

REDUCING POST-TRAUMATIC INSULIN RESISTANCE BY USING NON-GLUCOSE SOURCES OF ENERGY

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Abstract

The aim of this retrospective study of multiple-trauma patients is to demonstrate differences in the calculated insulin resistance (IR) between an “anti-insulin” group and a control group, discover any possible additional influences on the values considered, and demonstrate the contribution of parenteral nutrition to a decrease in IR.

The study involves the first two weeks after the trauma.

IR values were calculated from the glycemia and insulinemia, according to the homeostasis model assessment, HOMA.

No differences in the number of days from the trauma, the number of days from the operation, the age or the quotient of energy delivered and in turn in the values of BMI were observed between the two groups at the 5 % level of significance.

The “anti-insulin” model of parenteral nutrition was based mainly on the slow administration of only small amounts of glucose without insulin (insulin was administered only in diabetics) and on the use of predominantly non-glucose sources of energy.

The undesirable increase in insulinemia has an antilipolytic effect that results in a lack of free fatty acids as a source of energy for gluconeogenesis in the liver.

The IR calculations yielded a statistically very significant difference ($P < 0.001$) between the “anti-insulin” group and the control group. A very significant difference was also found between these groups in the nitrogen balance ($P < 0.0001$).

Key words

Insulin resistance, Insulinemia, Multiple trauma, Nitrogen balance, Parenteral nutrition, Non-glucose sources of energy

INTRODUCTION

An integral part of the treatment of every multiple injury is parenteral treatment, which may be used to correct a number of problems, in particular the supply of energy available to the affected organism. In parenteral nutrition some special features must be respected, among others, insulin resistance (IR) during the post-aggressive syndrome.

The problem of IR in traumatology was reported in the 1980s (1, 2).

The differences in the calculated IR between an “anti-insulin” group and a control group of patients have been followed in this retrospective study, and the contribution of parenteral nutrition to a decrease in the IR and to a possible improvement in the nitrogen balance has been demonstrated.

PATIENTS AND METHODS

PATIENTS

Multiple-trauma patients in the intensive care unit of the Traumatological Hospital in Brno were treated with different kinds of parenteral nutrition in a so-called “anti-insulin” group (7 patients) and a control group (10 patients). The results of 26 determinations in the “anti-insulin” group were always compared with 27 determinations in the control group.

The study involves the first two weeks after the trauma.

There were no significant differences between the “anti-insulin” group and the control group in any of the four criteria (the number of days after the trauma, the number of days after the operation, the age of the patients, and the proportion of the energy delivered).

Table 1

PATIENT CHARACTERISTICS			
	control group (n = 27)	anti-insulin group (n = 26)	t-test
	mean ± standard deviation range [minimum....maximum]		
age (years)	41.15 ± 17.986 [19 . . . 69]	33.15 ± 12.991 [17 . . . 58]	NS
days after trauma	7.07 ± 3.430 [1 . . . 14]	5.73 ± 2.359 [2 . . . 12]	NS
days after operation	4.94 ± 2.175 [1 . . . 8]	4.17 ± 3.157 [1 . . . 10]	NS
BMI	25.61 ± 3.292 [22.63 . . . 31.14]	25.45 ± 6.043 [18.37 . . . 37.11]	NS

NS = non-significant difference between groups at the $P < 0.05$ level

PARENTERAL NUTRITION SCHEDULE

“Anti-insulin” group

The “anti-insulin” model of parenteral nutrition was based mainly on: 1) the administration of insulin in diabetics only, 2) the slow administration of sugars ($0.25 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of glucose alone or $0.4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of a mixed solution of glucose in combination with fructose and sugar-derived alcohols), 3) the administration of branched-chain amino acids as a source of energy from the very beginning of the parenteral nutrition (3).

Glucose never accounted for more than 25 % of the energy contributed by the combination of sugars and sugar alcohols administered in the “anti-insulin” group.

Predominantly non-glucose sources of energy (fructose, sugar-derived alcohols, branched-chain amino acids, and fat emulsions) were used.

Control group

The control group included patients in which the parenteral nutrition did not correspond to the criteria of the “anti-insulin” group (mainly in a higher amount of glucose administered). There were patients in whom we were not able to manage the “anti-insulin” arrangement day by day (often the situation during weekends) or the parenteral nutrition was based on some other principle. However, in all cases the amount of energy (and nitrogen) administered was without statistically significant difference.

The stages of the “anti-insulin” parenteral nutrition

The arrangement of the parenteral nutrition approached the ideal condition displaying three stages (4) (Fig. 1). The pie charts show the percentage of energy contributed by each group of substances administered (sugars, amino acids, and fat emulsions, respectively). The surface areas of the pie charts are proportional to the energy administered in the corresponding stages.

It was generally desired that 40–50 % of the total amino acids be branched-chain amino acids and in turn that the glucose proportion of the sugars and sugar-derived alcohols be minimized. The proportions are given as bar charts (in Fig. 1).

The glucose proportion of the total sugars was reduced from the original 25 % to 15.6 % in the individual stages of the parenteral nutrition.

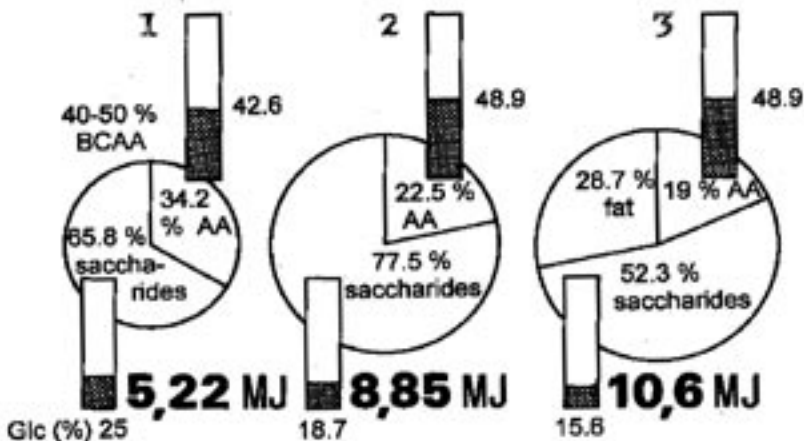


Fig. 1

Three stages of parenteral nutrition in the “anti-insulin” group.
(AA = amino acids, BCAA = branched-chain amino acids, Glc = glucose)

The rate of application of the amino acids and fat emulsions was $0.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

The “anti-insulin” model of parenteral nutrition and the composition of the infusions which were prepared to order have been described previously (5), as have the three (ideal) stages of the administration of parenteral nutrition (4).

The first stage of parenteral nutrition was most often used in the first two days after trauma. The second stage was applied usually during the next one or two days. The last stage (with the administration of fat emulsions) started in the second half of the week after trauma (usually from the fourth or fifth day, in the most favourable cases also from the third day after trauma).

Measurements

Blood glucose was determined enzymatically with the set “Bio-La-Test Oxochrom Glucose” (Pliva-Lachema, Brno), which contains glucose oxidase and peroxidase.

Immunoreactive insulin was measured with the “Abbott IMX Insulin Assay” set (microparticle enzyme immunoassay).

Insulin and glucose were determined in the morning collection of blood after the infusion of the “maintenance” (electrolyte) solution, usually the saline solution (0.9 % NaCl).

Calculations

The HOMA (homeostasis model assessment (6)) was used to express the IR. It enables the calculation of the IR from the stable basal serum glucose ([Glc], $\text{mmol} \cdot \text{L}^{-1}$) and serum insulin ([Ins], $\text{mU} \cdot \text{L}^{-1}$) concentrations; $\text{IR} = [\text{Glc}] \cdot [\text{Ins}] / 22.5$. The denominator in the fraction was modified and replaced with the number 1.22. This change made the limit of normal IR (calculated using both the highest normal glycemia and the highest normal insulinemia) equal to 100.

The energy contained in the administered infusions was given as a proportion of the basic energy expenditure (calculated by the Harris-Benedict equations) in the patients.

Statistical analysis

Because the distribution of all data was symmetrical, no transformations were performed.

The statistical graphics system Statgraphics (STCS Inc.) was used to evaluate the data. The results are presented as the mean \pm standard deviation (SD). All tests were two-tailed and a value of $P < 0.05$ was considered to be significant. Student’s *t*-test was used in assessing the statistical significance of the data.

RESULTS

The IR (364.4 ± 374.45 in the control group vs. 148.5 ± 164.18 in the “anti-insulin” group) showed a statistically significant difference ($P < 0.001$). A very significant difference ($P < 0.0001$) was found in the nitrogen balance.

To the nitrogen balance of a given day were added (when it was possible) the nitrogen balances of the two preceding days. A similar system was used in evaluating

the supply of energy administered. The values were then expressed as the average for three days.

The differences in the statistical significance of both groups were approximately the same for the comparison of balances (or energy) for individual days or for three-day averages.

Table 2

Insulin resistance, nitrogen balance, and energy administered.
 (The insulin resistance according to the homeostasis model assessment - "HOMA".
 The nitrogen balance in grams of nitrogen per day.
 The energy administered is expressed as a proportion of the energy in infusions to the calculated real need.)

INSULIN RESISTANCE, NITROGEN BALANCE, AND ENERGY ADMINISTERED			
	control group (<i>n</i> = 27)	anti-insulin group (<i>n</i> = 26)	<i>t</i>-test
	mean ± standard deviation range [minimum...maximum]		
insulin resistance	364.4 ± 374.45 [24.3 . . . 1300.8]	148.5 ± 164.18 [22.3 . . . 832.1]	*** (<i>P</i> < 0.001)
N-balance	-19.2 ± 9.470 [-38.47 . . . -7.42]	-8.66 ± 6.264 [-20.23 . . . +6.51]	**** (<i>P</i> < 0.0001)
energy administered	0.93 ± 0.289 [0.27 . . . 1.55]	0.90 ± 0.335 [0.21 . . . 1.57]	NS

NS = non-significant difference between groups at the *P* < 0.05 level

DISCUSSION

The benefits of the metabolic effect of fructose are again pointed up (7). Fructose (or fructose in combination with a fat emulsion) is considered to be an important nutrient that contributes to stabilization of the metabolism, especially in the post-aggressive phase. Therefore, we undertook a retrospective study with respect to the problem of insulin resistance (IR).

The IR itself takes place in peripheral tissues, especially those of skeletal muscles (1). IR is present to differing extents in tissues. The lipolysis of fat tissue is very sensitive to insulin, only a very small increase in insulinemia above the normal limit is required to inhibit it. This holds too for the IR because the adipose tissue is - in contrast to some other tissues - always sufficiently sensitive to insulin. The adipose tissue retains its sensitivity to insulin after trauma or in sepsis (8). Insulin inhibits the activity of the cAMP-mediated hormone-sensitive lipase in adipocytes (9). The intracellular cAMP itself is not responsible for the modulation of lipolysis; an increased insulin turnover may also contribute to IR in post-traumatic or septic stress (2).

An increase in insulinemia is undesirable because it blocks lipolysis in the adipose tissue. Fatty acids liberated by lipolysis serve as a source of energy in a stress situation, mainly for the liver. This is another reason for limiting the IR in patients in critical care.

Opinions on the role of adipose tissue are divided, because in most instances the function of insulin receptors has been taken from studies in which the binding of insulin to circulating monocytes and erythrocytes has been measured. However, such cells are not generally considered to be targets for insulin (10).

IR may be generally defined as the inability of insulin to stimulate the uptake of glucose from the blood. The rate of glucose uptake by skeletal muscle (GLUT 4, transporters stimulated by insulin) is reduced by half after an injury (1) ($0.36 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). This rate of glucose uptake is also the recommended maximum rate of glucose infusion into the organism without insulin application. The corresponding rate of glucose administration was $0.25 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in our infusions of glucose alone. For the mixed sugar solutions (fructose : glucose : xylitol = 2 : 1 : 1 w/w), which were administered with an infusion rate of $0.4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, the infusion rate for glucose was only $0.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

The slower administration of glucose should forestall any provocation of insulin secretion.

The euglycemic insulin clamp is generally accepted as the standard for considering IR (6), but it is hardly practical for daily use. Because of the difficulty in using the euglycemic clamp, the use of HOMA (6) with a statistically very significant ($P < 0.0001$) correlation was preferred.

Under normal conditions, the IR calculated by *Matthews et al.* (6) reflects the physiological ranges in the blood serum of glycemia ($3.9\text{--}6.1 \text{ mmol} \cdot \text{L}^{-1} = 70\text{--}110 \text{ mg/dL}$) and insulinemia ($10\text{--}20 \text{ mU} \cdot \text{L}^{-1} = 72\text{--}144 \text{ pmol} \cdot \text{L}^{-1}$), respectively. The true IR would then be greater than 5.45. However, the equation used for this calculation was purposely modified so that the IR limit was equal to 100. Hence the modification of HOMA for the given normal upper values and units is then: $\text{IR} = [\text{Glc}] \cdot [\text{Ins}] / 1.22$ (for normal values of IR up to 100).

The IR (calculated by using HOMA) is dependent on the time since the injury and on any surgical actions performed later. In our patient samples we did not have any “pure” post-traumatic cases, in which the metabolism would be altered solely by injury. Surgical interventions also took place on different days after the trauma.

From this point of view we could scarcely match pairs of patients in the control and “anti-insulin” groups who had the same time periods after both injury and surgical operation. Thus, the groups of patients include mixtures of the two time periods which were tested for statistical non-significance only as different whole groups.

Hence this arrangement shows greater variances.

Searching for match of drawn blood samples in any of the four criteria (given in *Table 1*) is the reason for different numbers of patients in the “anti-insulin” and the

control groups ($n = 7$ and 10 , respectively) in this (retrospective!!) study, however the number of samples ($n = 27$ and 26) was quite comparable.

The values of the IR in both groups were dependent upon age. No statistically significant differences between the ages of the patients in the control and the “anti-insulin” group were found.

The differences between the control and “anti-insulin” groups cannot be elucidated by means of body-mass indexes (BMI). The mean values of the BMI were practically the same in both groups.

The IR is in turn dependent on the time from the injury and on any consequently performed surgical actions. (The proper IR is usually described between 2 and 4, and sometimes up to 6 days after injury (I).)

The IR derived from glycemia is influenced by the energy delivered. No significant differences in the supply of energy (and nitrogen) were found in both groups (“anti-insulin” vs. control).

In our study we endeavoured to diminish the insulinemia by excluding the external application of insulin. The small portions of glucose applied limited increases in glycemia and thereby modified the internal secretion of insulin.

The IR could not be expressed as the sum of the insulinemias during the iv glucose tolerance test (ivGTT) or as an insulin clamp. These would have required the administration of glucose, which would have violated the arrangement of our study. Another reason was the retrospective nature of the study. (The IR presented in this way is less valid.)

Nearby all attempts to use the ivGTT led to substantial increases in IR in ensuing days. In traumatized patients the highest values that have been described (I) were up to $33 \text{ mmol} \cdot \text{L}^{-1}$ ($= 594 \text{ mg/dL}$) for hyperglycemia and up to $1000 \text{ mU} \cdot \text{L}^{-1}$ ($= 7200 \text{ pmol} \cdot \text{L}^{-1}$) for hyperinsulinemia. As *Table 2* shows, the hyperglycemia and hyperinsulinemia in our groups were inherently lower.

A very significant difference found in the nitrogen balance ($P < 0.0001$) is in contrast to reference (II), where we did not obtain a statistically significant difference in the nitrogen balance in similar comparable groups.

In our previous study (II) we observed statistically very significant differences in the concentrations of serum albumin (26.0 ± 5.82 vs. $32.7 \pm 5.84 \text{ g} \cdot \text{L}^{-1}$, $P < 0.001$), prealbumin (0.16 ± 0.075 vs. $0.31 \pm 0.123 \text{ g} \cdot \text{L}^{-1}$, $P < 0.001$), and transferrin (1.7 ± 0.59 vs. $2.3 \pm 0.87 \text{ g} \cdot \text{L}^{-1}$, $P < 0.001$) and slightly smaller differences in the activity of serum cholinesterase (38.9 ± 14.41 vs. $46.6 \pm 16.44 \text{ nkat} \cdot \text{L}^{-1}$, $P < 0.01$) – the values are given as the mean \pm SD and always as the control vs. the “anti-insulin” group, under conditions comparable to those in the present study.

In conclusion, IR may be reduced in the early post-traumatic phase by suitable use of parenteral nutrition. Favourable responses may also be achieved in some proteins of the blood plasma and in some cases in the nitrogen balance.

This metabolic response demands another study.

SNÍŽENÍ POSTTRAUMATICKÉ INZULINOVÉ REZISTENCE NEGLUKÓZOVÝMI ZDROJI ENERGIE

S o u h r n

Cílem této retrospektivní studie u pacientů s mnohočetnými poraněními je demonstrovat rozdíly ve vypočítané inzulinové rezistenci (IR) mezi „anti-inzulinovou“ skupinou a kontrolní skupinou, odhalit další vlivy na posuzované hodnoty a ukázat přínos parenterální výživy k poklesu IR.

Studie zahrnuje první dva týdny po traumatu.

IR byla vypočtena z glykemie a inzulinemie podle modelu hodnocení homeostaze, HOMA.

Na 5% hladině významnosti nebyly mezi skupinami nalezeny rozdíly v počtu dnů od úrazu, v počtu dnů od operace, ve věku a v kvocientu dodané energie a dále v hodnotách BMI.

„Anti-inzulinový“ model parenterální výživy byl převážně založen na pomalém podávání jen malých množství glukózy bez inzulinu (podávání inzulinu výhradně u diabetiků) a na používání převážně neglukózových zdrojů energie.

Nežádoucí vzestup inzulinemie má antilipolytický účinek, který má za následek nedostatek volných mastných kyselin, sloužících jako zdroj energie pro jaterní glukoneogenezi.

IR poskytla statisticky velmi významný rozdíl ($P < 0,001$). Velmi významný rozdíl byl nalezen také v dusíkové bilanci ($P < 0,0001$).

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