Proceedings of the Nutrition Society (2002), **61**, 329–335 DOI:10.1079/PNS2002168

The Annual Meeting of the Clinical Nutrition and Metabolism Group of the Nutrition Society with the British Association for Parenteral and Enteral Nutrition was held at the Harrogate International Centre, Harrogate on 13–15 November 2001

Clinical Nutrition and Metabolism Symposium on 'Endocrine and nutritional modulation of the metabolic response to stress'

Modulation of post-operative insulin resistance by pre-operative carbohydrate loading

Olle Ljungqvist, Jonas Nygren and Anders Thorell
Karolinska Institutet at Centre of Gastrointestinal Disease, Ersta Hospital and Dept of Surgery, Huddinge University Hospital, Stockholm, Sweden

Insulin resistance develops as a response to virtually all types of surgical stress. There is an increasing body of evidence that suggests that insulin resistance in surgical stress is not beneficial for outcome. A recent large study in intensive-care patients showed that aggressive treatment of insulin resistance using intravenous insulin reduced mortality and morbidity substantially. Similarly, in burn patients, intensive insulin and glucose treatment has been shown to improve N economy and enhance skin-graft healing. In surgical patients insulin resistance has been characterized in some detail, and has been shown to have many similarities with metabolic changes seen in patients with type 2 diabetes. This finding may be important since insulin resistance has been shown to be one independent factor that influences length of stay. When patients about to undergo elective surgery have been treated with glucose intravenously or a carbohydrate-rich drink instead of overnight fasting, insulin resistance was reduced by about half. A small meta-analysis showed that when post-operative insulin resistance was reduced by pre-operative carbohydrates, length of hospital stay was shortened. Overnight intravenous glucose at high doses improved post-operative N economy. This type of treatment has also been shown repeatedly to reduce cardiac complications after open-heart surgery. Furthermore, if the carbohydrates are given as a drink pre-operatively, pre-operative thirst, hunger and anxiety are markedly reduced. In summary, preventing or treating insulin resistance in surgical stress influences outcome. Fasting overnight is not an optimal way to prepare patients for elective surgery. Instead, pre-operative carbohydrates have clinical benefits.

Carbohydrates: Insulin resistance: Overnight fasting: Elective surgery

A stress-induced disturbance in glucose homeostasis has been known since Claude Bernard (1877) reported hyperglycaemia in association with haemorrhage. Over the years it has become evident that this hyperglycaemia is present in many situations of stress, despite elevated levels of insulin. This factor is probably the best-known sign of insulin resistance.

Insulin resistance is a mechanism by which the body responds to stress and injury in many species. The most obvious change in body metabolism is the elevation of glucose. In some situations of acute and severe stress this response is quite physiological and adequate; this is the case for acute haemorrhage, for instance. In haemorrhage glucose is released primarily from liver glycogen reserves into the bloodstream where this molecule acts as an osmole (for review, see Ljungqvist *et al*. 2000). The development of hyperglycaemia in haemorrhage ensures that fluid is shifted from the major reserves within the cells to the circulation by osmotic forces, and this process may be decisive for the outcome (Ljungqvist *et al*. 1987). Thus, in this particular instance, the development of insulin resistance is quite favourable. Outside modern medicine, it can also be argued

Corresponding author: Dr Olle Ljungqvist, fax +46 8 714 6665, email Olle.Ljungqvist@ersta.se

that this response to injury may be beneficial. By blocking glucose uptake to insulin-sensitive tissues, glucose reserves are directed to non-insulin-dependent tissues that are dependent on this particular substrate, including organs such as the brain and blood cells. This reaction makes sense in a situation where recovery and survival after injury may be decided by how the body best makes use of its reserves of nutrients.

In modern medicine, however, there may be several factors that need to be considered before discussing the benefits or drawbacks of insulin resistance, or whether it should be treated or not. First, many of the patients operated on today have diseases or injuries that would have been lethal and incurable only decades ago. Many major improvements have been introduced, particularly over the last century, to improve the outcome of surgical practice. Many of these improvements have one factor in common, they have directly or indirectly reduced the stress of the injury or operation inflicted on the patient. The introduction and improvement of anaesthesia is perhaps the most obvious example, but minimal invasive surgery, antibiotics and many other treatments are also important. It is in this context that there is a need to address the issue of whether insulin resistance after surgery is beneficial or detrimental, and if it should be minimized or treated. It is clear that insulin resistance is present in virtually all types of surgical stress situation, but it is only recently that we have come to realize that this phenomenon is likely to have a substantial impact on outcome.

A state of insulin resistance has been described following accidental trauma and in sepsis (Little *et al*. 1987), acute liver failure (Clark *et al*. 2001) and burn injury (Wolfe *et al*. 1979*b*). More recently, a series of studies have been performed to characterize insulin resistance after elective surgery. These studies have shown that the extent of insulin resistance which develops after surgery is related to recovery and outcome (Thorell *et al*. 1999).

The present paper will highlight some of the recent literature on the role of insulin resistance in surgical stress, and in particular the current knowledge on post-operative insulin resistance. There will be a specific focus of attention on how post-operative resistance and morbidity can be reduced by pre-operative nutritional modulation using carbohydrates, and the effect of this treatment on outcome.

Stress-induced insulin resistance and the effects of insulin treatment

Although it has long been known that hyperglycaemia develops in stress, it has only been acknowledged quite recently that this post-traumatic elevation of glucose is detrimental to the patient (Zerr *et al*. 1997; Khaodhar *et al*. 1999). Hyperglycaemia has been associated with increased incidence of infections after surgery (Zerr *et al*. 1997), burns (Gore *et al*. 2001) and general intensive care (Van den Berghe *et al*. 2001). Insulin has not only glucose-regulating effects, but also anabolic effects on protein and fat metabolism. These aspects of metabolism also become 'resistant' to insulin. Woolson, Hinton, Allison and coworkers (Hinton *et al*. 1971; Woolson *et al*. 1979) reported already in the early 1970s that administration of insulin to normalize glucose following accidental trauma and surgery had positive effects on protein balance. Brandi *et al*. (1990) further illustrated the general role of insulin on metabolism in post-operative patients. Their studies showed that treatment with sufficient amounts of insulin to normalize glucose levels during total parenteral nutrition after major surgery also normalized levels of non-esterified fatty acids and N balance. Thus, the loss of the normal actions of insulin in the post-stress situation has widespread metabolic consequences. Importantly, once insulin resistance is overcome by insulin treatment these metabolic derangements can be counteracted and even overcome.

Recent studies from Herndon, Wolfe and coworkers (Ferrando *et al*. 1999) in Galveston, Texas, USA have shown that insulin is very effective in attenuating muscle protein catabolism in severely-burned patients. The same group has also shown that insulin treatment has substantial effects on wound healing following grafting of burn sites. This mechanism was related to enhancement of collagen and laminin formation in the insulin-treated patients (Pierre *et al*. 1998).

Diabetic patients present an increased risk when subjected to injury, trauma and surgery. One of the distinct risk factors for these patients, being already insulin resistant before the injury or surgery, is the post-traumatic or surgical hyperglycaemia. Elevations in glucose in diabetic patients have been shown to be associated with impaired leucocyte function by affecting granulocyte adherence, chemotaxis, phagocytocis and microbial function (for review, see Khaodhiar *et al*. 1999). In the post-operative situation, just as in unstressed diabetes, poor glucose control enhances the risk of infections. Thus, in retrospective studies in diabetics it has been shown that with increasingly higher glucose levels after coronary surgery the risk of infection increased almost proportionally (Golden *et al*. 1999). Another study, designed as a 'before and after' study in the same type of patients, reported that if glucose was maintained below 11·3 mM during the first two post-operative days, the rate of deep sternal infections was reduced by about 60% (Furnary *et al*. 1999). Thus, even if perfect glucose control was not targeted or achieved, reinstating some of insulin's effects in these diabetic patients did have clinical effects.

Perhaps the most striking data ever presented on the role of insulin in the surgical patient subjected to stress are some very recent data (Van den Berghe *et al*. 2001). This report from the University of Leuven, Belgium is based on more than 1500 consecutive patients treated (primarily) at the surgical intensive care unit. The patients were prospectively randomized to receive either aggressive intravenous insulin to maintain glucose levels between 4·5 and 6 mM, or the conventional intermittent insulin treatment for glucose levels >12 mM. Intensive insulin treatment had massive clinical effects, including a reduction in intensive care unit mortality by 43%, in hospital mortality by 34% and marked reductions in morbidity. The reduction in mortality was significant ($P<0{\cdot}04$) only for the thoracic surgical patients that dominated the patient material. However, the improved survival was not related to improved cardiac outcome directly, but was attributed to a reduction in deaths from multiple organ dysfunction. Intensive care unit stay was

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

reduced by 22%, bacteraemia and polyneuropathy by 50%, need for haemofiltration by 42% and ventilatory support demand by 37%. Importantly, this study basically enrolled all patients entering the intensive care unit, and there was no selection to treating patients with existing diabetes or any other group of patients. In essence, the protocol was designed to ensure that in the aggressive insulin group any stress-induced insulin resistance was overcome by insulin treatment. Thus, treating hyperglycaemia in surgically-stressed patients was shown to be beneficial also in patients without diabetes. The mechanisms behind the reduction in infections may very well be the same as those discussed earlier for the diabetic patient. The shorter time on ventilatory support can possibly be an effect of the protein anabolic effects of insulin, also discussed earlier. For the other two major outcomes affected by insulin (the reduction in polynephropathy and the need for haemofiltration) there is an interesting association with diabetes. While these complications developed rapidly in surgically-stressed intensive care unit patients, they are also present in diabetic patients, but as a late phenomenon. The mechanisms behind what seems to be perhaps more than a coincidence needs further study.

Thus, with the data available, there seems to be little doubt that insulin action plays a key role not only for normal health, but perhaps even more so in situations of stress. Although there are situations when insulin resistance may in fact be beneficial, as discussed earlier, the data available indicates that stress-induced insulin resistance is an unwanted phenomenon in modern surgical practice. Following surgery and in subsequent situations of severe stress one of the key aims of all treatments is to reduce, minimize and shorten the catabolic phase related to the stress. Insulin resistance is a central feature of stress-induced catabolism, and the data available shows that patients benefit from treatments that minimize insulin resistance in any situation of surgical stress (see also Table 1).

Insulin resistance following elective surgery

Insulin resistance develops as a response not only to severe stress, but also following elective surgery. Thus, post-operative insulin resistance occurs in otherwise healthy patients as well as in patients with diabetes. During the last few years a series of studies have characterized post-operative insulin resistance. These studies show that insulin resistance develops even after minor surgical procedures such as hernia repair and laparoscopic cholecystectomy (Thorell *et al*. 1999). As the magnitude of the surgery increases, so does the extent of insulin resistance, as determined by using the hyperinsulinaemic normoglycaemic clamp method (Thorell *et al*. 1999). Following medium-size open upper gastrointestinal surgery (cholecystectomy) whole-body insulin resistance was present for at least 10 d, but was no longer present 20 d after the operation (Thorell *et al*. 1999). When studying the clinical impact of post-operative insulin resistance, Thorell *et al*. (1999) reported that this metabolic change was one of three independent factors explaining the variation in length of stay after uncomplicated elective surgery. The other two factors were the type of surgery performed and the blood loss (Thorell *et al*. 1999).

Similarities with type 2 diabetes mellitus

Early post-operative insulin resistance has several similarities with the insulin resistance found in type 2 diabetes mellitus (Table 2). In both instances whole-body insulin sensitivity is reduced. To some extent this reduction is due to a resistance to insulin in the liver, where glucose production is reduced to a slightly lesser extent in the post-operative phase. However, the main cause of insulin resistance and hyperglycaemia during the first couple of days of the post-operative phase is due to a marked decrease in insulin-stimulated glucose uptake in insulin-sensitive tissues, mainly skeletal muscle. This process has been shown to be associated with a change in the response of specific glucose-transporting proteins, in particular glucose transporter 4, to insulin stimulation. In response to insulin stimulation in healthy individuals these proteins are translocated from intracellular membranes to the cell membrane, where they facilitate glucose uptake. This process does not occur to the same extent in the post-operative situation, and this factor may at least in part explain the defect in glucose uptake after surgery. Inside the cell glucose oxidation is maintained even in the insulin-resistant patient after surgery,

Table 1. Summary of some of the clinical effects of intensive insulin treatment of insulin resistant states in surgically-stressed or injured patients presented in recent years*

Study groups	Outcome variable	Difference from controls (%)	Statistical significance of difference: *P*	Reference
Severe burns	Donor site healing time	−28	<0·05	Pierre *et al*. (1998)
Severe burns	Protein balance	Improved†	<0·05	Ferrando *et al*. (1999)
Cardiac surgery in diabetics	Deep sternal wound infection	−60	0·01	Furnary *et al*. (1999)
ICU (mainly thoracic surgical)	Mortality	−43	0·04	Van den Berghe *et al*. (2001)
ICU (mainly surgical)	Morbidity	Sepsis −46, renal failure −41	<0·05	Van den Berghe *et al*. (2001)

ICU, intensive care unit.
*In all studies normoglycaemia had been the target, except in the study by Furnary *et al*. (1999) where glucose was targeted to 11·3 mM. In some studies (Pierre *et al*. 1998; Ferrando *et al*. 1999) insulin infusions were given at such rates that additional glucose infusion had to be administered to avoid hypoglycaemia.
†Overall net protein balance over the leg was improved in the insulin group; no exact values were given in the paper.

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

Table 2. Summary of the effect of insulin on some of the key aspects of glucose metabolism in healthy volunteers, in patients shortly after surgery and in patients with type 2 diabetes*

Variable	Study group		
	Healthy	Post-operative	Type 2 diabetes
Whole-body insulin sensitivity	Not applicable	–	–
Hepatic glucose production	– – –	–	–
Whole-body glucose uptake	+++	(+)	(+)
Skeletal muscle GLUT 4 translocation	++	0	0
Non-oxidative glucose metabolism	++	(+)	(+)

+, –, The relative level of action or change from the basal non-insulin-stimulated situation (the range is from +++ (maximum activity) to – – – (maximum inhibition)); (+), a small but significant change; GLUT, glucose transporter 4.
*Information based on studies using the hyperinsulinaemic euglycaemic clamp technique, and the change occurring between the basal situation without insulin stimulation in the overnight fasted state and that during steady-state hyperinsulinaemia.

while the non-oxidative pathway is markedly less activated by insulin (Thorell *et al*. 1999).

Factors contributing to insulin resistance

Several factors influence the extent of post-operative insulin resistance. Multiple regression analysis showed that the type of surgery and peri-operative blood loss influenced the extent of post-operative insulin resistance which develops after surgery. Several other factors were also tested, but did not affect the extent of change. These factors include the patient-related factors such as age, gender and pre-operative insulin sensitivity or BMI, and surgical factors such as the length of the operation. In addition, there are factors related to current peri-operative practice that do have a marked influence on insulin resistance. In particular, the low-energy feeding of the patient during the day of surgery has an impact on insulin sensitivity. During the day of the operation the patients are often given only 50 g glucose in electrolyte solutions. When this treatment was given to healthy volunteers, approximately 30% of their insulin sensitivity was lost after 24 h (Nygren *et al*. 1997). If another common treatment, hypoenergetic glucose infusion (2 litres glucose; 5% (w/v)) was given on the following 2 d, then insulin sensitivity was reduced by about 50% (Svanfeldt *et al*. 2000). Immobilization during the same period of time had much less impact on insulin sensitivity.

Mediators of insulin resistance

It is not clear what causes insulin resistance after surgery. It has been suggested that release of stress hormones is the main mediator. However, it does not seem to be quite that simple. Studies in healthy volunteers have shown that insulin resistance develops in response to infusion of stress hormones. This response has been shown for adrenaline, cortisol, glucagon and growth hormone (tested individually). A further enhanced resistance was reported when these hormones were given in various combinations (for review, see Thorell *et al*. 1999). Although studies carried out 20–30 years ago showed that elective surgery caused a release of stress hormones, similar studies in more modern practice have not been able to confirm these findings. Hence, it has been difficult to establish a relationship between post-operative insulin resistance and changes in plasma levels of stress hormones (Thorell *et al*. 1999). However, these findings cannot be taken as evidence that these hormones may not be involved at all. The determination of plasma levels is just a crude measurement of an instantaneous situation, while endocrine effects may be fast or slow to develop. Moreover, it is largely not known how long the effects of a hormone remain in this type of situation. The inflammatory response, mediated by factors such as cytokines, is also likely to be involved in post-operative stress-induced metabolic alterations. Further studies of cytokines have revealed an association between interleukin-6 levels and the extent of insulin resistance after surgery, while no such relationship was found for several other cytokines (Thorell *et al*. 1996). Thus, the overall response to surgery and other types of stress is likely to be multifactorial and mediated by endocrine, inflammatory and as yet undefined factors.

Reducing post-operative insulin resistance by pre-operative carbohydrate treatment instead of fasting

Studies in animal models of severe stress, such as haemorrhage and endotoxaemia, showed that several key systems involved in the stress responses were markedly impaired if the animal had been fasted for a brief period before the onset of a given stress (for review, see Ljungqvist *et al*. 2000). These key systems included fluid homeostasis, stress hormone release, aspects of metabolism, muscle function and gut integrity (Ljungqvist *et al*. 2000). If the stress in these models was enhanced slightly further there was also a clear survival disadvantage, e.g. if the animals were fasted for 24 h, which is sufficient to deplete liver glycogen stores. In these studies there was a clear pattern indicating that the metabolic change caused by a recent meal (as opposed to fasting) and the loss of glycogen occurring even after a brief fast was sufficient to markedly alter the responses to stress. It was therefore reasonable to question whether the routine of fasting patients from midnight on the day of surgery was really the best way to prepare for the stress of surgery.

The routine of fasting was first suggested as a result of the first death due to anaesthesia to be reported (Anonymous, 1848). A young woman had eaten shortly before anaesthesia, vomited and aspirated and died from aspiration pneumonia. This incident occurred only 2 years after the very first reported general anaesthesia had been given, and

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

this complication was obviously a major setback for the pioneers at the time. For this reason it was suggested that the stomach should be allowed time to empty before anaesthesia. During the first half of the last century this routine became a rule, and has remained a central part of surgical and anaesthesiological practice throughout the world. However, this routine was questioned in the late 1980s. Since then a substantial amount of literature has been produced which clearly shows that this routine is outdated and causes unnecessary discomfort for the majority of patients undergoing elective surgery. For details on the literature on this topic, the reader is referred to American Society of Anesthesiologist Task Force (1999) recommendations. Many countries have therefore changed their fasting guidelines, and now recommend that most patients take clear fluids (water, coffee, tea without milk and clear juices) up to 2 h before surgery (Eriksson & Sandin, 1996). This change in routine has primarily improved the situation for the patient by reducing the discomfort of pre-operative thirst. However, these drinks are not likely to produce any major change in metabolism, since they do not (necessarily) contain sufficient energy.

The best known method for changing metabolism from the overnight fasted state to that of a fed state is the use of carbohydrates. The key change required to be achieved is a prompt insulin response, preferably to an extent similar to that observed after intake of a meal (i.e. from a fasted state of about 12 μU/ml to about 60–70 μU/ml). Intravenous glucose can be used for this purpose. The insulin response to glucose infusions is determined by the rate of delivery of glucose in a dose-dependent manner. Infusion of 5 mg/kg body weight per min has been shown to induce an insulin response to levels of about 60 μU/ml (Wolfe *et al*. 1979*a*). Glucose given at this rate as a 20% (w/v) intravenous infusion overnight has been shown to reduce post-operative insulin resistance by about 50% (Ljungqvist *et al*. 1994) and improve N economy (Crowe *et al*. 1984) after open elective abdominal surgery.

In a later study, this time in patients undergoing elective hip replacement, a combined infusion of insulin and a variable infusion of glucose was used (i.e. a hyperinsulinaemic normoglycaemic clamp was used, Nygren *et al*. 1998*b*). This treatment was started a few hours before the operation, maintained throughout the surgery and retained for a couple of hours after the operation. This protocol allowed the determination of insulin sensitivity in the period before, as well as immediately after, the operation. Control patients had the pre-operative determination of insulin sensitivity performed 1 week before the operation, they were given normal saline (9 g NaCl/l) before and during the operation, and a clamp was performed immediately after the surgery. This study showed that while control patients developed marked insulin resistance, released cortisol and oxidised fat instead of carbohydrates, there was no insulin resistance in the insulin- and glucose-treated group. Also, there was no cortisol release, and substrate oxidation was maintained. In addition to the two patient groups, yet another control study was performed in matched healthy volunteers. These healthy controls performed the prolonged study and were given insulin and glucose for the same period of time as the insulin- and glucose-treated patients, but without anaesthesia and surgery. The healthy controls displayed almost identical values to those of the insulin- and glucose-treated patients. Thus, this study shows that it is indeed possible to avoid some of the key catabolic developments using insulin and glucose treatments. This protocol, however, may not be feasible in clinical practice, since it necessitates very frequent monitoring of glucose levels and adjustments of glucose infusion rates.

The pre-operative glucose treatment has also been shown to be beneficial in the preparation of patients for cardiac surgery. The objective of this treatment is that glucose and insulin enhance the performance of the ischaemic heart (Lazar *et al*. 1997). By increasing delivery of ATP from the glycolytic pathway, cell membrane function and integrity is maintained not only in myocytes but also in endothelial and vascular smooth muscle cells. In the ischaemic heart this process results in reduced cellular oedema and improvement of the microcirculation. This outcome would in turn affect the situation after reperfusion. Accumulation of non-esterified fatty acid end products in the ischaemic heart may increase the levels of oxygen free radicals and this process is believed to affect ventricular function and increase the risk for arrythmias. Glucose can interfere with the formation of free radicals by esterifying non-esterified fatty acids by increasing the supply of α-glycerophosphate in the cells. In clinical studies glucose has been given alone or in combination with intravenous lipids (Lolley *et al*. 1985) or insulin and K (Oldfield *et al*. 1986). It has been given to patients about to undergo bypass surgery for arthrosclerotic disease (Lolley *et al*. 1985; Lazar *et al*. 1997), as well as in non-arthrosclerotic patients undergoing valve replacement (Oldfield *et al*. 1986). Regardless of the addition of other components along with the glucose, there has been a consistency in the findings of markedly reduced cardiac complications, most often recorded as episodes of fibrillation or need for vasopressor support. Thus, it seems clear that pre-operative carbohydrates are beneficial for patients about to undergo cardiac surgery.

Pre-operative oral carbohydrates

A much simpler approach to pre-operative carbohydrate treatment is using the oral route. Commercially-available feeds were initially tested for gastric emptying, but they were found not to pass through the stomach fast enough (Nygren *et al*. 1995). Subsequently commercially-available sports drinks containing about 6–8% (w/v) carbohydrates were tested. However, these drinks are designed not to elicit an insulin response. Thus, a mixture of carbohydrates containing a higher concentration was developed. Since gastric emptying of liquids is influenced by osmolality, polymers of carbohydrates were used to keep the osmolality of the drink low (Nygren *et al*. 1995). This drink was shown to cause a rise in insulin to levels seen after a normal meal and also to empty from the stomach within 90 min (Nygren *et al*. 1995). Subsequent studies in clinical settings confirmed the safety of this drink. To date approximately 1000 patients have consumed the drink when participating in research studies and about 6000 in regular clinical practice without a single adverse event being reported.

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

Table 3. Summary of studies on the effects of pre-operative carbohydrate treatment on post-operative insulin resistance. (All values for insulin sensitivity are given as the relative change in insulin sensitivity compared with the pre-operative determination)

Type of surgery	Type of pre-operative carbohydrates	Post-operative change in insulin sensitivity (%)		Statistical significance of difference: *P*	Reference
		Controls	Treatment group		
Open cholecystectomy	Overnight iv glucose	−55	−32	<0·01	Ljungqvist *et al.* (1994)
Hip replacement*	Insulin + glucose peri-operative	−40	+16	<0·01	Nygren *et al.* (1998*b*)
Colo-rectal surgery	Oral carbohydrates	−49	−26	<0·05	Nygren *et al.* (1998*a*)
Hip replacement*	Oral carbohydrates	−37	−16	<0·05	Soop *et al.* (2001)

iv, Intravenous.
* In the two studies of hip replacement insulin sensitivity was determined immediately after the operation and in the other two studies it was determined on the first post-operative day.

In studies of patients given this treatment 2–3 h before anaesthesia the efficacy of this treatment has been shown to be equally as good as the intravenous infusion of glucose with regard to post-operative insulin resistance (see Table 3). Providing the pre-operative carbohydrates as a drink has been shown to have several other benefits in the pre-operative phase. While any drink will reduce the discomfort of pre-operative thirst, the drink containing carbohydrates also diminished the discomfort of pre-operative hunger and anxiety (Hausel *et al*. 2001). The anxiolytic effect is likely to be mediated via insulin to increase serotonin levels in the hypothalamus (Wurtman & Wurtman, 1995; Orosco & Gerozissis, 2001). Serotonin is involved in the regulation of mood. This method of reducing pre-operative anxiolysis may have further implications on the use of premedications before anaesthesia. Furthermore, preliminary data indicate that patients treated with this drink record less fatigue after colo-rectal surgery compared with those fasted overnight (Hausel *et al*. 1999), suggesting that this treatment may affect recovery. In support of such a suggestion a Danish group reported that pre-operative treatment with a carbohydrate-containing drink with or without the addition of dipeptides may improve voluntary quadriceps muscle strength (Henriksen *et al*. 1999).

In other studies of outcomes there has been a retrospective analysis of three small prospective randomized trials (one matched-control study) primarily investigating post-operative insulin resistance (Ljungqvist *et al*. 2001). Some years later the files of these patients were retrieved and the length of stay was studied along with complication rates. There were no major complications in these patients, and a meta-analysis showed that while the studies were too small to show a significant reduction in length of stay individually, the combined effect was a significant ($P<0·02$) reduction of about 20% (Ljungqvist *et al*. 2001). Importantly, all these studies were performed in a situation where there was a shortage of hospital beds and no incentives to keep the patients in the hospital longer than absolutely necessary. The preliminary results of a prospective double-blind randomized trial were presented recently (Hofman *et al*. 2001). In eighty-nine patients undergoing major abdominal surgery in two centres in the UK, length of stay was reduced by about 1 d in patients treated with carbohydrates. This difference did not, however, reach statistical significance ($P=0·08$), and the data may be skewed by the fact that operating time was slightly longer in the controls compared with the treatment group.

Summary

Available data show that insulin resistance in stress and surgery does not benefit patient outcome. In surgical intensive-care patients recent findings show that aggressive treatment of insulin resistance targeting normoglycaemia using intravenous insulin to overcome the resistance to insulin results in marked improvements in outcome. The mechanisms behind the detrimental effects of insulin resistance in severely-stressed surgical intensive care unit patients, and the effects of intensive insulin treatment to overcome insulin resistance have been only partially elucidated. In elective surgical patients insulin resistance also develops, and this process can be avoided to a substantial extent by pre-operatively sensitizing the patients metabolically using pre-operative carbohydrates. The use of a carbohydrate-rich drink provided up to 2 h before the onset of anaesthesia changes the overnight fasted state to a fed state, and this process in turn minimizes the development of post-operative resistance. For patients who cannot drink pre-operatively the use of intravenous glucose at fairly high infusion rates (4–5 mg/kg body weight per min) has the same effect on post-operative insulin resistance. Although some of the mechanisms behind the effects of pre-operative carbohydrates on peri-operative well-being, post-operative insulin resistance and post-operative cardiac protection are known, there still remains important research to be done. It is difficult to completely dismiss as coincidence the similarities between the pattern of morbidity in the surgically-stressed patient and those found in the chronic diabetic patient. The reduction of post-operative insulin resistance is relevant in the surgical patient, since this variable has been shown to be detrimental in severely-stressed surgical patients and an independent variable affecting length of stay in the uncomplicated patient, and when minimized using pre-operative carbohydrates available data suggest that recovery is improved by reducing post-operative fatigue and length of stay.

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

References

American Society of Anesthesiologist Task Force (1999) Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: A report by the American Society of Anesthesiologist Task Force on preoperative fasting. *Anesthesiology* **90**, 896–905.

Anonymous (1848) Fatal application of chloroform. *Edinburgh Medical and Surgical Journal* **69**, 498.

Bernard C (1877) *Lecons sur le Diabete et la Glycogenese Animale (Lessons on Diabetic and Glycogenotic Animals)*, p. 210 Paris: Baillere.

Brandi LS, Frediani M, Oleggini M, Mosca M, Cerri C, Boni C, Pecori N, Buzzigoli G & Ferrannini E (1990) Insulin resistance after surgery; normalization by insulin treatment. *Clinical Science* **79**, 443–450.

Clark SJ, Shojaee-Moradie F, Croos P, Seed PT, Umpleby AM, Wendon JA & Miell J (2001) Temporal changes in insulin sensitivity following the development of acute liver failure secondary to acetaminophen. *Hepatology* **34**, 109–115.

Crowe PJ, Dennison A & Royle GT (1984) The effect of preoperative glucose loading on postoperative nitrogen metabolism. *British Journal of Surgery* **71**, 635–637.

Eriksson LI & Sandin R (1996) Fasting guidelines in different countries. *Acta Anaesthesiologica Scandinavica* **40**, 971–974.

Ferrando AA, Chinkes CL, Wolf SE, Martin S, Herndon DN & Wolfe RR (1999) A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Annals of Surgery* **229**, 11–18.

Furnary AP, Zerr KJ, Grunkemeier GL & Starr A (1999) Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Annals of Thoracic Surgery* **67**, 352–362.

Golden SH, Pleart-Vigilande C, Linda Kao WH & Francati FL (1999) Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* **22**, 1408–1414.

Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE & Desai M (2001) Association of hyperglycemia with increased mortality after severe burn injury. *Journal of Trauma* **51**, 540–544.

Hausel J, Nygren J, Almström C, Thorell A & Ljungqvist O (1999) Preoperative oral carbohydrates improve well being after elective colorectal surgery. *Clinical Nutrition* **18**, Suppl. 1, 80Abstr.

Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almström C, Lindh A, Thorell A & Ljungqvist O (2001) A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesthesia and Analgesia* **93**, 1344– 1350.

Henriksen MG, Hansen HV, Deli F, Haraldsted V, Rodt SA & Hessov I (1999) Preoperative feeding might improve postoperative voluntary muscle function. *Clinical Nutrition* **18**, Suppl. 1, 82Abstr.

Hinton P, Allison SP, Littlejohn S & Lloyd J (1971) Insulin and glucose to reduce catabolic response to injury in burned patients. *Lancet* **i**, 767–769.

Hofman Z, Van Drunen J, Yuill K, Richardson R, Davidson I, Cecil T, Moran B & Garden OJ (2001) Tolerance and efficacy of immediate pre-operative carbohydrate feeding in uncomplicated elective surgical patients. *Clinical Nutrition* **20**, Suppl. 3, 32 Abstr.

Khaodhiar L, McCowen K & Bistrian B (1999) Perioperative hyperglycemia, infection or risk? *Current Opinion in Clinical Nutrition and Metabolic Care* **2**, 79–82.

Lazar HL, Phillipides G, Fitzgerald C, Lancaster D, Shemin RJ & Apstein C (1997) Glucose-insulin-potassium solutions enhance recovery after urgent artery bypass surgery. *Journal of Thoracic and Cardiovascular Surgery* **113**, 354–362.

Little RA, Henderson A, Frayn KN, Galasko CBS & White RH (1987) The disposal of intravenous glucose studied using glucose and insulin clamp techniques in sepsis and trauma in man. *Acta Anaesthesiologica Belgica* **38**, 275–279.

Ljungqvist O, Jansson E & Ware J (1987) Effect of food deprivation on survival after haemorrhage in the rat. *Circulatory Shock* **22**, 251–260.

Ljungqvist O, Nygren J, Hausel J & Thorell A (2000) Preoperative nutrition therapy–novel developments. *Scandinavian Journal of Nutrition* **44**, 3–7.

Ljungqvist O, Nygren J, Thorell A, Brodin U & Efendic S (2001) Preoperative nutrition– elective surgery in the fed or the overnight fasted state. *Clinical Nutrition* **20**, Suppl. 1, 167–171.

Ljungqvist O, Thorell A, Gutniak M, Häggmark T & Efendic S (1994) Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. *Journal of the American College of Surgeons* **178**, 329–336.

Lolley DM, Myers WO, Jefferson FR, Sautter RD & Tewksbury DA (1985) Clinical experience with preoperative myocardial nutrition management. *Journal of Cardiovascular Surgery* **26**, 236–243.

Nygren J, Soop M, Thorell A, Efendic S, Nair KS & Ljungqvist O (1998*a*) Preoperative oral carbohydrate administration reduces postoperative insulin resistance. *Clinical Nutrition* **17**, 65–71.

Nygren J, Thorell A, Brismar K, Karpe F & Ljung (1997) Short-term hypocaloric nutrition but not bed rest decrease insulin sensitivity and iGF-1 bioavailability in healthy subjects: the importance of glucagons. *Nutrition* **13**, 945–951.

Nygren J, Thorell A, Jacobsson H, Schnell PO & Ljungqvist O (1995) Preoperative gastric emptying; the effects of anxiety and carbohydrate administration. *Annals of Surgery* **222**, 728–734.

Nygren J, Thorell A, Soop M, Efendic S, Brismar K, Karpe F, Nair KS & Ljungqvist O (1998*b*) Perioperative insulin and glucose infusion maintains normal insulin and glucose infusion maintains normal insulin sensitivity after surgery. *American Journal of Physiology* **275**, E140–E148.

Oldfield GS, Commerford PH & Opie LH (1986) Effects of preoperative glucose-insulin-potassium on myocardial glycogen levels and on complications of mitral valve replacement. *Journal of Thoracic and Cardiovascular Surgery* **1**, 874–878.

Orosco M & Gerozissis K (2001) Macro-nutrient cascade of events leading to parallel changes in hypothalamic serotonin and insulin. *Neuroscience and Behavioral Reviews* **25**, 167–174.

Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M, Wolfe RR & Herndon DN (1998) Effects of insulin on wound healing. *Journal of Trauma* **44**, 342–345.

Soop M, Nygren J, Myrenfors P, Thorell A & Ljungqvist O (2001) Preoperative oral carbohydrate treatment attentuates immediate postoperative insulin resistance. *American Journal of Physiology* **280**, E576–E583.

Svanfeldt M, Nygren J, Ljungqvist O & Thorell A (2000) Three days of postoperative hypocaloric feeding with or without immobilization cause marked insulin resistance in healthy volunteers. *Clinical Nutrition* **19**, Suppl. 1, 126Abstr.

Thorell A, Essén P, Andersson B & Ljungqvist O (1996) Postoperative insulin resistance and circulating concentrations of stress hormones and cytokines. *Clinical Nutrition* **15**, 75–79.

Thorell A, Nygren J & Ljungqvist O (1999) Insulin resistance – a marker of surgical stress. *Current Opinion in Clinical Nutrition and Metabolic Care* **2**, 69–79.

Van der Berghe G, Wouters P, Weeks F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P & Bouillon R (2001) Intensive insulin therapy in critically ill patients. *New England Journal of Medicine* **345**, 1359–1367.

Wolfe RR, Allsop JR & Burke JF (1979a) Glucose metabolism in man: responses to intravenous glucose infusion. *Metabolism* **28**, 210–220.

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press

Wolfe RR, Curkot MJ, Allsop JR & Burke JF (1979*b*) Glucose metabolism in severely burned patients. *Metabolism* **128**, 1031–1039.

Woolson AMJ, Heatley RW & Allison FP (1979) Insulin to inhibit protein catabolism after injury. *New England Journal of Medicine* **300**, 14–17.

Wurtman RJ & Wurtman JJ (1995) Brain serotonin, carbohydrate-craving, obesity and depression. *Obesity Research* **3**, Suppl. 4, 477S–480S.

Zerr K, Furnary A, Grunkemeier G, Bookin S, Kanhere V & Starr A (1997) Glucose control lowers the risk of wound infection in diabetics after open heart operation. *Annals of Thoracic Surgery* **163**, 356–361.

https://doi.org/10.1079/PNS2002168 Published online by Cambridge University Press