Circadian Variation of Insulin Requirement in Insulin Dependent Diabetes Mellitus The Relationship between Circadian Change in Insulin Demand and Diurnal Patterns of Growth Hormone, Cortisol and Glucagon during Euglycemia

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In 13 subjects with type 1 (insulin dependent) diabetes mellitus the 24 hour insulin requirements to maintain euglycemia were assessed by means of feed back controlled insulin infusion. For the study steady state conditions, i.e. bed rest and fasting were required. Venous blood samples were collected, at 2 hour intervals, for the measurement of glucagon, growth hormone and cortisol. During the day, the insulin demand showed small changes. However, the early morning requirement for insulin was twice as much as the daytime demand (dawn phenomenon). There was a significant difference ($p < 0.05$) in the insulin requirement between 6.00 to 8.00 hours in the morning and 12.00 to 16.00 hours in the afternoon. The plasma glucagon levels showed no significant changes during the euglycemic period (median range from 28.7 to 30.1 ng/ml) ($p < 0.05$). The median of the growth hormone level decreased throughout the night from a peak of 4.41 ng/ml at midnight to a nadir of 1.05 ng/ml at 4.00 hours. There was a significant difference ($p < 0.05$) between the growth hormone concentration between midnight and the early morning. The cortisol concentration indicated a circadian variation. The median was significantly higher from 4.00 to 8.00 hours in comparison with the median at 20.00 to 24.00 hours ($p < 0.05$). The results of the study showed that the early morning rise in the insulin demand is related to the increased early morning cortisol secretion and to the nocturnal peaks of growth hormone concentration ($p < 0.05$).

Key words: Insulin Dependent Diabetes Mellitus – Circadian Rhythms – Euglycemia – Glucagon – Growth Hormone – Cortisol – Diurnal Patterns – Insulin Requirement – Blood Glucose

Introduction

In a healthy person the blood glucose concentration is very closely controlled, usually between 70 to 120 mg/dl in a fasting person. After nutrition an increasing plasma glucose and insulin secretion, with a reciprocal decrease in the secretion of conterregulatory hormones, results in decreased glucose production by the liver and increased glucose utilization.

In diabetic patients a sufficient increase in insulin secretion is not possible and hyperglycemia results. Especially in type 1 diabetes (IDDM = insulin dependent diabetes mellitus) the lack of insulin tends to cause a failure in the blood glucose regulatory system. Therefore the homeostasis of the blood glucose is impaired and both hyperglycemia and hypoglycemia occur. *Davidson* (1991) suggested that in IDDM patients hyperglycemia may occur as a result of (1) waning insulin action, (2) hypoglycemia with an unopposed counterregulatory hormone response (Somogyi effect), or (3) the dawn phenomenon (early morning hyperglycemia).

Current literature reviews suggest that the insulin requirement during the day is varied. These circadian variations affect both healthy persons and diabetics (*Pickup* and *Williams* 1991; *Tato, Tato, Beyer* and *Schrezenmeir* 1991).

It is also known that the secretion of counterregulatory hormones (especially cortisol and growth hormone) follow a circadian rhythm. *Shapiro* and co-authors found that in healthy volunteers the insulin secretion also has a circadian rhythm. The authors suggested that the effects of circadian rhythm on glucose levels, insulin secretion and insulin clearance were previously underestimated and that these effects could be partially mediated by cortisol and growth hormone (*Shapiro, Tillil, Polonsky, Fang, Rubenstein* and *Van Cauter* 1988).

In IDDM, a diurnal change exists in insulin requirements. It is well documented that the postprandial insulin requirements of type 1 diabetic patients are usually highest after breakfast and glucose tolerance tends to improve as the day goes on. For this reason it is a well established rule that in insulin therapy a higher insulin dose per gramm carbohydrate is calculated for breakfast than for a later meal. Circadian changes in cortisol, growth hormone and catecholamines have been discussed as possible explanations for increased basal insulin requirements during the early morning and could also be responsible for the increased insulin requirement after breakfast (*Kerner, Schultz, Schock* and *Pfeiffer* 1982; *Mathiesen, Rubin, Christiansen, Svendsen, Lauritzen* and *Deckert* 1982; *Campbell, Bolli, Cryer* and *Gerich* 1985; *Edge, Matthews* and *Dunger* 1990; *Perriello, De Feo, Torlone, Fanelli, Santeusanio, Brunetti* and *Bolli* 1991).

In contrast with these findings, *Capani* and co-authors stated that circadian changes in postprandial carbohydrate tolerance are independent from the endogenous rhythms of the basal

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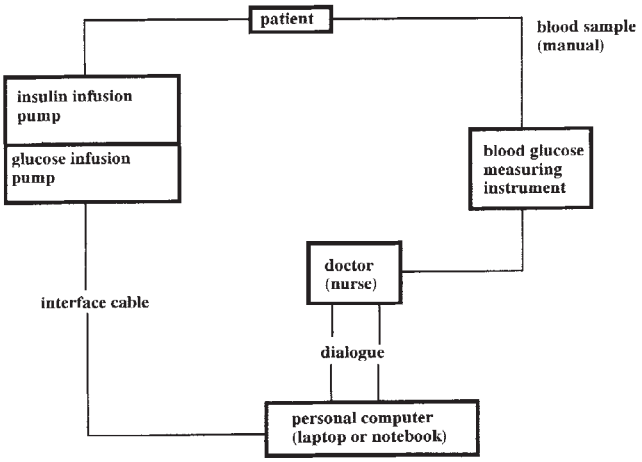

Fig. 1 Diagram representing course of the clinical experiment.

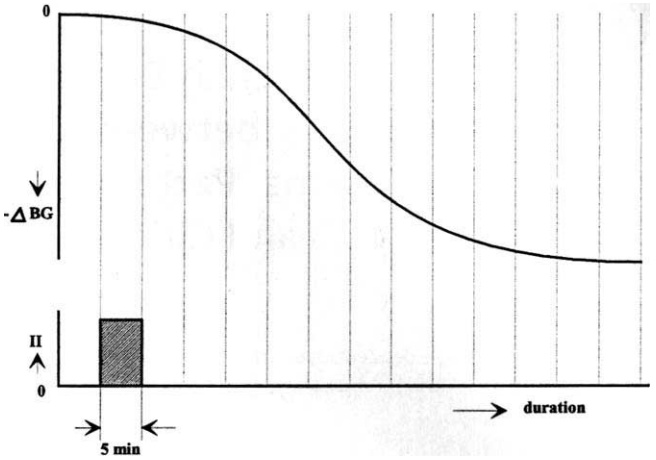

Fig. 2 Dynamic model of insulin activity. ΔBG: change in blood glucose II: insulin impulse

glucose metabolism. The causes for the circadian patterns of postprandial responses lie in exogenous factors like diet composition, caloric intake and therapeutic regime (*Capani, Casalini, Consoli, D'Emilio, La Nave, Loragno, Vitacolonna* and *Zappone* 1991).

The present study was undertaken to assess (1) the existence of the circadian rhythms in the insulin requirement of IDDM during steady state conditions without exercise and without oral nutrition, (2) the relationship between the insulin need at various times during the day and the level of cortisol, growth hormone and glucagon at these times, and (3) whether a circadian variation in insulin requirement occurs and if a relation to the levels of these hormones exists.

Material and Methods

Thirteen diabetics (7 men, 6 women) were studied. The patients were aged between 17–40 years (median = 27 years) and had a duration of diabetes of 7–20 years (median = 7 years). All subjects had no residual endogenous insulin secretion assessed by the plasma C-peptide intravenous glucose. Their HbA_1C ranged from 8.5 to 12.1 % (median = 10.4 %) and the median of body mass index was 22.8 kg/m^2 (ranging from 18.8 to 27.4 kg/m^2). All the diabetic patients were on a therapeutic regime of two to four daily injections of insulin. The subjects were healthy apart from their diabetes and did not present clinically overt diabetic complications. None of the patients at the time of the study were given any other medication apart from insulin.

All patients were studied over a 27 hour period with a semi-closed loop computer control system (Glucon), which is able to maintain euglycemia. The system consists of a PC with the Glucon software, two commercial infusion pumps for insulin and dextrose with a computer interface and a blood glucose measuring instrument (YSI glucose analyser). The insulin was given to a physiologic sodium chloride solution, with an addition of 5 % albumin to prevent the adsorption of insulin on tubing. A blood sample was taken manually and the blood glucose concentration was determined every 30 minutes using the blood glucose device. The blood glucose value was entered into the computer by means of the computer keyboard. The computer was able to control the infusion programme automatically (Fig. **1**).

The Glucon software was developed for the following uses:
- perioperative blood glucose management
- glucose clamping investigations

The Glucon software consists of two user programmes for the above mentioned applications. The user programme for perioperative blood glucose management is of no importance in this study and will therefore not be explained (for general information about this user programme see *Trümper, Kiesewetter* and *Möricke* 1994).

The other user programme is for glucose clamping investigations. This programme will now be explained in detail.

The aim of the control is to maintain a euglycemic blood glucose level. Hereby a constant dextrose dosage of 1 mg/kg/min is administered. It is only through appropriate insulin infusions that the blood glucose level can be controlled. It must therefore be possible to alter the basal insulin infusion automatically. This can be done with a dynamic model of insulin activity. This means, that every insulin impulse leads to a change in the blood glucose level (Fig. **2**).

In practice it is necessary to establish a theoretical blood glucose target value. This value was set at 110 mg%. The principle of controlling the blood glucose level is based on predictive calculations of the blood glucose level and the predictive calculation of the necessary insulin infusion rate by means of the dynamic insulin model. The predictive calculations of the blood glucose value take place every 10 minutes. In between these calculation values the blood glucose course is linearly interpolated. In this way a predictive blood glucose curve is obtained. The insulin infusion pattern is changed according to the difference between the predicted value and target value as follows:

Every 30 minutes the actual blood glucose (BG) value is taken and manually fed into the computer. After this the computer automatically uses the following algorithms (Fig. **3**).

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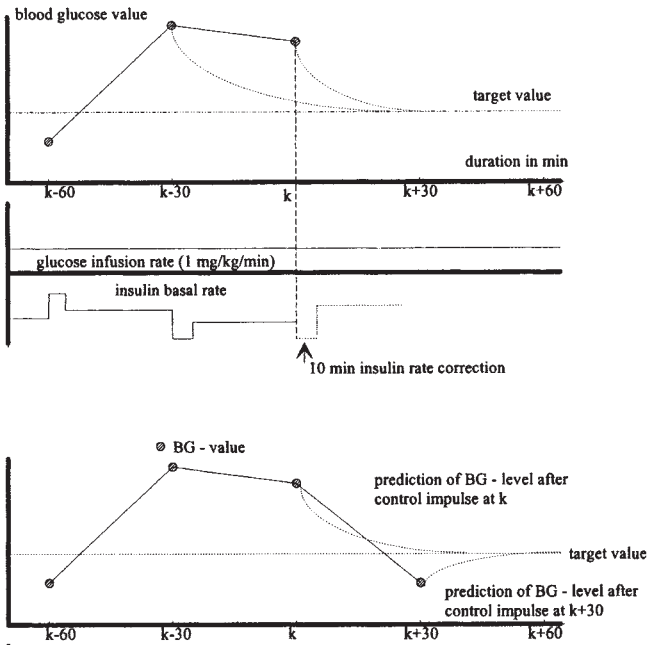

Fig. 3 Graphic representation of the computer algorithms.

1. The computer compares this actual value with the previously predicted value.
2. If both values are the same no change in the insulin infusion course occurs.
3. If the actual BG value deviated from the previously predicted value, the computer will take into account this difference.
4. The computer, with the help of the dynamic insulin model and empirical insulin activity factors, calculates the changes in the insulin infusion course, necessary to compensate the BG difference.
5. The necessary changes in insulin infusion course take place in 10 minute intervals and lead to a new insulin basal rate. If the actual BG value is higher than the predicted value a positive insulin impulse (10 minute interval) and a higher basal rate is calculated. If the actual BG value is lower then the predicted value a negative insulin impulse and a lower basal rate is calculated. A negative insulin impulse causes a temporary stop of insulin infusion.
6. These computerized insulin rates are transmitted via the interface cable to the insulin infusion pump.
7. Following the above mentioned procedure a new prediction of the BG level occurs.
8. After 30 minutes the next actual BG value is entered and the procedure is repeated (see 1.).

The algorithms will now be mathematically formulated as follows:

I. Clamp-algorithms

1. Calculation of the deviation (ΔBG) of the measured BG-value (BGm) from the predicted value (BGp) at time k:

$$\Delta BG\ (k) = BGp\ (k) - BGm\ (k)$$
(BG in mg/dl)

2. Calculation of the 10 minute insulin rate correction (IRC) to compensate the BG-deviation (ΔBG):

$$IRC,\ (k) = \Delta\ BG/IAF$$
(IRC in mU/kg/min)

IAF – insulin activity factor for the calculation of the necessary insulin dosage (see dynamic insulin model – Fig. **2**).

3. Calculation of the new insulin basal rate (IBR):

$$IBR_{new} = IBR_{old} + (\Delta BG\ [k]/IBRF)$$
IBRF – insulin basal rate factor resulting from dynamic insulin model

4. Calculation of new BG-prediction (BGp):

$$BGp_{new}\ (k+i) = BGp_{old}\ (k+1) - (IAF[i] \times IRC\ [k]) + \Delta BG\ (k)$$

II. Initial algorithm

The initial prestudy period is necessary to bring the initial BG-value in line with the pre-determined BG-target value (BGtv):

$$BGp\ (k + i) = BGtv$$
$$(i = 0 \ldots n)$$

$$IBR = IBR_{start}\ (\text{pre-determined})$$

The procedure of the study was as follows: Exogenous insulin was discontinued before admission; ultralente at least 44 hours, lente 36 hours, and soluble 8 hours before the study. The patients received their last meal at 22.00 hours the day before the examination. During the night and on the day of the study patients were restricted from exercising. In the morning the patients received in each arm a catheter in an antecubital vein. The catheter on the left was for an infusion of insulin and dextrose and the other for drawing blood samples. At 7.00 o'clock an infusion of 10% dextrose was started at a constant rate of 1 mg/kg/min and was maintained for 27 hours. The necessary insulin infusion for euglycemia was determined and controlled by the Glucon system. The first three hours, from 7.00 a.m. to 10.00 a.m., were used to normalize the initial high blood glucose level and to introduce a smooth insulin infusion rate (initial period). These three hours were not included in the actual study. This means that the evaluation of insulin infusion rates started at 10.00 a.m. continuing through to 10.00 a.m. the following day (24 hours). This evaluation was performed with a special evaluation feature which is part of the glucon programme. During the study all data and command procedures were registered for further analysis, and in addition the computer was able to give graph printouts of each patient. The necessary insulin infusion rates for maintaining euglycemia were evaluated as follows: The insulin infusion rate over 24 hours was divided in 2 hour periods, i.e. 10.00 to 12.00,

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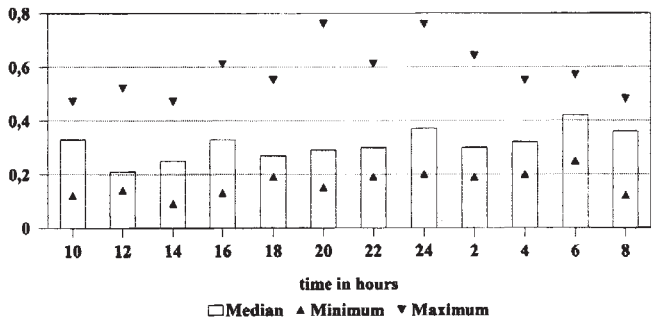

Fig. 4 Median of the 2 hour insulin requirements in mU/kg/min of 13 type 1 diabetics during a 24 hours euglycemic period.

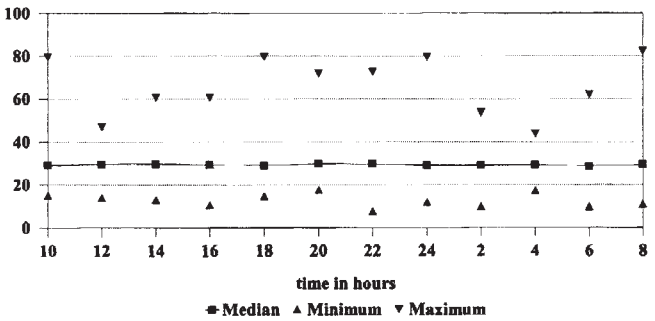

Fig. 5 Median of the glucagon concentration in ng/ml of 13 type 1 diabetics during a 24 hours euglycemic period.

12.00 to 14.00, etc. In each period the arithmetical mean value of all the insulin infusion rates was calculated giving 12 insulin requirement values for each patient. This will now be referred to as the "2 hour insulin requirement".

Venous blood samples were collected via the catheter in the right arm at 2 hour intervals throughout this period. The samples were prepared for the measurement of glucagon, growth hormone, cortisol, lactic acid and urea.

Growth hormone, cortisol and glucagon were measured with radioimmunoassays (*Schalch* and *Parker* 1964; *Farmer* and *Pierce* 1974; *Freyse, Fischer, Albrecht, Marx* and *Keilhacker* 1987). The measurement of lactic acid and urea was performed with photometry.

The data were analysed by non-parametric tests (Friedman test as a homogeneity test, multiple comparison of dependent samples by Wilcoxon and Wilcox, rank correlation coefficient by Spearman (r_s), Wilcoxon's test of pair differences). All tests were based on a significance level of 5 %.

Results

The blood glucose level ranged between 70 and 140 mg/dl. The Wilcoxon's test of pair differences was used to examine, whether there was a difference between the median value of blood concentration tested at 30 minutes intervals, and the blood glucose value of 110 mg/dl. No significant differences were found ($p = 0.05$) and this indicated euglycemic conditions.

Through the evaluation programme, as described above, it was possible to gain for all 13 patients 12 different 2 hour insulin requirements. The median value of the 2 hour insulin requirements was calculated on all 13 patients for each time period, i.e. 10.00 to 12.00, 12.00 to 14.00, etc. These median values had a circadian variation (Fig. **4**). During the day the 2 hour insulin requirements showed small changes (range between 0.21 to 0.33 mU/kg/min), but the early morning requirement for insulin was approximately twice as great (0.42 mU/kg/min) as the daytime requirements. Using the Friedman test we examined whether the time of day had an influence on the 2 hour insulin requirements. It was established that a significant influence existed ($p < 0.05$). In order to check at what time the greatest difference occurred, the multiple comparison of dependent samples by Wilcoxon and Wilcox was used. This test showed that the greatest difference in the 2 hour insulin requirements was between the time from 12.00 and 16.00 hours and the time from 6.00 and 8.00 hours (Fig. **4**).

The plasma glucagon levels showed no significant changes over the 24 hours period (Fig. **5**). The medians of plasma concentrations of this hormone during the study ranged from 28.7 to 30.1 ng/ml. The Friedman test showed that the time of day did not influence the glucagon concentrations.

The medians of lactic acid and urea during the 24 hours euglycemic period showed no great changes. The medians of lactic acid concentrations ranged from 9 mg/dl to 16 mg/dl and the medians of urea concentrations were between 24.1 to 26.5 mg/dl. Using the Friedman test it was examined, whether the time of the day had an influence on the medians of lactic acid and urea concentrations. It was found that no significant influence existed.

The medians of the cortisol concentrations of the 13 patients, which ranged from 8.0 to 14.6 ug/dl, indicated a circadian variation (Fig. **6**). Using the Friedman test it was shown, that the time of day had a significant influence on the cortisol concentrations. The multiple comparison by Wilcoxon and Wilcox was used to check at what time the greatest difference occurred. This test showed that the greatest difference in cortisol concentrations occurred between the time from 4.00 and 8.00 hours and the time from 20.00 and 24.00 hours (Fig. **6**).

Now we compared the medians of the 2 hour insulin requirements with the medians of the cortisol concentrations during the 24 hours euglycemic period. With the Spearman rank correlation coefficient we found a positive correlation between the diurnal variation of the 2 hour insulin requirements and the circadian rhythms of cortisol concentrations ($r_s = 0.585 > r_s^* = 0.4965$).

The medians of growth hormone concentrations during the daytime showed no changes. However, during the night changes occurred. The medians of the growth hormone levels decreased throughout the night from a peak of 4.41 ng/ml at 24.00 hours to a nadir of 1.05 ng/ml at 4.00 hours (Fig. **7**). Using the Friedman test we examined whether the time of day had an influence on the growth hormone levels. It was established that a significant influence existed ($p < 0.05$). In order to check

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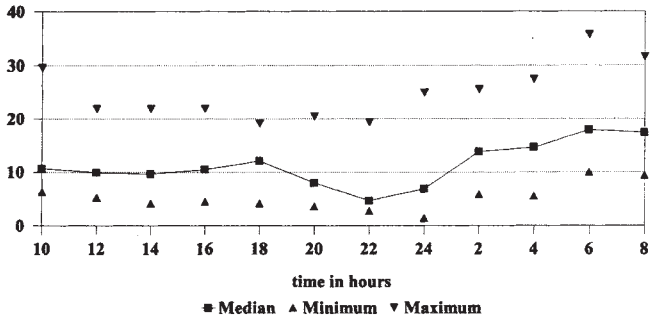

Fig. 6 Median of the cortisol concentration in ug/dl of 13 type 1 diabetics during a 24 hours euglycemic period.

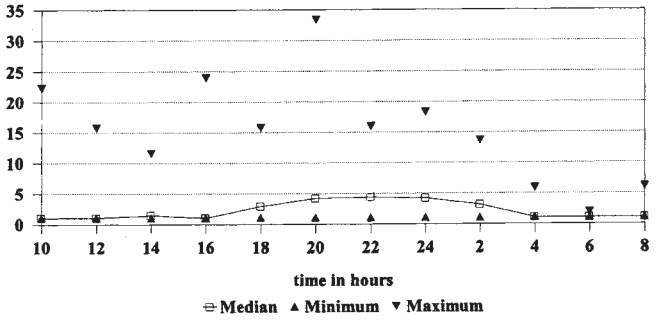

Fig. 7 Median of the growth hormone concentration in ng/dl of 13 type 1 diabetics during a 24 hours euglycemic period.

at what time the greatest difference occurs, the multiple comparison of dependent samples by Wilcoxon and Wilcox was used. This test showed that the medians of growth hormone concentrations differed the most between the time from 20.00 to 24.00 hours and the time at 6.00 hours (Fig. **7**).

Using the Spearman rank correlation coefficient we examined whether a correlation existed between the circadian variations of 2 hour insulin requirements and the diurnal changes of growth hormone concentrations. We compared the medians of the 2 hour insulin demands with the medians of growth hormone concentrations and found no significant correlation. From literature it is known that the effects of growth hormone on carbohydrate metabolism start with a lag period of 4 to 6 hours. Therefore we shifted the medians of 2 hour insulin requirements as follows. We compared the median of the growth hormone concentration at 10.00 hours with the median of the 2 hour insulin requirement, i.e. between 12.00 and 14.00 hours. Thus we shifted all 12 median values forward by 2 hours. The same procedure was carried out with a forward time shift of 4, 6 and 8 hours. Then we used the Spearman rank correlation again and it was established that a positive correlation existed with a forward time shift of 6 hours ($r_s = 0.5392 > r_s^* = 0.4965$) and 8 hours ($r_s = 0.596 > r_s^* = 0.4965$).

Discussion

The present study follows the insulin requirement of type 1 diabetics during a 24 hours euglycemic period which was performed under steady state conditions (bed rest and fasting). The data shows that a circadian variation exists with a high insulin demand in the early morning. *Clarke* and co-authors observed an increase in insulin requirements from 6.00 to 8.00 hours compared to the requirements during the night (*Clarke, Thomas* and *Santiago* 1980). This early morning increase in insulin requirement of type 1 diabetics is often referred to as the "dawn phenomenon". This term was first described by *Schmidt* and co-authors and was suggested to emphasize its different pathophysiologic mechanisms (*Schmidt, Hadji-Georgopopoulos, Rendell, Margolis* and *Kowarski* 1981). The nature of these mechanisms is not exactly known. Theoretically, both an increase of glucose production as well as a decrease of glucose utilization might be involved. Both phenomena are most likely mediated by hormones. It is documented that the circadian rhythm of counterregulatory hormones like cortisol and growth hormone are responsible for the dawn phenomenon (*Campbell* et al. 1985; *Perriello, De Feo* and *Bolli* 1988; *Edge* et al. 1990).

Clarke, Thomas and *Santiago* (1980) and later *Bolli* and *Gerich* (1984) found that with Biostator studies in type 1 diabetics the increase in insulin demand doubled at 6.00 hours in respect to midnight. Current results show that the extent of the morning increase in the insulin requirement was over-estimated. *Periello* and co-authors investigated 114 type 1 diabetics with an intravenous feedback insulin infusion from 22.00 to 8.00 hours and registered the blood glucose and insulin infusion. They found, that the required insulin infusion for euglycemia at midnight (0.113 ± 0.05 mU/kg/min) decreased to a nadir at 2.40 hours (0.102 ± 0.03 mU/kg/min) and rose to a peak at 6.40 hours. In our investigation the median of the 2 hour insulin requirement was 0.3 mE/kg/min between 2.00 and 4.00 hours and 0.42 mE/kg/min between 6.00 and 8.00 hours. This is an increase in early morning insulin requirement of 40% and confirmed the data of *Periello* and co-authors. The threefold higher insulin infusion rate in our study is a result of the constant dextrose infusion (1 mg/kg/min). The latter was not used by *Periello* and co-authors (*Periello* et al. 1991).

The higher increase in morning insulin requirement of the early Biostator studies is a result of aggregation and loss of available insulin after prolonged use (*Brennan, Gebhart* and *Blackard* 1985; *Harris, Davidson* and *Rosenberg* 1989). In our study, the effect of insulin loss from the infusion solution by adsorption on to the tubing was prevented by the addition of albumin.

During the euglycemic period the glucagon level did not show significant changes. Literature reviews suggested that hypoglycemia is a potent stimulus to glucagon release. Free fatty acids and amino acids also stimulate glucagon secretion (*Muehlhauser, Berger, Sonnenberg, Koch, Joergens, Schernthaner* and *Scholz* 1985). Both were prevented during the study design with euglycemia, steady state conditions and fasting. The circadian variation of insulin requirements in IDDM glucagon appears not to be so important. These data were confirmed by other investigators (*Tuttle, Marker, Dabsky, Schwartz, Shaw, Clutter, Holloszy* and *Cryer* 1985; *Shilo, Sotsky* and *Shamoon* 1988).

Also prevented in the study design was the Somogyi phenomenon (posthypoglycemic hyperglycemia). It did not appear to be so important with respect to the dawn phenomenon. Sim-

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ilarly, it has recently been shown that nocturnal hypoglycemia does not appear to cause clinically important daytime hyperglycemia in type 1 diabetic patients. At the very least, the magnitude of the Somogyi phenomenon was overestimated in the past (*Hirsch, Smith, Havlin, Shah, Clutter* and *Cryer* 1990).

The adrenergic mechanisms do not play an important role in the hormonal regulation of glucose turnover. However catecholamines play a main role in the prevention and removal of exercise induced hypoglycemia (*Clutter, Rizza, Gerich* and *Cryer* 1988; *Sotsky, Shilo* and *Shamoon* 1989). With the study design (no exercise, euglycemia) the counterregulatory factors of adrenergic mechanisms were prevented.

Euglycemic clamp studies have shown that the hepatic glucose output can be effectively reduced by an intravenous insulin infusion (*Bratusch-Marrain, Komjati* and *Waldhäusl* 1986; *Waldhäusl* 1986). They demonstrated that during a euglycemic clamp study the hepatic glucose output was suppressed with an insulin dosage of 1 mU/kg/min. In our study a constant dextrose dosage was administered (1 mg/kg/min). The median of the necessary insulin dosage to maintain euglycemia ranged from 0.21 to 0.42 mU/mg/min. Tracer investigations to establish whether changes in the hepatic glucose output occurred were not carried out. It could be indirectly shown that in our study with a continual dextrose rate of 1 mg/kg/min, the hepatic glucose output was constant. The latter was proven by measuring lactic acid and urea concentrations during the euglycemic period. It was determined that the time of day had no significant influence on the lactic acid and urea concentrations. Lactic acid has a central position in the glucose metabolism and is a main substrate of the gluconeogenesis in the liver. If the hepatic glucose output was not to be constant during the euglycemic period, the lactic acid level in the serum would be significantly different. Urea is an end product of protein catabolism. By increasing gluconeogenesis from amino acids in the liver there would be an increase of urea in the serum.

The results of this study show that a positive correlation exists between the diurnal variation of insulin requirements and the circadian rhythm of cortisol concentrations. This confirms the findings of *Bright* and co-authors. Using an euglycemic clamp in 5 type 1 diabetics they found a significant increase in the insulin demand in the morning (6.00 to 9.00 hours) in relationship to the demand at night (1.00 to 6.00 hours) and a positive correlation between the morning rise in insulin requirement and the higher cortisol level in the early morning. With a suppression of cortisol secretion, through drugs, they achieved a distinct decrease in the insulin demand but not a significant decrease in the early morning rise of insulin demand (*Bright, Melton, Rogol* and *Clarke* 1980). The morning increase in cortisol secretion seems not to be the only factor for the dawn phenomenon. Other investigators using healthy volunteers in euglycemic clamp studies found a circadian rhythm in insulin secretions with an increase in the early morning like a dawn phenomenon in IDDM. They suggested that the effects of the circadian rhythm and of sleep in relationship to the glucose level, the insulin secretion and insulin clearance were underevaluated in the past and could be partially caused by cortisol and growth hormone (*Arslanian, Ohki, Becker* and *Drash* 1990; *Van Cauter, Blackman, Roland, Spire, Refetoff* and *Polonsky* 1991; 1992).

Current literature shows that the effects of growth hormone on carbohydrate metabolism start with a time lag period of 4 hours and have a duration of 4 hours. *Kollind* and co-authors investigated 8 type 1 diabetics between 4.00 and 12.00 hours. The patients received somatostatin, glucagon, insulin and dextrose infusions. At 4.00 hours the authors caused a hypoglycemia with an additional insulin bolus. Then the patients received a body mass related growth hormone infusion and in the next study sodium solution. In both studies they found no differences in the concentration of blood glucose, free plasma insulin, glucagon, catecholamines and cortisol. In the growth hormone infusion study a hyperglycemia occurred after 4 hours and had a duration of 4 hours (*Kollind, Adamson, Lins* and *Carstedt* 1988). These findings confirm the results of former investigations where the nocturnal growth hormone release was suppressed by somatostatin (*Arias, Kerner* and *Pfeiffer* 1984; *Campbell* et al. 1985; *Davidson, Harris, Ziel* and *Rosenberges* 1988). *Periello* and co-authors found that the effects of growth hormone on carbohydrate metabolism are caused by decreasing hepatic and extrahepatic sensitivity to insulin (*Periello, De Feo, Torlone, Fanelli, Santeusanio, Brunetti* and *Bolli* 1990). Our results implicate a positive correlation between the early morning rise in insulin requirement and the increase of growth hormone concentration before midnight.

Conclusion

This study clearly supports a circadian variation in insulin demands in type I diabetics. It was also shown that this circadian rhythm exists, although external influences such as oral nutrition and physical activities were excluded in the study design. The circadian changes in cortisol and growth hormone concentration appear to be responsible for the concordant variation in insulin demand and this offers an explanation for the dawn phenomenon.

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