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The pathophysiology of Refeeding syndrome - Relation between insulin and triiodothyronine

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Abstract

Cancer, anorexia and alcoholism are diseases often associated with a prolonged semi starvation inducing reduced insulin secretion and other metabolic adaptions to the reduced energy intake. At resumption of adequate food intake, the increase insulin secretion and the cellular uptake of glucose, phosphate and potassium will increased. This may lead to a flow of electrolytes from plasma to the intracellular space affecting mainly phosphate, potassium and magnesium. The consequence being the refeeding syndrome with clinical manifestations of edemas, confusion, cardiac arrhythmias or even death. The precise pathophysiological background is not known, but experiments in rats have shown low p-insulin and p-T_3. Low p-T_3 is believed to be insulin dependent explained by the deiodinase which catalyze conversion of T4 to T3. Refeeding of three days fasten rats has shown increasing p-insulin followed by increasing p-T_3. The aim of this study was to evaluate, if the same mechanism could be responsible in humans.

In ten patients at high risk of developing refeeding syndrome four developed the syndrome, and the remaining six served as control. There was no significant difference in the percentage changes of p-insulin and p-T_3 between the group of refeeding patients and the control group and no correlation between p-insulin and p-T_3 in the refeeding-group of. No significant difference in the percentage changes of p-insulin and p-T3 and the severity of the refeeding syndrome and no relation between the severity of the refeeding syndrome and caloric intake. In the contrary there was a significant non-correlation ($p<0.05$) between the increase in p-insulin and p-T_3. The theory of increasing p-insulin followed by increasing p-T_3 found in rats is hardly applicable to humans.

Key words

Head and Neck cancer; Refeeding syndrome; Pathophysiology.

Introduction

Cancer, anorexia and alcoholism are diseases often associated whit a prolonged reduced caloric intake. The body adapts to the semi starvation by reduced insulin secretion and changes in the glucose metabolism. At the sudden resumption of adequate food intake, the increase insulin secretion and the cellular uptake of glucose, phosphate and potassium will increased. This may lead to a decrease of electrolytes in plasma mainly phosphate, potassium and magnesium which triggers the Refeeding Syndrome (RFS). Refeeding syndrome is an acute condition where fluid- and electrolyte imbalance occurs and can cause oedema, confusion, coma, arrhythmias or even death.

Millward et al [1] showed, that p-T_3 (tri-iodo-thyronine) and p-insulin decreased during fasting in rats, hypothetically because T_4-deiodinase, that catalyzes the conversion of T_4 to T_3 in many tissues, is insulin dependent, and a decline in p-insulin would lead to a lesser production of T_3. Also in rats it has been shown, that first p-insulin and later p-T_3 is increasing by feeding rats after three weeks of fasting [2].

We wanted to investigate, if the same phenomenon occurs in patients during refeeding syndrome by investigating, if the time sequence is the same as in rats.

Material and methods

Patients at high risk of developing refeeding syndrome were included based on defined inclusion criteria. The subjects were divided into two groups (refeeding and control group) based on development of refeeding syndrome (p-phosphat < 0.85 mmol/L) and clinical symptoms. Blood samples, diet registration and information about tobacco and alcohol consumption were collected in three days for each subject. Data were analyzed whit a focus on changes of p-insulin and p-T_3, dietary intake and severity of the refeeding syndrome.

Results and Discussion

Ten patients (Table 1) where included, of whom four developed refeeding syndrome, while six did not. We found no significant difference for the percentage changes of p-insulin and p-T_3 between the group of refeeding and the control group and no correlation between p-insulin and p-T_3 in the refeeding- group. In fact, the results of the time relation between the increase in insulin and T3 was maximally non-correlated ($p<0.05$). To obtain a confirmation of the Millward-hypothesis the next 22 refeeding patients should show perfect relations between increases in insulin followed by increases in triiodothyronine to reach significance. On this basis we stopped the inclusion of patients in this experiment. No significant difference was found in the percentage changes of p-insulin and p-T_3 and the severity of the refeeding syndrome, and no relation between the developed refeeding syndrome (p-phosphate) and caloric intake. None of the other measured blood parameters (TSH, T_4, c-peptide, glucose, hemoglobin, albumine, carbamide, creatininum, sodium, potassium and magnesium) was significantly different for the two groups. The theory of increasing p-insulin followed by increasing p-T_3, found in rats cannot be confirmed by the subjects who develop refeeding syndrome this study.

Table 1: Ten patients at high risk of developing the refeeding syndrome. Four patients developed the syndrome, six did not. Median, range. w

	Refeeding syndrome	No refeeding syndrome
Number M/F	4/0	05/1
Age (yr)	51, 44-62	63, 55-89
BMI (kg/m^2)	18.7, 16.7-20.7	16.6, 12.1-22.8

Table 2: p-insulin (pmol/L) and p-T_3 (nmol/L), day one to three after start of feeding in patients with and without refeeding syndrome (RFS) (normal values for the laboratory).

Patients	p-Insulin (10-125 mol/L)			p-T_3 (1.4-2.8 nmol/L)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
RFS-group						
A	112	69	49	1.2	1.5	1.4
E	40	66	70	1.5	1.8	1.4
H	33	20	31	1.4	1.5	1.6
I	*	39	68	0.9	0.9	0.9
Median [range]	40 [33-112]	52.5 [20-69]	68 [31-70]	1.3 [0.9-1.5]	1.5 [0.9-1.8]	1.4 [0.9-1.6]
Non-RFS-group						
B	16	14	21	0,9	1,1	1
C	31	12	-	1,9	1,5	-
D	3	2	2	0,9	0,7	0,8
F	6	11	16	1,2	1,2	1,1
G	62	50	55	1,4	1,7	1,6
J	57	24	-	2,2	2,3	-
Median [range]	31 [3-62]	14 [2-52.5]	21 [2-58.5]	1.3 [0.9-2.2]	1.5 [0.7-2.3]	1.1 [0,8-1.6]

*blood sample hemolyzed
- no data as the patients was discharged on day two

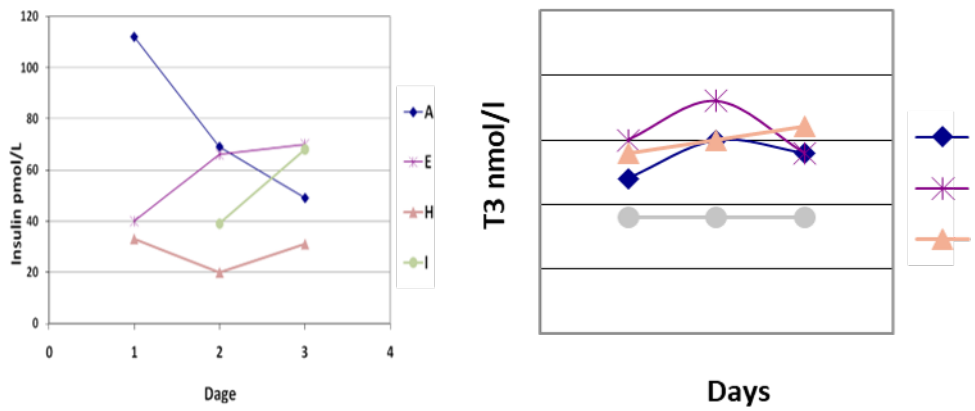

Figure 1: Plasma insulin and T3 for the first 3 days after start of feeding in 4 patients with refeeding syndrome.

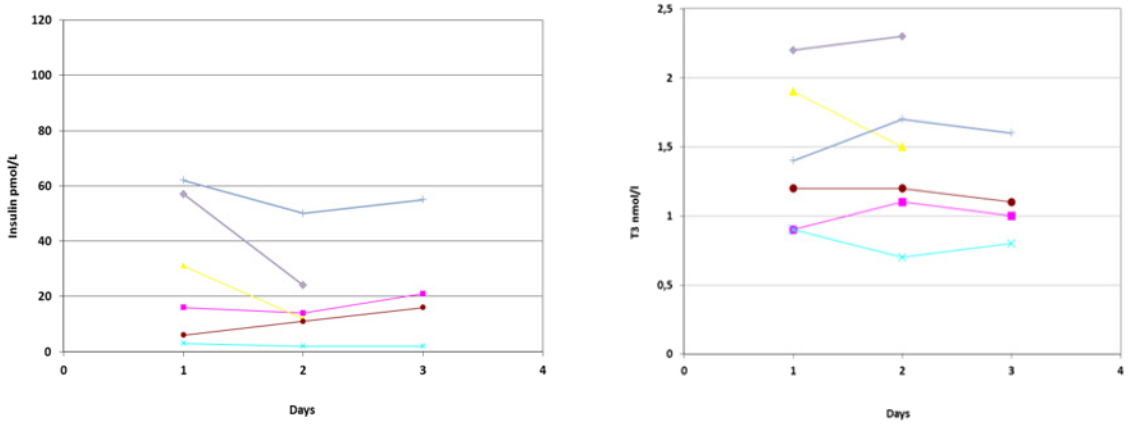

Figure 2: Plasma insulin and T3 for the first 3 days after start of feeding in 6 patients at risk of the refeeding syndrome, but who did not develop the clinical condition.

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