies when there's a big drop in cabin pressure, King and colleagues wrote.

Diabetes Care 2011.

Diabetescope

Value of Intensive Treatment for Early Diabetes Questioned

When early type 2 diabetes is detected by screening, intensive management doesn't seem to cut the risk of certain complications later on.

Researchers found no statistically significant effect of intensive multifactorial treatment on the prevalence of diabetic peripheral neuropathy and peripheral arterial disease compared with routine care.

Earlier this year in *The Lancet*, some of Dr. Charles' co-authors on this paper were among those reporting on the international ADDITION study, in which intensive management of screen-detected type 2 diabetes yielded a nonsignificant reduction in cardiovascular events over five years.

The current study focused on 1,533 Danish participants in ADDITION. They were managed in general practices that were randomized to deliver either intensive multifactorial treatment or routine care.

Six years after screening, the prevalence of an ankle-brachial index of 0.9 or less was 9.1% in the routine-care arm and 7.3% in the intensive treatment arm. Similarly, abnormal test results for neuropathy were seen in 34.8% and 30.1% in the routine and intensive treatment groups, respectively.

They also point out that the prevalence of peripheral neuropathy and peripheral arterial disease were high, so clinicians should be aware of these high prevalences.

The researchers offered another caveat: "It is conceivable" that when diabetes is in its initial stages, "a longer duration of intensive treatment is necessary to observe an effect." They added, "A future repeated examination of our participants after a longer follow-up period will show whether this is the case."

Diabetes Care 2011.



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Hypoglycaemia Unawareness

Introduction

While the benefits of good glycaemic control are now firmly established, the extent to which individuals can reach tight glucose targets varies widely between individuals. Some maintain tight levels of glucose control with minimal side effects while, in others, the limitations of current methods of insulin delivery/replacement mean that even moderate levels of glucose control result in high rates of hypoglycaemia. Recent epidemiological work has demonstrated that severe hypoglycaemia is not a problem confined to type 1 diabetes. Indeed, since type 2 diabetes is around 20 times more prevalent than type 1, the overall challenge of managing hypoglycaemia is probably greater in this population.

Epidemiology and definitions

It is difficult to obtain accurate estimates of incidence and prevalence and to compare rates in different populations due to a lack of an agreed definition, and also because awareness of hypoglycaemia is rarely all or nothing. Many patients experience an occasional severe hypoglycaemic episode without warning (i.e. require the assistance of a third party to aid recovery), but usually can recognise symptoms and take appropriate action. Frier has argued that unawareness of hypoglycaemia be classified as normal, partial or total and, indeed, that impaired awareness of hypoglycaemia should be the preferred term to describe this syndrome. He and others have also proposed the use of standard questionnaires to identify those with various degrees of awareness.

Despite these difficulties it is worth highlighting some relevant studies. Pramming et al. found diminished warning symptoms in 20% of 411 patients with type 1 diabetes, close to the 23% of patients with partial or complete unawareness reported by Hepburn et al. out of a total population of 301. Mühlhauser et al. reported around 25% of 523 patients who had difficulty in identifying hypoglycaemia. unawareness affects around a quarter of all patients with type 1

diabetes, a proportion which rises to close to 50% in patients with a duration of diabetes over 20 years.

Since hypoglycaemia unawareness reflects diminished physiological protection to hypoglycaemia, it seems likely that these patients would be vulnerable to severe episodes. In a prospective study, Gold et al. confirmed this by showing that individuals with partial or complete unawareness were seven times more likely to suffer severe episodes compared to those who continued to claim to recognise hypoglycaemia.

Normal protective responses and unawareness development

Activation of the autonomic nervous system during hypoglycaemia represents a classic stress response involving the release of counterregulatory hormones and activation of both parasympathetic and sympathetic pathways. Increases in glucagon and adrenaline make the greatest contribution to glucose recovery through stimulation of hepatic glycogenolysis and gluconeogenesis, increased rates of lipolysis, and decreased rates of peripheral glucose uptake. Sympathoadrenal activation leads to symptoms such as sweating, palpitations and tremor. Diminished glucose delivery to the brain starts to impair cerebral function (neuro glycopenia) at glucose levels of around 3–3.2mmol/L, but since autonomic responses are normally activated at glucose levels above this threshold (at 3.5–3.8mmol/L), mildly impaired cognitive function (manifested by mild increase in reaction time or slight loss of concentration) usually goes unnoticed by the patient. If glucose levels are falling rapidly and counterregulatory responses fail to raise blood glucose sufficiently, then neuro glycopenic features will predominate; these include confusion, altered emotion and loss of temper and, finally, diminished consciousness (Figure 1). Since the glucose thresholds for the release in

counterregulatory hormones and cognitive dysfunction are close together, even in those with an intact autonomic response, there is sometimes little time for patients to take action by taking refined carbohydrate. Thus, all patients treated with sulphonyl ureas or insulin are at risk of an occasional severe episode.

In those individuals with a degree of hypoglycaemia unawareness, their glucose

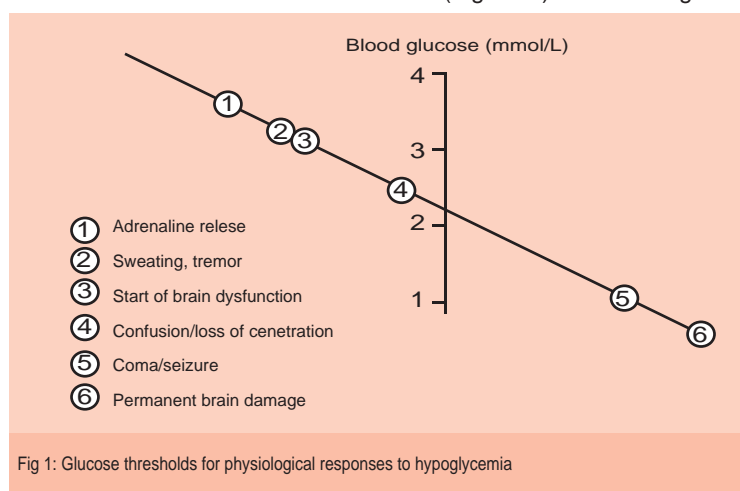


Fig 1: Glucose thresholds for physiological responses to hypoglycaemia

Hypoglycemia Unawareness

concentration has fallen well into the hypoglycaemic range before any symptoms occur due to a fundamental alteration in the relationship between the glucose threshold for impaired cerebral function and that for the onset of autonomic symptoms. It appears that, in those with hypoglycaemia unawareness, autonomic responses occur at or below the glucose threshold for the onset of cognitive decline, thus the patient may have few clues to impending hypoglycaemia before brain function is severely impaired (Figure 2). Glucose concentrations reach levels where the patient is unable to treat themselves and they will remain incapacitated until the effect of the insulin or sulphonylurea wears off or they can be treated by a third party. If hypoglycaemia is prolonged, the individual is potentially at risk of permanent cognitive damage and even death. However, such an outcome is extremely rare, probably because counterregulatory responses are eventually activated and help to maintain glucose concentrations above those which result in irreversible structural damage. Nevertheless, severe hypoglycaemia is associated with significant morbidity as episodes of sudden confusion, bizarre behaviour, or loss of consciousness can have major professional or personal consequences, leading to fractures, road traffic accidents, burns, seizures, or loss of a job, driving licence or partner. Life is particularly difficult for family and friends who in extreme cases have to ensure that those affected are constantly accompanied.

Mechanisms underlying the development of unawareness

Factors causing hypoglycaemia unawareness are discussed below and are listed in Table 1. Protective physiological responses are intact at the time of diagnosis but become defective with increasing duration of diabetes. Within a few years it is possible to detect a progressive reduction in glucagon release in response to hypoglycaemia and, by 10–15 years' duration of diabetes, the response is virtually flat. Recent work indicates that the failure of glucagon release is due to progressive beta-cell destruction preventing paracrine cross-talk between alpha and beta cells.

Lack of glucagon release not only reduces the ability to

- Long duration of diabetes
- Antecedent hypoglycaemia
- Very tight glycaemic control
- Alcohol
- Increasing age
- Antecedent exercise
- Sleep

Table 1. Factors causing hypoglycaemia unawareness

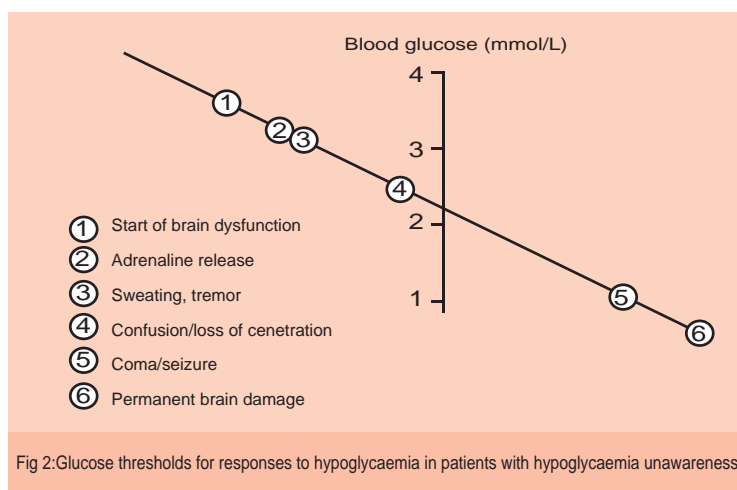
resist the glucose lowering effects of insulin at hypoglycaemic levels but also increases dependency upon the other important response, activation of the sympathoadrenal system. Since this mechanism is responsible for both raising blood glucose and generating hypoglycaemic symptoms, it is critically important to individuals with diabetes. However, increasing duration of diabetes

is also associated with a progressive decline in sympathoadrenal responses to hypoglycaemia. It is important to appreciate that the sympathetic nervous system retains the ability to release adrenaline in response to other stimuli such as exercise. Nevertheless, the cause of this progressive afferent defect (a failure of the body to recognise hypoglycaemia as a stimulus to activation) with increased duration of diabetes remains unknown.

An additional mechanism also contributes to the failure of the sympathoadrenal system to respond to hypoglycaemia: the effect of episodes of antecedent hypoglycaemia, particularly during periods of tight glycaemic control. Repeated episodes of moderate levels of experimental hypoglycaemia have been shown to impair increases in adrenaline, other counterregulatory hormones and hypoglycaemic symptoms in non-diabetic individuals and in those with diabetes. It appears that these episodes are sufficient to reset the threshold for the activation of the sympathoadrenal system (and symptoms) below concentrations which impair cerebral function. This may explain at least in part the epidemic of severe hypoglycaemia which was seen in the DCCT among those with the tightest levels of glycaemic control.

The underlying mechanism which drives the failure of the sympathoadrenal response following hypoglycaemia remains poorly understood. It appears to involve alterations in neurotransmission in areas of the brain which can sense

falling glucose concentrations and coordinate stress and feeding responses, in particular the hypothalamus, the thalamus and the amygdala. Both human and animal models are being used to identify key pathways which may provide candidates for therapeutic intervention, but much experimental work remains to be undertaken. Alcohol is



frequently an important contributor to severe hypoglycaemic episodes due to multiple mechanisms. It inhibits glucose counterregulation through effects on the liver, reduces some of the peripheral autonomic responses such as tremor and impairs cognitive function, reducing the ability of individuals to recognise when their blood glucose is low. Additional factors which contribute to impaired responses include increasing age, antecedent exercise and sleep, but the precise way in which these contribute to the clinical syndrome of hypoglycaemia unawareness is also unclear.

How can hypoglycaemia unawareness be reversed?

The observation that only a few hours of moderate hypoglycaemia can induce defective protective responses to subsequent episodes suggests that these acquired defects are functional rather than structural. It follows that if hypoglycaemia could be prevented this might lead to recovery of both impaired sympathoadrenal responses and symptomatic awareness. A series of reports involving relatively small numbers of patients with type 1 diabetes have confirmed that as little as two to three weeks of hypoglycaemia avoidance can restore hypoglycaemia awareness, at least in part. In all three studies, warning symptoms of hypoglycaemia improved, but the effect on recovery of counterregulatory hormones was inconsistent. One study demonstrated that not only was the level of adrenaline release greater after strict hypoglycaemia avoidance, but also that it occurred at a glucose level above the threshold for cognitive decline. However, a report from another centre found no improvement in counterregulatory hormone release. Most, although not all, of these individuals had a relatively short duration of diabetes and the extent to which unawareness can be reversed in patients with long duration of diabetes is still unclear.

Clinical strategies to prevent or reverse unawareness

The overall approach to unawareness reversal programmes is relatively simple, consisting of working with patients individually and using insulin therapy flexibly to match it to eating and other activities. A number of approaches are utilised with the overall aim of minimising the risk of hypoglycaemia while retaining glycaemic control (Table 2). In practice, it is highly labour intensive,

needing considerable commitment from both the health care professional (usually a diabetes nurse specialist) and the patient themselves. We and others have found a multidisciplinary clinic including a clinical psychologist particularly helpful. A number of obsessional patients pursue normal glucose levels, constantly injecting additional corrective doses of insulin despite the attendant risk of severe hypoglycaemic episodes.

Skills training in insulin self-management

The basis of any hypoglycaemia avoidance/reversal programme is ensuring that individuals are provided with the skills to use insulin flexibly. Structured training courses to initiate flexible intensive insulin treatment have demonstrated both improved glycaemic control and major reductions in the incidence of severe hypoglycaemia (in contrast to the DCCT) as well as improvements in quality of life. Sustained benefits have been demonstrated in large numbers of individuals with type 1 diabetes in real clinical practice, across a range of centres to a wide age and diverse mix of patients.

Cox and colleagues have developed a related approach specifically for individuals who have problems with hypoglycaemia utilising a focus on estimation of blood glucose levels and improved decision making. Blood glucose awareness training (BGAT) attempts to improve recognition of both external cues and pathophysiological changes to hypoglycaemia. One trial reduced the incidence of severe hypoglycaemia by one-third, maintained for 12 months without a deleterious effect on HbA1c. It may be that the success of this approach is also related in part to the improved ability of patients to self-manage their diabetes.

<p>Minimising risk of excess insulin delivery</p> <ul style="list-style-type: none"> • Skills training in insulin selfmanagement • Insulin analogues • Continuous subcutaneous insulin infusion
<p>Improving hypoglycaemia awareness</p> <ul style="list-style-type: none"> • Continuous glucose monitoring systems with in-built alarms
<p>Drugs</p> <ul style="list-style-type: none"> • Caffeine • Modafinil • Fluoxetine
<p>Restoring beta-cell function</p> <ul style="list-style-type: none"> • Islet cell transplants • Whole cell transplants
<p>Table 2. Strategies utilised to diminish the risk of hypoglycaemia while maintaining glycaemic control</p>

Improving insulin delivery

When human insulins were first introduced there were concerns that patients were suffering more frequent episodes of hypoglycaemia and many patients continue to believe fervently that human insulin caused hypoglycaemia unawareness. However, none of the trials set out to test this hypothesis found convincing evidence that human insulin was responsible (although many were relatively underpowered). It remains possible that human insulin may have induced episodes of hypoglycaemia and subsequent unawareness due to slight differences in insulin kinetics, but it is perhaps more likely that improved glycaemic control following

Hypoglycemia Unawareness

input from professionals at the time of switching explained the phenomenon.

Both short- and long-acting insulin analogues have more physiological and predictable profiles than animal or human insulins. It is therefore logical to consider the use of these newer insulin analogues or continuous subcutaneous insulin infusion (CSII) in individuals with hypoglycaemia unawareness. There is evidence that using analogues in combination can improve glycaemic control without increasing hypo glycaemia, although the benefits are relatively modest. A meta-analysis of long-acting analogue insulins versus NPH insulins in patients with type 1 diabetes showed an ~30% reduction in both nocturnal and severe hypoglycaemia. This is in contrast to a systematic review in patients with type 2 diabetes in which the frequency of hypo glycaemia was reduced, but the number of severe episodes of hypoglycaemia was not improved. CSII is probably the most effective conventional way of delivering basal insulin and is an obvious option in individuals with hypoglycaemia problems. One meta-analysis of randomised controlled trials concluded that use of CSII reduces rates of severe hypoglycaemia while also improving glycaemic control. However, a systematic review which included a different meta-analysis concluded that, although there are fewer problems with hypoglycaemia while on pump therapy, most studies were too small to demonstrate a clinically significant decrease in the incidence of severe episodes.

Hypoglycaemia warning systems

Continuous glucose monitoring systems (CGMS) have been available for many years, but still are only used in relatively few individuals. There are a number of obstacles to their routine use such as life of the sensor, accuracy of readings at low blood glucose levels, cost and the time lag between blood glucose and subcutaneous (interstitial) glucose levels. Technology is improving and newer 'real-time' systems have a built-in alarm to warn patients of imminent low or high glucose levels. However, overnight alerts do not always wake the patient and false alarms are common. Randomised controlled trials of these devices have been disappointing, and lack of agreement of the definition of biochemical hypoglycaemia has hindered metaanalysis. Many patients stop using them after a few weeks due to the inconvenience of attaching and detaching the device. One systematic review showed that there was no improvement in glycaemic control, as measured by HbA1c, although episodes of nocturnal hypoglycaemia were reduced. Nevertheless, there is considerable anecdotal experience and some trial evidence indicating that, by refining blood glucose profiles in well-motivated patients (in the trial, HbA1c <7.5% [58mmol/mol] at recruitment), continuous glucose monitoring systems can help patients avoid episodes of hypoglycaemia.

Therapeutic interventions

Caffeine, an adenosine antagonist, reduces cerebral blood flow and has been shown to increase symptoms during experimental hypoglycaemia. In a small randomised controlled trial, the ingestion of caffeine versus placebo reduced the duration of nocturnal hypo glycaemia by ~50%, as measured using a CGMS. The effect on hypoglycaemia during the day was not significant. There is no evidence that caffeine (or theophylline which has a similar pharmacological effect) can reverse hypoglycaemia unawareness, or that rates of severe hypoglycaemia are attenuated in a clinical setting.

An alternative approach has been to use drugs that interact with ATP sensitive K⁺ channels (modafinil), or block serotonin reuptake (fluoxetine) to augment the sympatho adrenal response. Human studies have been confined to small-scale laboratory based work with variable degrees of minor benefit, and trials in individuals with diabetes are awaited.

Transplantation

Evidence suggests that hypoglycaemia unawareness may be reversed by islet cell transplantation. In one retrospective study of 31 patients, an increase in recognition of hypoglycaemic symptoms persisted even if the graft had partially or totally failed. This improvement in symptoms was also observed in another study in which the glycaemic thresholds for release of counterregulatory hormones returned to 'normal'. Interestingly, rates of severe hypoglycaemia are reduced and warning symptoms re-established despite a failure of transplantation to restore the magnitude of counterregulatory hormone responses. A more invasive option is transplantation of a whole pancreas. It has been shown to provide independence from exogenous insulin, as well as reversal of hypoglycaemia unawareness in both the short and medium term. However, such a procedure is associated with considerable perioperative morbidity, and requires life-long immune-suppression and exposure to its concomitant risks. Currently, it is usually undertaken in those individuals with end-stage kidney failure who benefit from a combined pancreas-kidney transplant. However, it should be considered as a treatment option for patients with severe hypoglycaemia unawareness who have failed to respond to other approaches.

Conclusion

The inadequacy of current insulin therapy in reproducing the physiology of the beta cell means that hypoglycaemia and unawareness will continue to present a major clinical challenge. It remains unclear as to why many individuals with insulin treated diabetes experience little or no hypoglycaemia while some are affected by multiple severe episodes. The latter have presumably developed

Key Points

- In hypoglycaemia unawareness warning symptoms occur at or below the glucose threshold for the onset of cognitive impairment, thus the patient may have few (or no) clues to impending hypoglycaemia
- Reversal of hypoglycaemia unawareness is very labour intensive, and consists of working with patients to avoid all episodes of hypoglycaemia. Therapeutic options include skills training, utilising technology and transplantation
- Insulin replacement is currently sub-optimal, and thus hypoglycaemia unawareness is best avoided by equipping patients with the skills to flexibly utilise insulin to avoid both hyper- and hypoglycaemia and thus self-manage their diabetes effectively

particularly rapid and severe loss of the protective physiological mechanisms which oppose hypoglycaemia but the precipitating factors, in particular the contribution of their own behaviour in self-managing their diabetes, are still unclear.

Unless there is a revolution in insulin treatment, technology will contribute an increasing role in hypoglycaemia unaware patients. New 'smart pumps', which combine CSII with a continuous glucose monitor and which can halt the infusion of insulin when a patient is hypoglycaemic, show promise. Complete closed loop systems which can adjust insulin infusion rates automatically according to the prevailing glucose level are in early clinical trials. It seems unlikely that such devices could ever be manufactured cheaply enough to be used widely. In the short term, hypoglycaemia unawareness is probably best prevented by developing educational approaches to ensure that all patients have the ability to use flexible insulin therapy.

Ref: Hypoglycaemia unawareness. Jackie Elliott, Simon Heller.
Practical Diabetes VOL. 28 NO. 5.

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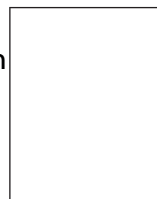
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Editorial Note:

Dear Doctor,
This issue of your diabetes newsletter is focused on "Hypoglycaemia Unawareness". We appreciate your comments and queries. Please participate in quiz competition & win prizes.

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