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Insulin Treatment in Cancer Cachexia: Effects on Survival, Metabolism, and Physical Functioning

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Abstract

Purpose: The present study was designed to evaluate whether daily insulin treatment for weight-losing cancer patients attenuates the progression of cancer cachexia and improves metabolism and physical functioning in palliative care.

Experimental Design: One hundred and thirty-eight unselected patients with mainly advanced gastrointestinal malignancy were randomized to receive insulin (0.11 ± 0.05 units/kg/d) plus best available palliative support [anti-inflammatory treatment (indomethacin), prevention of anemia (recombinant erythropoietin), and specialized nutritional care (oral supplements + home parenteral nutrition)] according to individual needs. Control patients received the best available palliative support according to the same principles. Health-related quality of life, food intake, resting energy expenditure, body composition, exercise capacity, metabolic efficiency during exercise, and spontaneous daily physical activity as well as blood tests were evaluated during follow-up (30-824 days) according to intention to treat.

Results: Patient characteristics at randomizations were almost identical in study and control groups. Insulin treatment for 193 ± 139 days (mean $\pm$ SD) significantly stimulated carbohydrate intake, decreased serum-free fatty acids, increased whole body fat, particularly in trunk and leg compartments, whereas fat-free lean tissue mass was unaffected. Insulin treatment improved metabolic efficiency during exercise, but did not increase maximum exercise capacity and spontaneous physical activity. Tumor markers in blood (CEA, CA-125, CA 19-9) did not indicate the stimulation of tumor growth by insulin; a conclusion also supported by improved survival of insulin-treated patients ($P < 0.03$).

Conclusion: Insulin is a significant metabolic treatment in multimodal palliation of weight-losing cancer patients.

Alterations in the classic hormone system are major effector mechanisms behind changes in whole body metabolism and nutritional state during tumor progression (1). Most hormones are involved, but insulin resistance appeared early as a presumable abnormality contributing to weight loss (2), although changes in the noradrenergic system (3), growth hormone/insulin-like growth factor I (IGF-I) axis (4, 5), thyroid hormones, and glucocorticoids contribute, but additional hormones such as leptin, ghrelin, and other neuroendocrine factors are also important (6–9). Most hormonal changes are interrelated to other metabolic pathways as increased activities of eicosanoids, growth factors, and cytokines (10–12). Accordingly, our previous studies have confirmed clinical improvements by systemic anti-inflammatory treatment (13, 14), prevention of anemia (15), and nutritional support to patients with cancer (4). However, reevaluation of alterations in body composition in our cancer patients on multimodal treatment unexpectedly revealed that whole body fat, which predicts survival, was lost despite effective supportive care indicated by stable lean body mass during tumor treatment (8). Based on these and other observations, it seemed appropriate to consider antilipolytic treatment to attenuate cachexia progression. Consequently, a simple concept would be to treat weight-losing cancer patients with insulin as suggested half a century ago (16). Therefore, the present study was designed to evaluate whether daily treatment with long-acting insulin for weight-losing cancer patients would attenuate the progression of cancer cachexia and improve host metabolism without harmful side effects in unselected cancer patients.

Materials and Methods

Study population

One hundred and thirty-eight patients with advanced gastrointestinal malignancies were randomized at the Department of Surgery,

Sahlgrenska University Hospital, Göteborg, Sweden between 2000 and 2005 to receive daily insulin treatment plus best available palliative support (study group) versus best available palliative support (control group; Table 1). Inclusion criteria consisted of manifest weight loss due to generalized malignant disease and solid tumor type. Exclusion criteria were tablet- or insulin-dependent diabetes, brain metastases, expected survival of <6 months, impaired kidney function (serum creatinine >200 μmol/L), increased body temperature to 37.8°C, and persistent cholestasis (serum bilirubin >21 μmol/L). Study and control patients experienced a comparable extent of generalized disease, i.e., frequency of liver and lung metastases.

Intervention

Insulin treatment. Insulin treatment started when unstable weight reappeared corresponding to 2% to 3% of referral weight in combination with serum albumin <36 g/L. This level was chosen because it coincides with a sharp increase in reverse serum T_3 (rT_3), indicating an overall shortage of energy availability (7). Insulin was provided as s.c. injections of long-acting insulin (Insulatard, Flexpen, Novonordisk AB, Copenhagen, Denmark) once daily at increasing doses aimed to approach 10 to 16 units/d. Insulin started at 4 units/d with a stepwise increase of 2 units for 5 to 7 days until the intended dose levels were reached based on pure clinical grounds and our treatment experience accounting for disease state, weight loss, and patients' subjective feeling. Blood glucose was not monitored, but patients were recommended to decrease insulin by 2 units or interrupt medication if any strange sensation appeared not manageable by juice, milk, or food intake. It was recommended that the insulin dose be provided with breakfast or lunch intake. Patients who mainly relied on parenteral nutrition received s.c. insulin at the start of daily infusions. Two patients experienced insulin coma: one self-administering nurse who was particularly trained with insulin injections and may have deliberately provided an inappropriately high dose. She displayed cognitive sequelae for a comparatively long time period afterwards. Another female took insulin at 6 a.m. in the morning against our prescriptions and went back to sleep without eating breakfast. She experienced no sequelae afterwards. Otherwise, no complications to insulin were seen. Hypoglycemic-like sensations were very infrequent. Altogether, 54 study patients received insulin treatment, whereas only one control patient was provided insulin due to increasing blood glucose.

Best available support

Indomethacin, erythropoietin treatment, and nutrition care. All patients received our best standard treatment, which included oral indomethacin when deemed appropriate (13), recombinant erythropoietin when necessary (15), and specialized nutrition care according to defined criteria (4, 17). Indomethacin (25-50 mg twice daily) was provided to patients with elevated erythrocyte sedimentation rate (>35 mm h^{-1}) and abnormal C-reactive protein (≥10 μg/mL). All patients who received indomethacin were prophylactically treated with Ome-

prazol to protect against gastric ulcer and micro-bleeding. Indomethacin was provided on average at 85 ± 3 mg/d in study patients and 78 ± 2 mg/d in controls during 24% and 29% of the entire follow-up period. Altogether, 89 patients received indomethacin without any difference between study and control patients.

S.c. injection of recombinant erythropoietin (Eprex; Janssen-Cilag, Stockholm, Sweden; dose range, 12,000-40,000 IU/wk) was continuously given twice weekly when blood hemoglobin concentration decreased below subnormal limits (128 g/L for men and 120 g/L for women) until hemoglobin levels were normalized (15). Thus, patients without insidious anemia did not receive erythropoietin. Erythropoietin was provided on average at $20,137 \pm 1,372$ units/wk to study patients and $22,000 \pm 2,216$ units/wk to the controls during 6% and 4% of the entire follow-up period, respectively. Altogether, 41 patients received erythropoietin without any difference between study and control patients.

All patients had food intake assessed by a dietitian at inclusion, and repeatedly, according to 4-day records (18). The estimated energy balance was derived as intake minus resting energy expenditure because most patients had a low level of daily physical activity. Nutrition care consisted of supplemental oral nutrition when food intake decreased to <90% of the expected intake (19). Oral nutritional support consisted of nutritional counseling and provision of oral supplements (450-600 kcal/d) according to individual taste preferences (Semper, Nutricia; Fresenius Kabi, Bad Homburg, Germany). Home parenteral nutrition was provided when oral intake decreased further to ~70% to 80% of the expected levels (4). Parenteral nutrition was administered via a peripherally inserted central catheter (Piccline) placed through the cephalic vein and provided as an "all in one" (Kabimix Basal, Kabiven; Fresenius Kabi), including additives (vitamins, minerals, trace elements; Fresenius Kabi) according to general daily recommendations (provided at night 20-25 kcal/kg/d; 0.10-0.15 g nitrogen/kg/d; infused over 12-18 h). Study patients received, on average, $1,008 \pm 58$ kcal/d and controls $1,221 \pm 93$ kcal/d on home parenteral nutrition during 5% and 4% of the entire follow-up period. Enteral tube feeding was not provided (17). Altogether, 64 patients received home parenteral nutrition without any difference between study and control patients.

Treatments continued until death or until the patient was unable or unwilling to participate. All study and control patients had generalized disease without available specific treatment, although 11 patients received palliative chemotherapy with reduced doses (50-70% of standard; gemcitabine as first line, fluorouracil/leucovorin; Oxaliplatin as second line) without differences between study and control patients. Analgesics (paracetamol, morphine) were provided according to individual needs. The current study was approved by the Ethics Committee of the Medical Faculty at Göteborg University.

Measurements at inclusion and follow-up

Measurements were done for use in randomization using a computerized algorithm (20), accounting for tumor type, tumor stage, previous tumor treatment (surgery, chemotherapy, or radiotherapy), age, gender, height, nutritional status (body weight, weight loss, serum albumin concentration, arm muscle circumference, triceps skinfold), liver function tests (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels); serum creatinine levels, blood hemoglobin concentration and erythrocyte sedimentation rate; and previous use of analgesics, β-blockers, and nonsteroidal anti-inflammatory drugs. These measurements were part of patient follow-up measurements at ~2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 months after inclusion. Physiologic variables at rest included heart rate, systolic and diastolic blood pressure, body temperature, respiratory rate, and energy expenditure. Analgesics were assessed before and during follow-up.

Nutritional assessment. Body composition was measured by dual-energy X-ray absorptiometry (17).

Table 1. Diagnoses among patients randomized to insulin treatment and controls

	Insulin	Controls	Total
Esophageal/gastric carcinoma	29	24	53
Liver, bile duct carcinoma	3	9	12
Pancreatic carcinoma	24	20	44
Colorectal carcinoma	6	9	15
Primary tumor unknown	4	1	5
Miscellaneous	3	6	9
Total	69	69	138

Table 2. Patient characteristics at randomization in study (insulin) and control patients

	Insulin (69)	Controls (69)
Weight (kg)		
Before disease	76 ± 1.9	74 ± 2.0
At inclusion	69 ± 1.6	66 ± 1.7
Weight loss (%)	10 ± 1	10 ± 1
Age	70 ± 1	70 ± 1
Height (cm)	172 ± 1	170 ± 1
Serum creatinine (μmol/L)	96 ± 4	89 ± 3
Serum bilirubin (μmol/L)	12 ± 2	11 ± 1
ALP (μkat/L)	7 ± 1	10 ± 2
ASAT (μkat/L)	0.6 ± 0.06	0.7 ± 0.07
ALAT (μkat/L)	0.6 ± 0.09	0.6 ± 0.09
Blood hemoglobin (g/L)	122 ± 2	124 ± 2
ESR (mm/h)	38 ± 3	39 ± 3
C-reactive protein (mg/L)	28 ± 6	32 ± 6
Serum albumin (g/L)	34 ± 0.5	34 ± 0.7

NOTE: Mean ± SE (normal values). ALP, alkaline phosphatase (normal value, <5); ASAT, aspartate amino acid transferase (normal value, <0.8); ALAT, alanine amino acid transferase (normal value, <0.8); ESR, erythrocyte sedimentation rate (<28).

Blood tests. Blood chemistry analyses included hemoglobin, glucose, insulin, C-peptide, triglycerides, free fatty acids, WBC and thrombocyte counts, erythrocyte sedimentation rate, C-reactive protein; albumin, electrolyte, and creatinine levels; liver function tests, and tumor markers (CEA, CA 19-9, CA-125).

Indirect calorimetry. Resting energy expenditure was measured by indirect calorimetry (Deltratrac; Datex, Helsinki, Finland) in the morning after an overnight fast (18, 21).

Maximum exercise test. Maximum physical capacity (in watts) was the point at which the patient experienced subjective exhaustion and stopped (15). Oxygen uptake and carbon dioxide production were measured during exercise (ref. 15; Medical Graphics Corp., St. Paul, MN).

Quality of life. Health-related quality of life was assessed by one global (SF-36) and one cancer-specific instrument (EORTC QL40; ref. 22).

Daily physical activity. Spontaneous daily activity was measured by the ActiGraph system (MTI Health Services, Fort Walton Beach, FL; ref. 23). Activity counts represent a quantitative measure of physical activity over time.

Analysis and sample size

The study was designed to test whether insulin treatment, in addition to the best available supportive care, would improve the metabolic effects of insulin [body composition, food intake; maximum exercise capacity including metabolic efficiency (watts, watts/oxygen uptake)] with an α of 0.05 and β of 0.80. Estimates on primary variables indicated that 120 to 130 randomized patients would allow the detection of 15% to 20% improvements in any of the primary variables. Survival was only deemed a secondary study variable and power estimates on survival were therefore not done in the study design. Statistical evaluations were done by nonparametric analysis between and within groups over time by the log-rank technique according to "intention to treat." Statistical computations included all observations on all patients at inclusion and during the entire follow-up. In presentations, data are grouped corresponding to "at inclusion", "at 4, 8, and beyond 12 months follow-up." Post hoc testing was not done because the hypothesis being examined covered the entire treatment period for each individual. Survival curves were calculated by Kaplan-Meier analysis and statistical testing was done according to Mantel-Cox log-rank analysis. Survival time was calculated from the day of study inclusion until death confirmed as signed registration in the National Swedish Cancer Register.

Results

One hundred thirty-eight patients were randomized to receive study (n = 69) or control (n = 69) treatment. Patient characteristics at inclusion were almost identical (Table 2). The number of patients receiving insulin, indomethacin, erythropoietin, palliative chemotherapy, β-blocker, and home parenteral nutrition are indicated in Table 3. Insulin was provided between 7 and 548 days [193 ± 139 days (mean ± SD); 150 days (median)] at an average dose of 10 ± 6 units/d (mean ± SD); range 4 to 30 units/d. The average insulin dose was 0.11 ± 0.05 units/kg/d (mean ± SD). One patient in the

Table 3. Number of patients on various regimens at defined follow-up (4, 8, and 12 mos)

	Group	Months of follow-up				Between groups over time
		0	4	8	12	
Insulin	O		7	4	2	—
	I	69	39	22	8	
	C	69	34	16	5	
Indomethacin	I	24	20	8	5	ns
	C	29	19	11	6	
Recombinant erythropoietin	I	3	5	3	1	ns
	C	0	3	3	1	
Palliative chemotherapy	I	0	4	0	1	ns
	C	1	2	2	1	
Beta-blocker	I	13	8	3	2	ns
	C	13	5	2	1	
Home parenteral nutrition	I	3	4	1	4	ns
	C	4	2	0	4	

NOTE: Nonparametric log-rank technique.
Abbreviations: O, patients randomized to insulin without insulin treatment; I, insulin-treated patients; C, controls; ns, not significant.

control group received insulin due to increased blood glucose (~ 0.05 units/kg/d).

Food intake. Insulin treatment did not stimulate overall daily caloric intake during the entire follow-up, although insulin caused numerically higher intake between 4 and 12 months (Table 4). However, carbohydrate intake was significantly increased by insulin, whereas fat and protein intake did not increase.

Body composition. Body weight did not differ among study and control patients during follow-up, whereas body fat, in trunk and leg compartments, was significantly higher during follow-up in study patients ($P < 0.03$). Lean tissue mass did not differ among study and control patients during follow-up (Table 4).

Clinical and biochemical characteristics. Blood hemoglobin, serum albumin, and erythrocyte sedimentation rate did not differ between study and control patients during follow-up,

also true for resting energy expenditure as well as whole body carbohydrate and fat oxidation. However, carbohydrate oxidation increased over time in insulin-treated patients (Table 5).

Circulatory measures (pulse rate, blood pressure) did not differ between the groups over time. Insulin improved metabolic efficiency during exercise ($P < 0.04$; Fig. 1), whereas maximum exercise capacity and pulse rate 1 min after maximum work load did not differ. Serum-free fatty acids was significantly lowered by insulin during follow-up, whereas triglycerides, IGF-I, C-peptide, and glucose did not differ among study and control patients during follow-up (Table 5). As expected, serum insulin was significantly higher in study patients compared with controls ($P < 0.003$). Serum insulin and C-peptide showed a trend to increase over time in study patients ($P < 0.06$-0.09).

Tumor markers. Alterations in tumor markers did not show consistent changes during follow-up. CEA increased during

Table 4. Daily food intake and composition in study (insulin) and control patients at randomization and follow-up analyzed as intention to treat in relationship to alteration in body composition

Group	Months of follow-up				Between groups over time (*P*)
	0	**4**	**8**	**12**	
Food intake (kcal/d)					
I	$1,799 \pm 97$	$1,900 \pm 158$	$1,946 \pm 220$	$2,017 \pm 236$	ns
C	$1,784 \pm 74$	$1,710 \pm 112$	$1,869 \pm 139$	$1,602 \pm 99$	
Carbohydrate (g/d)					
I	208 ± 10	232 ± 21	224 ± 17	219 ± 25	<0.009
C	199 ± 9	199 ± 9	204 ± 13	171 ± 11	
Fat (g/d)					
I	75 ± 6	75 ± 8	79 ± 15	84 ± 13	ns
C	72 ± 4	69 ± 7	79 ± 9	66 ± 4	
Protein (g/d)					
I	70 ± 4	73 ± 5	79 ± 12	87 ± 11	ns
C	70 ± 3	66 ± 5	73 ± 6	63 ± 3	
Body weight					
I	67.6 ± 1.7	67.1 ± 2.7	70.3 ± 4.9	76.8 ± 5.4	ns
C	67.2 ± 2.2	67.7 ± 4.0	65.6 ± 7.2	69.7 ± 4.2	
Body fat					
I	16.8 ± 1.0	17.1 ± 1.5	18.3 ± 2.2	18.9 ± 2.6	<0.02
C	15.9 ± 1.0	17.0 ± 1.7	14.9 ± 2.4	14.1 ± 1.2	
Fat trunk					
I	8.88 ± 0.64	8.82 ± 0.86	9.88 ± 1.41	10.63 ± 1.71	<0.03
C	8.13 ± 0.61	8.92 ± 1.0	7.92 ± 1.67	7.23 ± 0.85	
Fat arm					
I	1.63 ± 0.10	1.68 ± 0.15	1.76 ± 0.20	1.82 ± 0.26	ns
C	1.58 ± 0.10	1.71 ± 0.18	1.57 ± 0.26	1.43 ± 0.13	
Fat leg					
I	5.60 ± 0.34	5.91 ± 0.53	5.97 ± 0.63	5.75 ± 0.72	<0.03
C	5.42 ± 0.30	5.61 ± 0.51	4.69 ± 0.63	4.69 ± 0.29	
LTM					
I	47.6 ± 1.2	48.6 ± 1.7	49.9 ± 2.2	51.3 ± 2.4	ns
C	46.9 ± 1.3	47.4 ± 2.1	49.2 ± 3.4	49.2 ± 2.1	
LTM trunk					
I	24.6 ± 0.5	24.6 ± 0.9	25.3 ± 1.2	26.3 ± 1.3	ns
C	24.3 ± 0.7	24.9 ± 1.1	25.2 ± 1.7	24.4 ± 0.9	
LTM arm					
I	4.9 ± 0.2	5.1 ± 0.3	5.2 ± 0.3	5.3 ± 0.3	ns
C	4.7 ± 0.2	4.8 ± 0.3	5.0 ± 0.5	5.4 ± 0.4	
LTM leg					
I	14.8 ± 0.4	15.3 ± 0.6	15.7 ± 0.7	16.0 ± 0.7	ns
C	14.6 ± 0.4	14.3 ± 0.7	15.5 ± 1.1	15.8 ± 0.8	

NOTE: Mean $\pm$ SE. Body composition (kg) was measured by DEXA technique. Food intake is the average of 4 days' recordings as described in Materials and Methods.
Abbreviations: I, insulin-treated patients; C, controls; LTM, lean tissue mass.

Table 5. Time course changes of clinical characteristics in study (insulin) and control patients analyzed as intention to treat

	Group	Months of follow-up				Between groups over time (*P*)	Within groups over time (*P*)
		0	4	8	12		
Inflammation							
Hemoglobin (g/L)	I	123 ± 2	126 ± 3	124 ± 6	129 ± 3	ns	ns
	C	125 ± 2	122 ± 3	128 ± 4	127 ± 2	ns	ns
ESR (mm/h)	I	38 ± 3	30 ± 4	34 ± 8	35 ± 5	ns	ns
	C	38 ± 3	43 ± 6	31 ± 7	18 ± 5	ns	ns
Serum albumin (g/L)	I	34 ± 1	33 ± 1	32 ± 2	33 ± 1	ns	ns
	C	34 ± 1	32 ± 2	34 ± 2	33 ± 1	ns	ns
Resting energy expenditure (kcal/d)	I	1,490 ± 30	1,422 ± 51	1,477 ± 74	1,647 ± 97	ns	ns
	C	1,453 ± 39	1,477 ± 73	1,421 ± 96	1,428 ± 58	ns	ns
RQ	I	0.80 ± 0.01	0.82 ± 0.01	0.81 ± 0.02	0.85 ± 0.02	ns	ns
	C	0.81 ± 0.01	0.82 ± 0.01	0.80 ± 0.02	0.82 ± 0.01	ns	ns
Carbohydrate* oxidation (g/d)	I	104 ± 9	125 ± 17	113 ± 19	181 ± 26	ns	<0.02
	C	117 ± 10	126 ± 16	93 ± 21	119 ± 9	ns	ns
Fat oxidation* (g/d)	I	90 ± 4	73 ± 6	84 ± 10	73 ± 10	ns	ns
	C	80 ± 5	79 ± 7	87 ± 14	77 ± 7	ns	ns
Pulse rate at rest (beats/min)	I	73 ± 1	70 ± 2	75 ± 3	76 ± 3	ns	ns
	C	73 ± 2	73 ± 3	69 ± 4	64 ± 1	ns	ns
Systolic blood Pressure (mm Hg)	I	134 ± 2	135 ± 5	131 ± 3	126 ± 4	ns	ns
	C	138 ± 3	132 ± 3	132 ± 5	130 ± 3	ns	ns
Diastolic blood pressure (mm Hg)	I	76 ± 1	74 ± 2	74 ± 2	76 ± 2	ns	ns
	C	76 ± 1	75 ± 2	79 ± 3	76 ± 1	ns	ns
Maximum exercise capacity (W)	I	88 ± 7	95 ± 10	96 ± 23	100 ± 10	ns	ns
	C	79 ± 7	85 ± 14	132 ± 55	141 ± 14	ns	<0.01
Pulse rate (1 min after exercise)	I	114 ± 4	117 ± 5	98 ± 14	87 ± 4	ns	ns
	C	114 ± 34	103 ± 7	125 ± 19	132 ± 4	ns	<0.01
Glucose (mmol/L)	I	6.2 ± 0.2	6.6 ± 0.3	7.2 ± 0.7	7.8 ± 0.5	<0.01	ns
	C	6.2 ± 0.2	6.1 ± 0.2	5.8 ± 0.4	5.1 ± 0.2	ns	ns
Serum insulin (units/L)	I	8 ± 2	9 ± 2	12 ± 3	21 ± 5	<0.003	<0.06
	C	8 ± 1	8 ± 1	5 ± 1	6 ± 1	ns	<0.09
C-peptide (nmol/L)	I	0.8 ± 0.1	0.7 ± 0.09	1.0 ± 0.2	1.2 ± 0.3	ns	
	C	0.8 ± 0.1	0.8 ± 0.11	0.56 ± 0.13	0.62 ± 0.16	ns	<0.06
IGF-I (μg/L)	I	117 ± 8	113 ± 12	108 ± 12	90 ± 9	ns	ns
	C	106 ± 7	107 ± 11	106 ± 17	129 ± 5	ns	ns
Serum-free fatty acids (mmol/L)	I	0.57 ± 0.03	0.66 ± 0.09	0.44 ± 0.05	0.39 ± 0.05	<0.04	<0.03
	C	0.67 ± 0.03	0.57 ± 0.05	0.67 ± 0.16	0.59 ± 0.02	ns	ns
S-TG (mmol/L)	I	1.10 ± 0.07	1.13 ± 0.10	1.20 ± 0.17	1.03 ± 0.10	ns	ns
	C	1.17 ± 0.08	1.11 ± 0.12	0.96 ± 0.15	1.26 ± 0.72	ns	ns

NOTE: Mean ± SE.
Abbreviations: I, insulin-treated patients; RQ, respiratory quotient; C, controls; ESR, erythrocyte sedimentation rate.
*Measured at rest.

follow-up in the insulin group, whereas CA-125 was unchanged and CA 19-9 decreased over time in study patients compared with controls (Table 6).

Health-related quality of life. The general (SF-36) and cancer-specific instruments (EORTC Q40) did not indicate improved conditions in quality of life in study patients during follow-up compared with controls.

Survival and daily physical activity. Survival was significantly improved in insulin-treated patients (*P* < 0.03; Fig. 2A and B) compared with controls [study patients, 224 ± 163 days; controls, 175 ± 148 days (mean ± SD); 181 versus 128 days (median)]. This improvement was not related to increased daily spontaneous activity (Fig. 3).

Discussion

Palliative care for patients with cancer is based on various modalities appearing from basic knowledge in cachexia
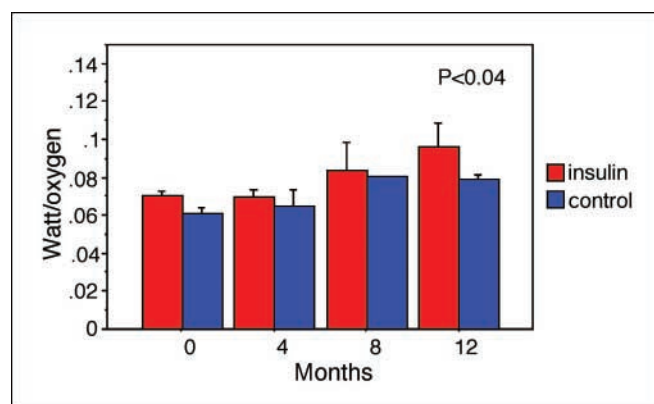

Fig. 1. Metabolic efficiency in study (insulin) and control patients during performance of a near-maximum exercise test at follow-up as described in Materials and Methods (*P* < 0.04 was calculated as the difference between groups over time as described in Results).

Table 6. Time course changes of tumor markers in systemic venous blood during follow-up in study (insulin) and control patients analyzed as intention to treat

Tumor markers	Group	Months of follow-up							Between groups over time (P)	Within groups over time (P)
		0	2	4	6	8	10	12		
CA 125 (u/L)	I	80 ± 19	178 ± 69	125 ± 51	47 ± 11	112 ± 47	76 ± 30	111 ± 32	ns	ns
	C	109 ± 22	96 ± 23	113 ± 25	170 ± 42	110 ± 45	233 ± 67	204 ± 92		
CE A (u/L)	I	312 ± 259	989 ± 849	278 ± 239	503 ± 495	760 ± 747	1,633 ± 1,623	1,518 ± 1,041	<0.07	<0.01
	C	505 ± 467	809 ± 794	1,390 ± 1,354	104 ± 96	21 ± 10	34 ± 22	5 ± 3		
CA 19-9 (u/L)	I	1,494 ± 1,188	2,911 ± 1,714	336 ± 182	349 ± 308	1,107 ± 1,066	3,499 ± 3,155	98 ± 52	<0.03	<0.009
	C	9,244 ± 4,964	1,316 ± 569	4,917 ± 3,136	3,838 ± 3,082	2,146 ± 1,879	5,279 ± 4,797	19 ± 7		<0.08

NOTE: Mean ± SE.
Abbreviations: I, insulin-treated patients; C, controls; u/L, units/L.

research and pain treatment. Conceptually, it is easiest to evaluate the importance of new treatments in homogenous groups of patients within short time periods. However, patients' request do not allow simple models. Efforts to improve health-related quality of life, physical functioning, decreased fatigue, vomiting, and pain represent all necessary alternatives to offer cancer patients. We have earlier reported that systemic anti-inflammatory treatment by nonsteroidal anti-inflammatory drugs (indomethacin), prevention of anemia by provision of recombinant erythropoietin, and supportive nutrition represent significant treatments of weight-losing cancer patients (8, 13–15). Therefore, it is necessary to include such treatments as best available care on an individual patient basis. Presently, we have evaluated the effect of insulin treatment on top of the best available support. Our test model includes both advantages and disadvantages. The advantage is a realistic treatment situation, whereas it may be that various combinations of interventions interact differently among patients; a fact difficult to compensate for in statistical computations on cohorts with a limited number of patients. However, it is our experience that this kind of complex modeling provides valuable clinical information and represents the only realistic alternative in the scientific development of palliative care (4).

Early studies on cachectic cancer patients showed glucose intolerance in combination with altered whole body carbohydrate metabolism (24–28), in which animal work implied that insulin would beneficially overcome some of these problems (29–31). Observations indicated that glucose intolerance might appear early in cancer, even before weight loss and anorexia (32). Glucose intolerance was also observed independently of the presence of tumor tissue (33), indicating hormonal and enzymatic adaptations in host liver, fat (34), and muscles (35). Defective insulin production and increased insulin clearance during feeding may also contribute to glucose intolerance in cancer. However, graded doses of insulin infusions to cancer patients confirmed insulin resistance in glucose homeostasis of peripheral tissues (36), whereas insulin effects on amino acid flux did not indicate resistance (35, 37), which agrees with the findings of insignificant effects on muscle mass by insulin in the present study, although IGF-I had clear-cut effects to protect muscle wasting in experimental tumor bearers (38).

Several of our previous studies on patients with cancer suggested metabolic abnormalities related to insulin (39), both in feeding (26, 40) and fasted states (24). It has been repeatedly emphasized that loss of lean tissue in cancer disease is most
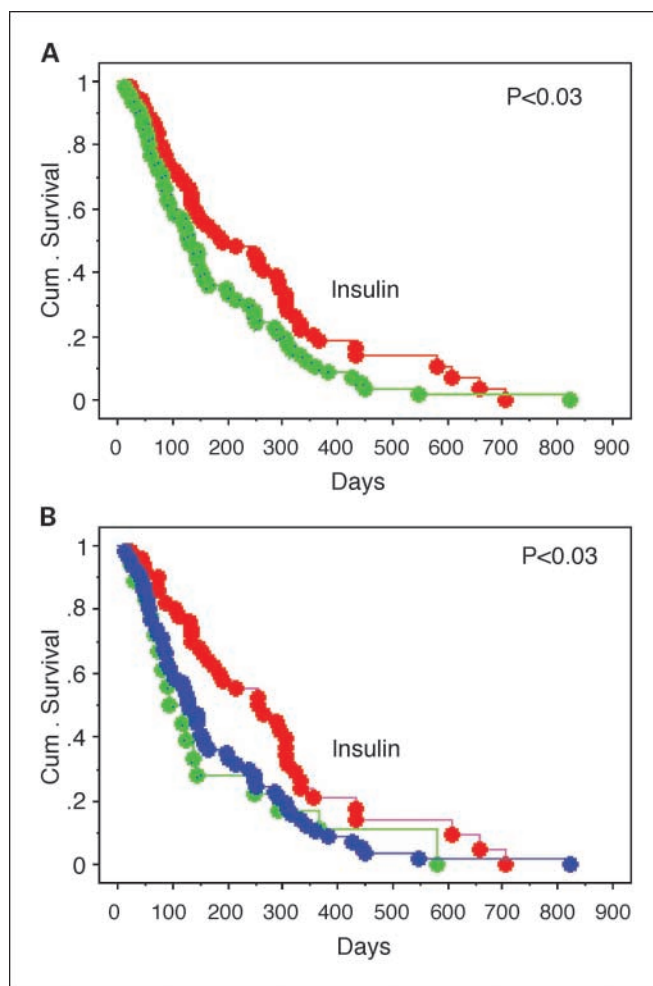

Fig. 2. *A*, survival analysis in study (insulin) and control patients analyzed as intention to treat. *B*, survival analysis in study (insulin) and control patients analyzed per protocol: control patients (*green*), study patients who did not receive insulin (*blue*).

important in the progression of cachexia hampering well-being and physical functioning. However, recent analyses on longitudinal measurement of body compositions implied that loss of body fat remained or even progressed despite appropriate caloric intake and stable lean tissue mass (8). Based on this information, it is obvious that additional factors are necessary for the improvement of integrative anabolism in feeding patients with cancer (26). Therefore, it was logical to assume that insulin might have a role in improving anabolism or at least attenuating catabolism during disease progression.

Study and control patients were extremely well balanced regarding clinical characteristics at inclusion. Insulin treatment stimulated carbohydrate intake, although the increase of overall caloric intake did not reach statistical significance. Serum insulin increased over time in study patients, whereas it decreased in control patients. A similar pattern was observed on circulating C-peptide, supporting that exogenous insulin did not counteract endogenous production. Higher serum insulin did not change IGF-I levels, which may explain the dissociated effects by insulin on whole body fat and lean tissue, although it has never been shown that insulin in itself is a major factor to control long-term muscle protein balance in man (37, 41, 42). As expected, serum-free fatty acids decreased significantly following insulin treatment, which was probably translated into significantly improved whole body fat in study patients, particularly in trunk and leg compartments dependent on both increased lipogenesis and decreased lipolysis (24, 26, 40). Observations that lean tissues (protein metabolism) were less affected compared with whole body fat is in line with our previous findings in acute experiments with insulin to normal individuals (41). Interestingly, the overall effects of insulin were translated into increased metabolic efficiency, derived as oxygen consumed per watt produced at maximum work load. This may imply facilitated physical functioning, perhaps due to improved glycogen content and glucose transporting in muscles (43). However, this positive effect was not translated into elevated maximum exercise capacity or increased spontaneous physical activity, which may be more dependent on overall cardiovascular and mental functioning than integrative metabolism. Also, self-reported evaluation of health-related quality of life indicated that positive objective metabolic effects by insulin may not be translated into improved self-scored physical functioning, which agree with previous observations in non–cancer patients (44).

Previous epidemiologic and cellular work has suggested that insulin and IGF-I may be risk factors in cancer (45, 46). There are several explanations for this phenomenon, particularly in cell culture experiments (47). However, complex *in vivo* conditions are usually the net result of both positive and negative factors. Although there is no doubt that both insulin and IGF-I may stimulate tumor growth, such effects may be
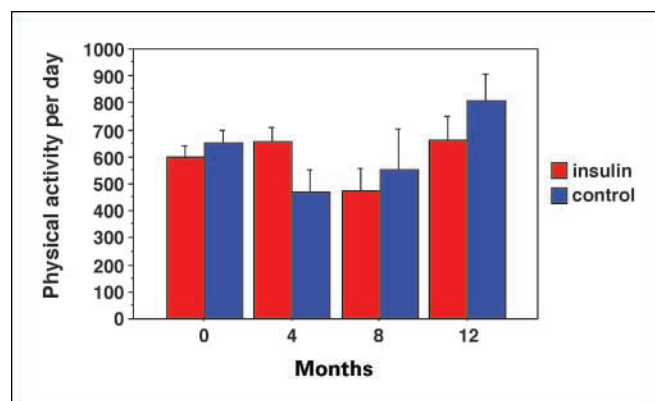

Fig. 3. Average (5 d) daily physical activity in study (insulin) and control patients at follow-up registered by the Actigraph technique as described in Materials and Methods. Observations were not statistically different over time between groups or within groups.

overcome by counteracting or improved metabolic status by insulin, a concept which has support in experimental models (30, 31, 38), in which recent conclusions on the Warburg effect and anaerobic glycolysis in malignant tumors seem to be increasingly interesting in light of the present results with improved survival of insulin-treated patients (48). There are also other clinical conditions in which insulin decreased mortality, in part, unrelated to effects on glucose homeostasis (49). The effects of insulin in improving postoperative outcome and function in non–cancer patients are also well-recognized (50). Fat tissue, which is probably a major target during insulin supplementation to cachectic cancer patients, is well recognized to produce a variety of signals and metabolic factors in response to hormones (51), although the present effects of insulin on net metabolism and functional outcome in long-term treatment of patients with cancer remains unclear. Importantly, there was no indication of any harm by insulin to our patients confirmed indirectly by measurements of tumor markers, which did not indicate any systematic disease progression. This conclusion was also strengthened by significantly prolonged survival of insulin-treated patients.

In conclusion, the present study shows that daily insulin treatment in catabolic cancer patients had significant effects towards improved micronutrient intake and intermediary fat metabolism, which caused increased net retention of body fat associated with improved metabolic efficiency during a close to maximum work load, without indications that insulin stimulated disease progression. The present observations show that insulin treatment is a powerful complement in multimodal palliative care of weight-losing cancer patients as suggested half a century ago (16).

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