Carbohydrate tolerance and food frequency

BY DAVID J. A. JENKINS

Clinical Nutrition & Risk Factor Modification Center, St Michael's Hospital, 61 Queen Street East, 6th Floor, Toronto, Ontario M5S 3E2, Canada

Dietary and pharmacological approaches to slowing the rate of glucose absorption and blunting the insulin response show promise in the treatment of diabetes and hyperlipidaemia. These approaches include dietary fibre, low-glycaemic-index foods and gastrointestinal digestive enzyme inhibitors. One common feature is that they spread the nutrient load over time. A potentially simpler approach is to take more frequent smaller meals over a longer period of the day. Early studies suggested that frequent glucose and insulin administration to diabetic patients improved diabetes control. More recent acute studies of one test meal or 1 d blood metabolite profiles have identified a significant economy in insulin secretion when glucose is sipped or when meal frequency is increased in both diabetic or non-diabetic subjects. In diabetic subjects improvement in mean blood glucose levels has also been reported. However, despite the demonstration of an alteration in response over time in glucose tolerance in healthy volunteers, no longer-term improvement in glycaemic control was reported in the only study in diabetes to examine a change from three to nine meals daily over a 1-month period. The disparity between longer-term and acute studies requires further investigation. At present, although this nutritional approach holds considerable theoretical promise, specific advice is premature.

Meal frequency: Carbohydrate tolerance

The possible advantage of nibbling *v.* gorging has attracted attention since the time of Sanctorius in the seventeenth century. More recently in the 1930s Ellis (1934) suggested advantages of increased frequency of glucose and insulin administration in the treatment of difficult cases of diabetes, and 30 years ago Fabry *et al.* (1964) attracted attention once again to a broad range of health advantages relating increased meal frequency to the prevention of chronic diseases.

These findings were associated with a flurry of activity suggesting that increased meal frequency reduced serum cholesterol levels (Gwinup *et al.* 1963*a*; Cohn, 1964; Jagannathen *et al.* 1964), improved glucose tolerance (Gwinup *et al.* 1963*b*), and reduced enzyme levels in adipose tissue associated with fatty acid storage (Bray, 1972). Unfortunately, the other part of the message was often not made with sufficient force, i.e. if increased meal frequency was advocated a commensurate reduction in meal size had to be stressed. As a result increased meal frequency was interpreted as 'snacking' between (large) meals with the undesirable consequences of increased energy intake. Such a situation might be particularly undesirable for those who were most likely to be given the advice; the obese, hypertensive, diabetic and hyperlipidaemic. Consequently, the concept of increased frequency fell from favour and was proscribed by diabetes associations (Special Report Committee of the Canadian Diabetes Association, 1981) and relatively little further research was undertaken for about 20 years.

More recently there has been renewed interest in the concept of nibbling *v.* gorging. Studies have confirmed the cholesterol-lowering effect of increased meal frequency in experimental feeding studies (Jenkins *et al.* 1989; Arnold *et al.* 1993; McGrath & Gibney,

1994) and in population studies (Edelstein *et al.* 1992; Wolever *et al.* 1995). Increased meal frequency has also been shown to have advantages for carbohydrate tolerance in type II diabetes (Jenkins *et al.* 1992; Bertelsen *et al.* 1993). As a result one of the most recent dietary guidelines for diabetes now advocates increased meal frequency for its potential beneficial impact on diabetes control (Franz *et al.* 1994). Despite this advice, the only longer-term study of diabetes to have been carried out to this point has failed to note a benefit on indices of either carbohydrate or lipid metabolism (M. Arnold, M. Ball and J. Mann, unpublished results). In many ways, this position is similar to studies of dietary fibre where some studies show benefit while others do not; consequently the level of debate is such that certain major diabetes associations no longer advocate increased fibre consumption (Franz *et al.* 1994).

THE ANALOGY WITH DIETARY FIBRE

Both dietary fibre and increased meal frequency have been proposed to have beneficial effects on serum lipids and glucose tolerance. For their effects on carbohydrate tolerance the mechanisms may be similar. In fact increased food frequency may be a useful model system in which to demonstrate the effects of fibre in slowing nutrient absorption. Studies with viscous types of dietary fibre, such as guar, pectin, locust bean or oat gums, have shown them to flatten the glycaemic and insulinaemic response in normal, post-gastrectomy and diabetic subjects when added to carbohydrate-containing test meals (Jenkins *et al.* 1976, 1978; Holt *et al.* 1979; Blackburn *et al.* 1984; Flourie *et al.* 1984; Braaten *et al.* 1991; Wood *et al.* 1994; Mann, 1997). When this effect was examined in relation to the viscosity of the gums used it was demonstrated that the greater the viscosity the greater the effect (Jenkins *et al.* 1978; Wood *et al.* 1994). Indeed, when the fibre was hydrolysed and viscosity lost, no effect was seen (Jenkins *et al.* 1978; Wood *et al.* 1994). In addition when markers of absorption and excretion, such as xylose, were added to the fibre-rich test meals a significant prolongation of xylose excretion was seen but there was no difference in total urinary excretion between fibre and control treatments (Jenkins *et al.* 1978). These results indicated that the flatter glucose and insulin responses were not simply the result of malabsorption, but, in view of the delayed excretion pattern of the xylose, a reduced rate of absorption was likely to be the cause. Both delayed gastric emptying and slower small intestinal absorption have been implicated as the reason for the reduced rate of absorption. Tc-labelled gastric-emptying studies have shown that viscous fibres such as pectin reduce the rate of gastric emptying (Holt *et al.* 1979; Leeds *et al.* 1981). However, the reduction in glycaemia and insulinaemia do not relate to the delay in gastric emptying. Small intestinal perfusion studies have indicated a reduction in the rate of glucose absorption in the small intestine (Blackburn *et al.* 1984; Flourie *et al.* 1984). The reduced postprandial glycaemic and insulinaemic areas, therefore, appear to be the result of a reduced rate of absorption brought about by spreading the nutrient load over time.

SIPPING AND NIBBLING: EFFECTS OF SPREADING THE NUTRIENT LOAD

In order to assess the effects of spreading the carbohydrate load over time on the postprandial glycaemic and insulinaemic areas we gave 50 g glucose in solution to healthy volunteers either as a bolus or sipped at an even rate over 210 min (Jenkins *et al.* 1990). The bolus resulted in the expected rise in both glucose and insulin with an undershoot in blood glucose at 180 min (Fig. 1). Coincident with the undershoot was a rise in counter-regulatory hormones, including growth hormone, and a rebound in previously suppressed

FFA levels. On the other hand, with sipping there appeared to be minimal perturbation of the milieau interieux (Fig. 1). The most significant feature was the greater than 50% reduction in postprandial insulin area. At 4 h an intravenous glucose tolerance test was performed to give an idea of any change in glucose disposal rate. As suspected the K_G (glucose disappearance constant) was significantly more rapid following sipping than following the bolus (Fig. 2). Together the data suggested that spreading the nutrient load

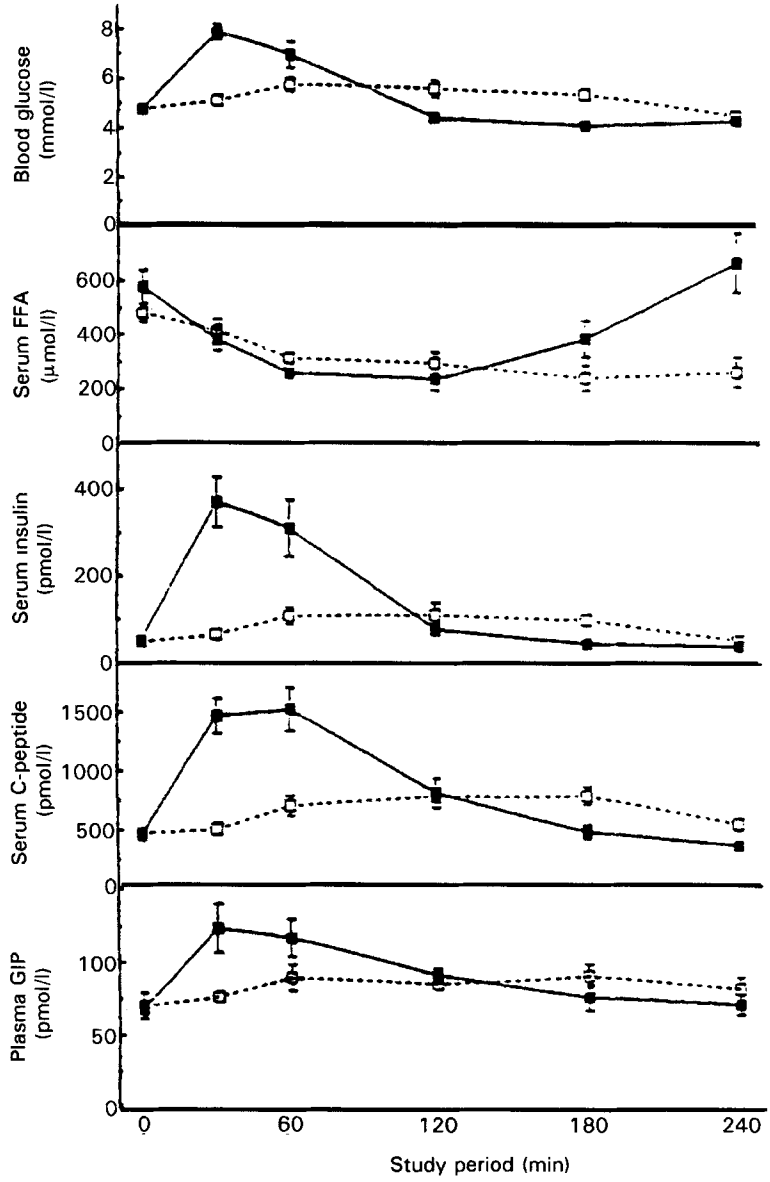

Fig. 1. Mean blood glucose, serum free fatty acid (FFA), insulin, and C-peptide, and plasma gastric inhibitory polypeptide (GIP) after taking a bolus of glucose solution over 5 min (50 g in 700 ml water) at time 0 (■) or sipping the same solution over 210 min at an even rate (□). Points are means with their standard errors represented by vertical bars for nine subjects. (From Jenkins *et al.* 1990.)

resulted in prolonged suppression of the inhibitory effects of FFA on glucose uptake (Randle *et al.* 1963). As a result glucose was cleared from the circulation with a major economy in insulin secretion.

A similar picture was also seen when a type II diabetic subject on oral hypoglycaemic agents was given 240 g glucose in solution either as three 80 g glucose loads in drinks, in bolus, taken 4 h apart or as 240 g glucose in solution sipped at an even rate over 12 h (Fig. 3). The same economy of insulin secretions was seen and significantly less glucose was lost in the urine (Jenkins *et al.* 1983). In healthy volunteers addition of fat and protein

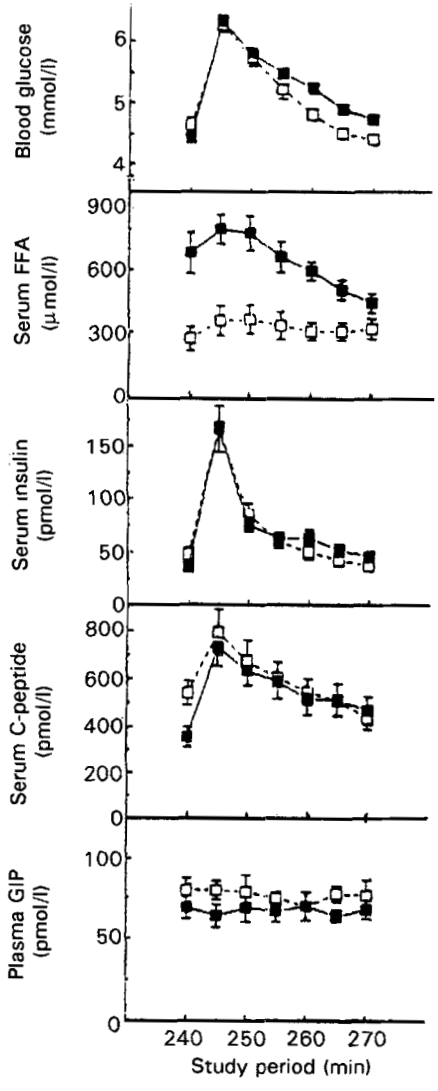

Fig. 2. Mean blood glucose, serum free fatty acid (FFA), insulin and C-peptide, and plasma gastric inhibitory polypeptide (GIP) after taking 5 g intravenous glucose. (■), Post-glucose bolus, (50 g glucose in 700 ml water over 5 min); (□), post-sipping (50 g glucose in 700 ml water over 210 min at an even rate). Points are mean values with their standard errors represented by vertical bars for nine subjects. (From Jenkins *et al.* 1990.)

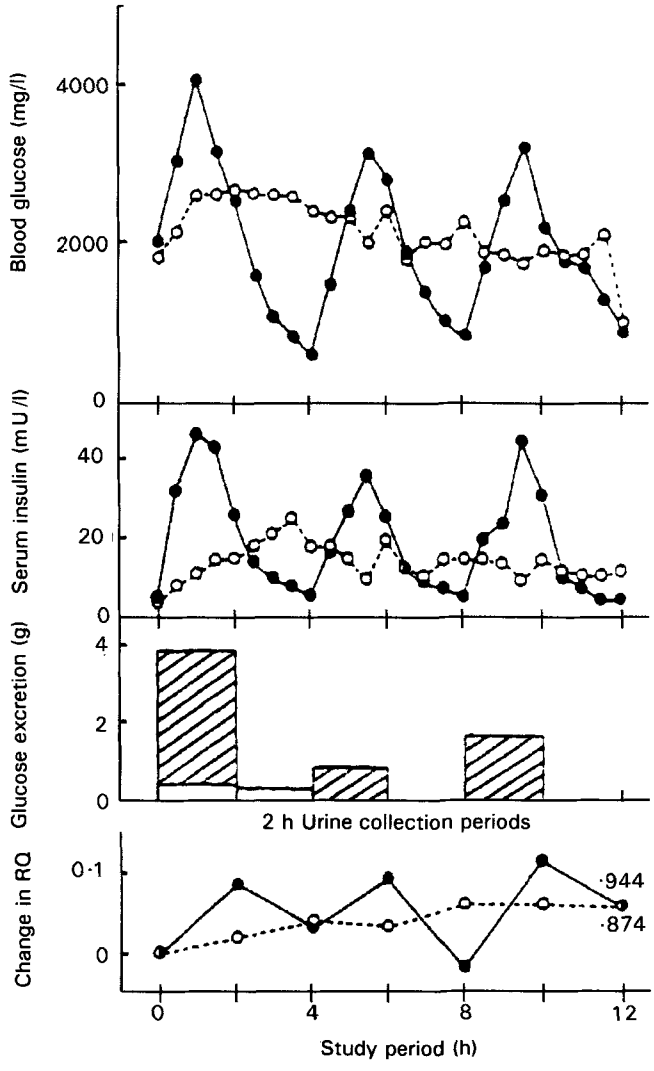

Fig. 3. Blood glucose, insulin and RQ response and 2 h urinary glucose loss, measured over 12 h, are shown in a subject whose diabetes was controlled by diet. On one occasion, 80 g glucose drinks were taken at 0, 4 and 8 h (●—●, ▨) and on another occasion 5 g glucose in solution was taken every 15 min by continuous sipping (○- - -○, □). (From Jenkins *et al.* 1983.)

as liquid formula demonstrated the same insulin economy when three meals were compared with sipping over a 12 h period (Fig. 4; Wolever, 1990).

Using whole foods, studies have shown that one-hourly or 1·33-hourly, as opposed to four-hourly, meal feedings of the identical food to non-insulin-dependent diabetes mellitus subjects resulted in significantly lower mean blood glucose and insulin levels over 8–12 h periods, with reduced 24 h urinary C-peptide losses (Jenkins *et al.* 1992; Bertelsen *et al.* 1993; Fig. 5). These studies have been extended to demonstrate the negative correlation between three, six, nine and twelve meals taken over a 12 h period and the incremental area under the glucose response curve (Fig. 6). The insulin reduction was significant at six meals and was not further reduced by twelve meals (Segura *et al.* 1995).

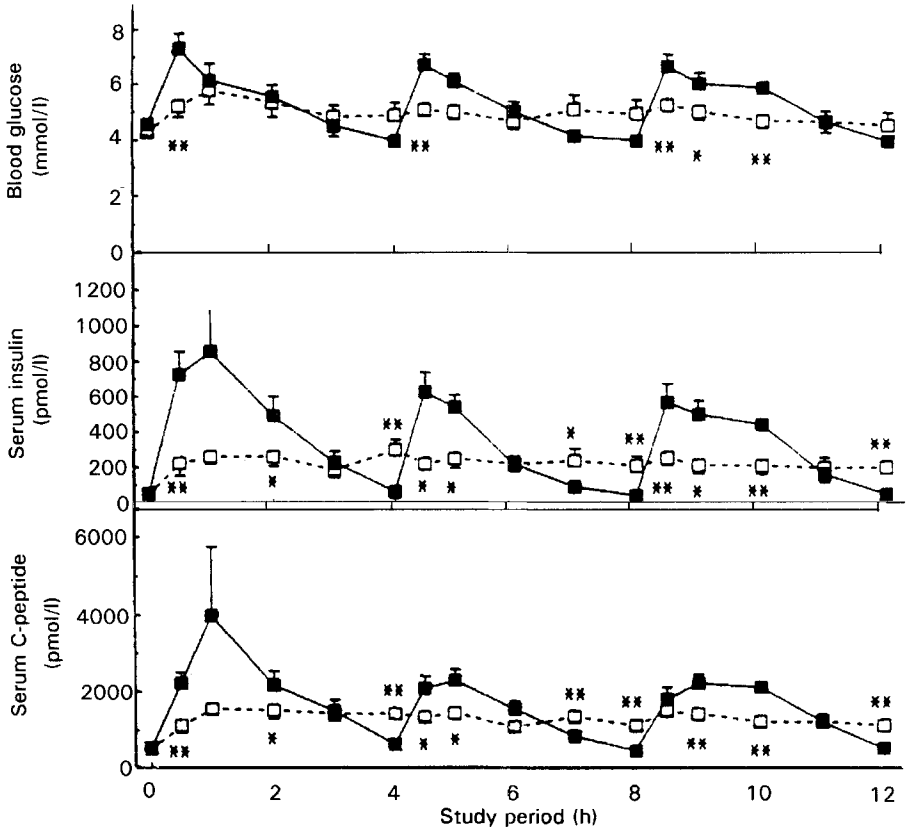

Fig. 4. Mean concentrations of blood glucose and serum insulin and C-peptide in seven healthy men who took the same amount of liquid formula either as three meals at 0, 4, and 8 h (■) or by continuous sipping (□). Points are mean values with their standard errors represented by vertical bars. Mean values were significantly different from those for the same subjects taking three meals: $*P < 0{\cdot}05$, $**P < 0{\cdot}01$. (From Wolever, 1990.)

Longer-term studies are still required. The older literature suggests improvement in glucose tolerance when meal frequency is increased (Arnold *et al.* 1994). However, our studies of healthy volunteers failed to show improvement in glucose tolerance to a standard test meal after 2 weeks of semi-continuous eating (seventeen meals daily) as opposed to three meals (Jenkins *et al.* 1989). In addition, studies of hyperlipidaemic and type II diabetic patients over 4-week periods failed to show a difference between three and nine meals daily in lipids or glycated haemoglobin ($Hb_{A1}c$) respectively (Arnold *et al.* 1994; Mann, 1997). It may be, therefore, that for carbohydrate metabolism there are no residual effects and that the advantage is only present as long as small frequent meals are taken. The question remains as to what 'adaptation' takes place between 2 and 4 weeks and to what extent compliance confounds long-term studies of increased meal frequency.

MEAL FREQUENCY, HYPERINSULINEMIA, AND ITS SEQUELAE

One of the key features of the more extreme models of increased meal frequency discussed is the apparent reduction in insulin need. This is of special interest at a time when insulin

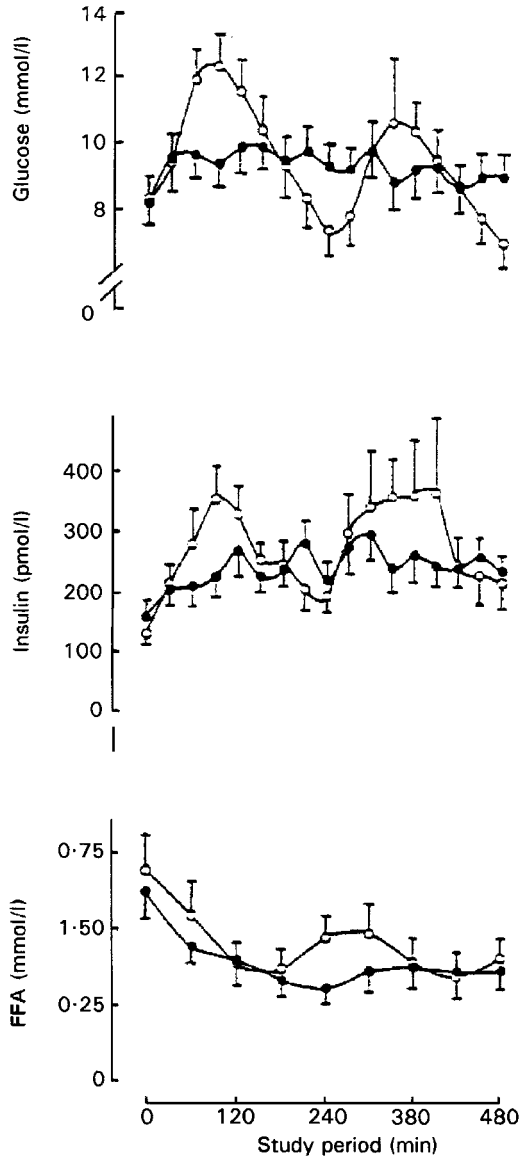

Fig. 5. Blood glucose, insulin, and free fatty acid (FFA) levels in twelve non-insulin-dependent diabetes mellitus patients after isoenergetic diets taken as six meals (●) or two meals (○). Points are mean values with their standard errors represented by vertical bars. (From Bertelsen *et al.* 1993.)

resistance and the hyperinsulinaemic syndrome are receiving much attention as possible causes of ill health (Reaven, 1988). Raised insulin levels have been associated with treated and untreated hypertension. No studies have been conducted with meal feeding patterns to determine the effects of food frequency and hypertension. Hyperuricaemia is associated

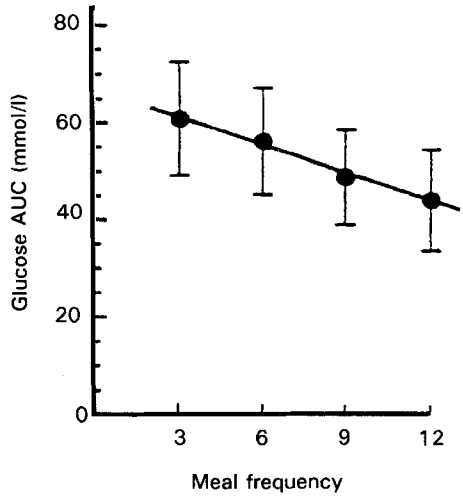

Fig. 6. Linear regression of incremental area under the plasma glucose curve (AUC) on meal frequency. The regression equation is: AUC = 67–1·9 × N, where N is the number of meals; correlation coefficient, $r - 0{\cdot}996$ ($P = 0{\cdot}0045$). (From Segura *et al.* 1995.)

with raised insulin levels and insulin resistance (Facchini *et al.* 1991). It is considered that the effect is related to the action of insulin on the kidney and the increased re-absorption of Na and uric acid in the distal convoluted tubule in hyperinsulinaemic states (Facchini *et al.* 1991). Studies of nibbling, where reduced 24 h C-peptide excretion was noted, have also demonstrated reduced serum uric acid levels and increased urinary uric acid losses during nibbling (seventeen meals daily for 2 weeks) as opposed to three-meal diets (Jenkins *et al.* 1995).

Raised insulin levels have also been associated with increased risk of CHD in epidemiological studies (Ducimetiere *et al.* 1980). Insulin stimulates hydroxymethyl-glutaryl-CoA (HMGCoA) reductase (*EC* 1.1.1.88), one of the rate-limiting enzymes in cholesterol synthesis (Lakshmanan *et al.* 1973). Mevalonic acid is a marker of HMGCoA reductase activity (Brown & Goldstein, 1980). In this respect it is of interest that the change in serum cholesterol on the nibbling *v.* three-meal diets was significantly related to the change in urinary mevalonic acid excretion. It may be that one of the reasons for the lower cholesterol levels seen with increased meal frequency is due to a reduction in the insulin stimulus to HMGCoA reductase. This also was the conclusion of Jones *et al.* (1993), who noted reduced insulin levels on nibbling and demonstrated reduced cholesterol synthesis in isotope studies.

FURTHER STUDIES

Longer-term studies of increased meal frequency are required in the diabetic population to determine the overall effects on carbohydrate tolerance, glycaemic control and markers of protein glycation such as $Hb_{A1}C$. The minimum number of meals required for an effect needs to be defined, together with differences between 2- and 4-week studies. The interactions must be explored with other factors such as soluble fibre, low-glycaemic-index foods or increased monounsaturated fat intakes; any or all of which may enhance the effect

of increased meal frequency and reduce the number of daily feedings required. In the treatment of diabetes the psychological and physiological effects of meal frequency in the long term need to be defined clearly (Tai *et al.* 1991; Bellisle *et al.* 1997), since the anxiety over possible weight gain was one of the original reasons for advice to increase food frequency falling from fashion. In this context it is also important that snacking encourages the desired dietary pattern and mix of macro- and micronutrients (Gatenby *et al.* 1995; Gatenby, 1997). Finally, the effects of food frequency must be assessed in long-term prospective studies of health and longevity, allowing for many potentially-confounding variables (Tai *et al.* 1991; Gatenby *et al.* 1995; Gatenby, 1997; Bellisle *et al.* 1997).

CONCLUSION

Spreading the nutrient load appears to have advantages in reducing the need for insulin in the disposal and tissue uptake of carbohydrate. Increased meal frequency together with viscous soluble fibres, low-glycaemic-index carbohydrate foods and inhibitors of gastrointestinal carbohydrate digestion share these properties. However, meal frequency might be argued to be a cleaner 'model' since it involves only an alteration in rate of substrate delivery, not a change in other chemical components of the diet. In reducing the risk for chronic diseases such as diabetes the possibly linked effect on serum lipids would be a further advantage of maximizing meal frequency. These alterations must be balanced against the long-term effects of weight change and nutrient selection as data on these modalities become available.

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