

# **Factors affecting the plasma insulin concentration shortly after accidental injury in man**

**K. N. FRAYN,<sup>1</sup> P. F. MAYCOCK, R. A. LITTLE, D. W. YATES\* & H. B. STONER<sup>2</sup>**

*MRC Trauma Unit, University of Manchester, Manchester, England, and \*Accident and Emergency Department, Hope Hospital, Salford, England*

## **SUMMARY**

There are conflicting reports on plasma insulin concentrations in the acutely injured. Plasma insulin and glucose concentrations have been measured in 504 patients within 8 h of injury, and related to the severity of injury as assessed by the injury severity score (ISS). As in previous surveys of injured patients, an extremely wide range of insulin concentrations was found (2–141 mU/l). Most of the variability occurred at lower severities of injury. In very severely injured patients (ISS  $\geq$  30), insulin concentrations were uniformly suppressed ( $<$  20 mU/l), especially in relation to the hyperglycaemia in these patients. Two small subgroups, patients dying within 3 h of injury and known psychiatric patients on psycho-active drugs, differed from the general pattern in displaying elevated insulin concentrations despite very severe injuries.

The results bear out the idea that insulin secretion is usually acutely suppressed by adrenaline after severe injury; after less severe injuries, however, the response is much less uniform.

## **INTRODUCTION**

The hyperglycaemic reaction to stress or injury results from changes in both production and utilization of glucose (Frayn, 1982), but the hormonal mechanisms involved are not entirely clear. In particular, there are conflicting reports on the plasma insulin response to injury. In early work on the glucose intolerance in acute burn injury, it was shown

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*Correspondence: Dr R. A. Little, MRC Trauma Unit, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, England.*

<sup>1</sup>*Present address: The Sheikh Rashid Diabetes Unit, The Radcliffe Infirmary, Oxford OX2 6HE, England.*

<sup>2</sup>*Present address: Department of Surgery, Hope Hospital, Salford M6 8HD, England.*

that the plasma insulin response to exogenous glucose was suppressed (Allison *et al.*, 1968), and a number of studies have shown that injured patients have insulin concentrations which are generally lower than expected for their hyperglycaemia (for example, Meguid *et al.*, 1974). However, a notable feature of most surveys of acutely injured patients is that plasma insulin concentrations are extremely variable, ranging from very low to very high values (Vitek *et al.*, 1979; reviewed by Frayn, 1982). An understanding of the behaviour of plasma insulin after injury is important not only in relation to control of glucose metabolism but also in connection with protein metabolism, as it has been suggested that the protein wasting observed at later stages may be initiated by a 'catabolic' hormonal environment soon after injury (Shuck *et al.*, 1977; Liddell *et al.*, 1979).

In an attempt to elucidate the factors affecting the plasma insulin concentration acutely after injury in man, the present authors have now analysed results collected from a large number of patients studied within a few hours of accidental injury. This includes results from patients reported earlier (Stoner *et al.*, 1979). In that series, however, there were insufficient numbers of severely injured patients for the patterns reported in the present work to become clear.

## METHOD

As described previously (Stoner *et al.*, 1979) venous blood samples were taken from patients with various types of accidental injury as soon as possible after their arrival in the Accident and Emergency Department, and before any definitive treatment had been started. Only one sample was obtained from each patient. Plasma concentrations of glucose, insulin and ethanol were measured by methods described previously (Stoner *et al.*, 1979). The patient's injuries were assessed using the injury severity score (ISS; Baker *et al.*, 1974).

### Statistical methods

Significance tests were based on non-parametric methods where possible (Siegel, 1956), except that the F-test has been used for assessing differences in variance (Snedecor & Cochran, 1967). Plasma concentrations of glucose and of insulin both demonstrated considerable skewness which was largely removed by conversion to logarithms and, for the calculation of variances and correlation coefficients, they have been treated as log-normally distributed.

## RESULTS

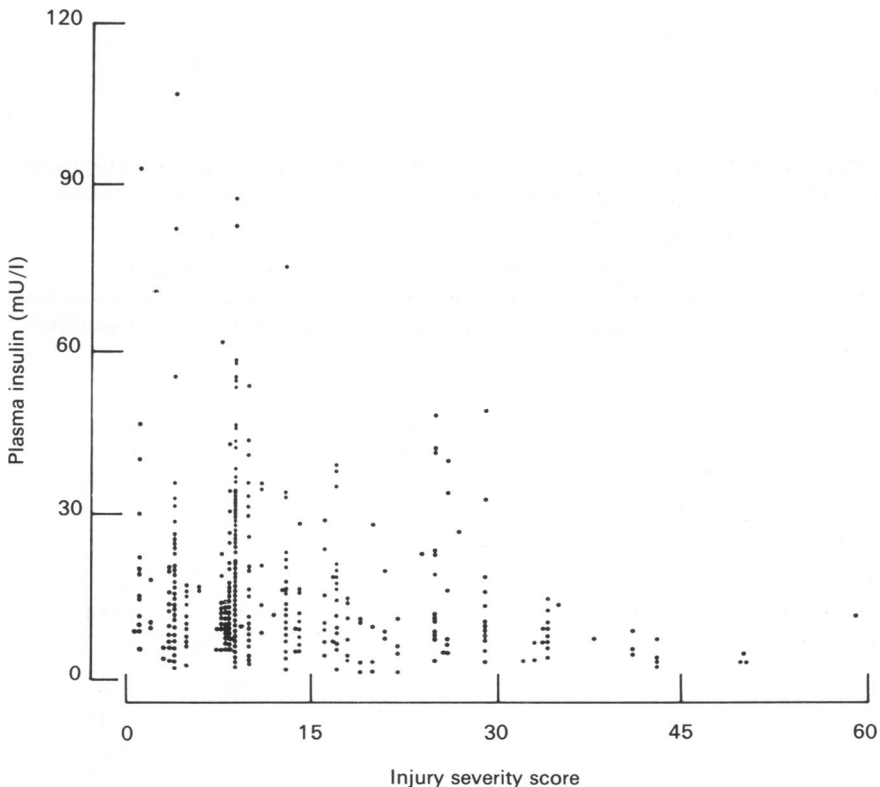
Five hundred and four patients (327 male), aged from 3–95 years (median: 41), with injury severity scores from 1–66, were studied. The samples were taken within 8 h of

injury (range: 10 min–8 h; median: 102 min). Of these patients, 10 (nine male) with ISS 34–66 died within 3 h of injury, and 18 (14 male) with ISS 25–66 died within 24 h.

In the group as a whole, the previous picture of great variability in plasma insulin concentrations was confirmed, with an overall range of 2–141 mU/l. Insulin concentrations were not correlated with ISS (Kendall's rank correlation test:  $P > 0.05$ ) but glucose concentrations were positively related to severity ( $P < 0.001$  by Kendall's test).

In the very severely injured patients, insulin concentrations were mostly low, with some exceptions. Closer investigations of these exceptions showed that they all belonged to one of two small groups: those 10 patients who died within 3 h of injury and a group of four known psychiatric patients, on treatment with psycho-active drugs, who had all fallen from a height. These two subgroups have, therefore, been separated for further analysis.

In the remaining patients, there was a weak negative correlation between plasma insulin concentration and ISS (Fig. 1). This relationship with ISS also showed that the variability in insulin concentrations was greatest at lower severities of injury (Fig. 1).



**Fig. 1** Relationship between plasma insulin concentrations and severity of injury in patients studied within 8 h of injury. There is a significant negative relationship between insulin and ISS ( $P < 0.02$  by Kendall's rank correlation test;  $n = 477$ ).

**Table 1** Plasma glucose and insulin concentrations in recently injured patients<sup>1</sup>

ISS range	0-6	7-12	13-29	≥30
<i>Glucose (mmol/l)</i>				
<i>n</i>	123	222	114	29
Median	5.4	6.0 <sup>b</sup>	7.3 <sup>ab</sup>	7.9 <sup>a</sup>
Range	3.4-24.5	3.0-15.6	3.0-14.8	3.9-10.9
<i>Insulin (mU/l)</i>				
<i>n</i>	120	217	111	29
Median	12	13	11	8 <sup>ab</sup>
Range	2-107	3-88	2-75	3-15 <sup>cd</sup>
<i>Correlation</i>				
<i>r</i>	+0.27	+0.38	+0.25	-0.19
<i>P</i>	<0.02	<0.001	<0.02	NS

<sup>1</sup> Two groups of patients have been excluded for reasons given in the text, those dying rapidly ( $\leq 3$  hours) after injury and known psychiatric patients taking psychoactive drugs; these groups are shown in Table 2. ISS = Injury severity score.

NS = Not significant ( $P > 0.05$ ).

Significance of differences between groups assessed by Wilcoxon Rank Sum test:

Difference from ISS 0-6 group: <sup>a</sup>  $P < 0.001$ ;

Difference from adjacent group to left: <sup>b</sup>  $P < 0.001$ .

Significance of differences in variance by F-test on log data:

Difference from ISS 0-6 group: <sup>c</sup>  $P < 0.01$ ;

Difference from adjacent group to left: <sup>d</sup>  $P < 0.01$ .

Correlation refers to the correlation between log concentrations of glucose and insulin within each group; *r* is the correlation coefficient, *P* the significance assessed by Kendall's rank correlation method.

**Table 2** Plasma glucose and insulin concentrations in very severely injured patients<sup>1</sup>

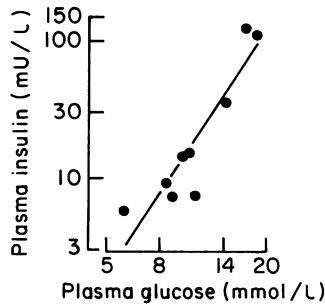
Group	Survived ( $> 3h$ )	Died ( $\leq 3h$ )	Psychiatric
<i>Glucose (mmol/l)</i>			
<i>n</i>	29	10	4
Median	7.9	10.4*	9.0
Range	3.9-10.9	5.9-19.0	7.4-10.1
<i>Insulin (mU/l)</i>			
<i>n</i>	29	10	4
Median	8	15*	36*
Range	3-15	6-141	10-61
<i>Correlation</i>			
<i>r</i>	-0.19	+0.92	+0.74
<i>P</i>	NS	<0.01	NS

<sup>1</sup> All patients shown have an injury severity score (ISS)  $\geq 30$ . They have been divided into those dying within  $\leq 3$  hours of injury, known psychiatric patients on psychoactive drug treatment and other patients with ISS  $\geq 30$  taken from Table 1.

Significance of differences assessed by Wilcoxon Rank Sum test:

Difference from survivors (left hand group): \* $P < 0.01$ ;

Differences between centre and right-hand groups not significant. (Other notes as in Table 1.)



**Fig. 2** Relationship between plasma concentration of glucose and insulin in patients dying within 3 h of injury. Both are plotted on logarithmic scales. The least mean squares regression line is shown. Correlation coefficient = 0.92,  $n = 10$ ;  $P < 0.01$  by Kendall's rank correlation test.

Above an ISS of 30, excluding the two subgroups described above, plasma insulin concentrations were uniformly low (all  $< 20$  mU/l), especially when considered with respect to the hyperglycaemia in these very severely injured patients (Fig. 1, Table 1). When the patients were grouped according to severity of injury (Table 1) it was clear that median plasma insulin concentrations decreased at higher ISS values, whilst plasma glucose concentrations rose with increasing ISS. Within each of these severity groups up to an ISS of 30 there was a weak but significant positive correlation between glucose and insulin concentrations, but this was lost in patients with  $\text{ISS} \geq 30$ .

In the two separate subgroups, despite injury severity scores of at least 30 in all patients, several high plasma insulin concentrations were observed (Table 2). In the case of those dying soon after injury, these were associated with very high plasma glucose concentrations (Table 2), and there was a marked positive correlation between plasma glucose and insulin concentrations within this group (Fig. 2).

The other factors considered, namely age of the patient, time after injury and the presence of an elevated plasma ethanol concentration, had relatively little effect on the plasma insulin concentration. The effect of age was assessed by comparing results in patients aged from 17–30 years with those in patients over 59 years of age, in groups divided according to ISS as in Table 1. Neither glucose nor insulin concentrations were affected by age in any group. The changes in plasma insulin and glucose concentrations with time after injury were assessed by comparing results from samples obtained within 2 h of injury with those obtained at or later than 2 h, in groups divided according to ISS. Neither plasma glucose nor insulin concentrations were affected by time after injury.

Sixty-three patients had plasma ethanol concentrations above 10 mmol/l (46 mg/dl). In these patients the hyperglycaemic response was reduced, as shown by a significant depression of the regression line against ISS (analysis of covariance:  $P < 0.01$ ). In the whole group, ethanol also depressed the plasma insulin concentration (median in ethanol-negative patients: 12.9,  $n = 431$ ; in ethanol-positive patients: 9.7 mU/l,  $n = 60$ ;  $P < 0.005$  by Wilcoxon Rank Sum test). This effect was investigated in more detail by looking at the effects of ethanol in different severity groups (Table 3) and also at different times after injury ( $< 2$  or 2–8 hours). In general, in groups in which there was a significant depression of plasma insulin by ethanol, so also was there an effect on plasma

**Table 3** Effect of ethanol on plasma glucose and insulin concentrations in injured patients<sup>1</sup>

Ethanol	ISS range							
	0-6		7-12		13-29		≥30	
	-	+	-	+	-	+	-	+
<i>Glucose (mmol/l)</i>								
<i>n</i>	121	2	199	23	84	30	25	4
Median	5.4	(5.0)	6.2	5.5*	7.8	6.4**	7.9	7.3
Range	3.4-24.5	4.4-5.6	3.0-15.6	3.0-11.2	4.2-14.8	3.0-12.2	3.9-10.9	4.5-9.9
<i>Insulin (mU/l)</i>								
<i>n</i>	118	2	196	21	82	29	25	4
Median	12	(10)	13	9*	12	10	8	9
Range	2-107	9-10	4-88	3-62	2-75	2-49	3-15	5-10

<sup>1</sup> Patients dying within 3 h of their injuries and psychiatric patients were excluded as described in the text. Patients with a plasma ethanol concentration > 10mmol/l were classified as positive. Effect of ethanol within each group assessed using Wilcoxon Rank Sum test: \* $P < 0.02$ ; \*\* $P < 0.005$ . Further subdivision according to time after injury did not affect the pattern of results.

glucose; there was no evidence for any specific depression of the plasma insulin concentration by ethanol not mediated by a lowering of the glucose concentration. The relationship between the effects of ethanol and time after injury could not be investigated for later times since only five patients with elevated plasma ethanol were seen more than 3 h after injury.

## DISCUSSION

Previous studies of the plasma insulin response to stress or injury have been conflicting. Since Allison and others first observed deficient insulin secretion during operation, in myocardial infarction and in acute burn injury (Allison *et al.*, 1967, 1968), many studies in experimental animals have confirmed this response to shock (for example, Cerchio *et al.*, 1971; Hiebert *et al.*, 1972). However, other studies have shown insulin levels to rise with the hyperglycaemia associated with injury and to respond to glucose administration (Vigaš *et al.*, 1972; Frayn, 1976a). To some extent, this seems to be a species-related phenomenon; high insulin levels are observed in the dog and suppression in the monkey at similar severities of haemorrhagic shock (Hiebert *et al.*, 1976), but even within a species either type of response may be seen (for example, in the rat: Frayn, 1976a; Turinsky *et al.*, 1977). The wide variability of plasma insulin concentrations, seen in most studies of injured patients and confirmed here, may, therefore, represent the operation of different mechanisms in different patients.

In general, it seems that, the more severe and 'stressful' the injury, the greater the tendency to suppress insulin secretion. In the rat, for instance, Noble Collip drum trauma suppresses insulin secretion when administered to conscious rats (Vigaš *et al.*,

1973), but insulin levels rise if the rats are anaesthetized when the injury is produced (Nelson & Filkins, 1979). In rats given a full skin thickness (and, therefore, painless) dorsal scald injury under anaesthesia, insulin levels also rise (Frayn, 1976a) but restraint alone, which is a marked stressor in the rat (Kvetňanský, 1980), causes impairment of insulin secretion (Shah *et al.*, 1977). The variability in plasma insulin concentrations seen in man at lower severities of injury may, therefore, reflect different degrees of 'stress' response, while in the very severely injured (ISS > 30) the severity is such that only suppression is seen.

The suppression of plasma insulin concentrations after severe injury reflects mainly an impairment of insulin secretion (Hiebert *et al.*, 1972). Insulin clearance is affected little (Meguid *et al.*, 1981) if at all (Frayn, 1976b). The impairment of secretion has been shown in animal experiments to be due to an  $\alpha$ -adrenergic effect on the pancreas, since it is abolished by adrenal medullectomy (Vigas *et al.*, 1973) and lessened by  $\alpha$ -blockade (Cerchio *et al.*, 1973). In man, it is not possible to do a controlled trial of the effects of adrenergic blockade but the results in the four psychiatric patients were interesting in this connection. One at least of these patients was taking chlorpromazine (drug histories in the other three were unknown), a relatively strong  $\alpha$ -adrenergic blocker (Baldessarini, 1980), and this might account for the elevated insulin concentrations seen in this group (Table 2) despite their severe injuries. The role of adrenaline in this response to injury is also supported by the results of Frayn *et al.* (1985), showing that, in patients with an ISS greater than 30, plasma adrenaline concentrations are usually above 2.2 nmol/l, the threshold concentration above which, in experimental work in man, plasma insulin concentrations are suppressed (Clutter *et al.*, 1980).

The high plasma insulin concentrations seen in those patients dying soon after injury (Fig. 2) were unexpected. Although we have not measured the plasma adrenaline concentration in such patients, it seems probable that it would be high since adrenaline levels increase exponentially with increasing severity of injury (Frayn *et al.*, 1985). Some of these patients did, however, have very high plasma glucose concentrations and the strong relationship between plasma insulin and glucose concentrations in this group (Fig. 2) suggests that the stimulus of massive hyperglycaemia was sufficient to overcome the suppression of insulin release by adrenaline. There is evidence that this can occur in man (Porte *et al.*, 1966).

The mechanism of the elevation of plasma insulin concentrations in the less severely injured patients is less clear. In animal experiments in which this response is seen, the plasma insulin concentration rises approximately in proportion to the hyperglycaemia (Frayn, 1976a; Nelson & Filkins, 1979). The levels reached in some patients, however, were higher than would be predicted from their hyperglycaemia. This might, perhaps, reflect stimulation by amino acids, although plasma amino acids respond little to acute injury on average (Stoner *et al.*, 1979). It seems probable, however, that these elevated plasma insulin concentrations do not have their expected effects on metabolism. In animal experiments (Frayn, 1976a; Nelson & Filkins, 1979) insulin resistance is seen soon after injury. In man, glucose turnover studies have not been performed at this stage after injury. Glucose tolerance and the response to exogenous insulin are, however, impaired (Thomsen, 1938; Howard, 1955; Shuck *et al.*, 1977), and glucose oxidation reduced (Little *et al.*, 1981), suggesting that, in man, insulin resistance may also be an early response to injury.

Apart from the relationships with severity, this study did little to clarify other causes of variability in plasma insulin concentrations soon after injury. Age and time after injury had little effect, although our data are not ideal for investigating the latter since, in the urban environment of Salford, patients with severe injuries arrive in hospital very quickly. The plasma insulin concentration was depressed by ethanol in some groups (Table 3) but this effect appeared to be mediated through the effect of ethanol on the plasma glucose concentration described previously after injury (Stoner *et al.*, 1979), rather than through any specific suppression of insulin release. This is in contrast to the observations of Vitek *et al.* (1982), who showed that a high ethanol concentration leads to a sustained depression of the insulin concentration in relation to that of glucose after injury. This effect was manifest at around 5 h after injury, however, and so we were unable to investigate it fully.

In conclusion, the results indicate that suppression of insulin secretion is seen almost invariably after very severe injuries (ISS > 30). The results in the psychiatric patients, together with the findings of Frayn *et al.* (1985), support the suggestion first made by Allison *et al.* (1967) that this suppression is due to a high plasma adrenaline concentration. In many patients with less severe injuries, however, high plasma insulin concentrations are seen, presumably reflecting a response to the hyperglycaemia of injury and possibly associated with insulin resistance.

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