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Insulin Resistance in Patients with Cancer[1]

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ABSTRACT

Disturbed glucose metabolism is a well-recognized feature in cancer. This study was designed to elucidate the role of peripheral tissues for glucose metabolism in this disease. Ten cancer patients and 11 appropriate controls were subjected to insulin challenge (0.10 unit/kg body weight) and i.v. glucose tolerance test. The fractional uptake or release of insulin, glucose, free fatty acids, glycerol, acetoacetate, and lactate in the forearm was determined. In isolated skeletal muscle fibers obtained from biopsies from the rectus abdominal muscle, the incorporation rate of glucose carbon into glycogen and CO_2 and the incorporation of palmitic acid carbon and leucine carbon into CO_2 as well as insulin stimulation of the incorporation of glucose carbon into glycogen and leucine carbon into proteins were determined.

In cancer patients the response of blood glucose to insulin challenge was smaller than in controls. Neither the elimination rate of insulin from plasma nor the fractional uptake of glucose in the forearm was significantly changed in these patients. The incorporation rate of glucose carbon into glycogen and CO_2 was significantly decreased, and the insulin stimulation of this incorporation was smaller in cancer patients than in controls. The incorporation rate of palmitic acid and leucine into CO_2 did not differ between the groups.

Peripheral tissues are of importance for the disturbed glucose metabolism in cancer disease since skeletal muscles showed specifically lowered capacity for glucose utilization with and without insulin stimulation *in vitro*. All of these results were compatible with an insulin resistance in the liver and in the skeletal muscles in cancer.

INTRODUCTION

In subjects with metastatic cancer, disturbed glucose metabolism has been reported repeatedly (5, 11, 29). The mechanism for this disturbance is not clear. Recently, we reported evidence for decreased insulin response to glucose challenge suggesting a β-cell insufficiency in patients with uncontrolled cancer growth (17). However, the role of peripheral tissues (muscle and adipose tissue) for the glucose uptake in cancer has not been clearly outlined. Evidence has been presented that skeletal muscle enzyme activities and the capacity of muscle tissue to metabolize glucose are of importance for glucose tolerance and insulin sensitivity of the organism (2, 3, 9, 10, 19). By analogy decreased glucose uptake and decreased insulin sensitivity in muscle tissue could be expected in cancer patients, who have low activities of enzymes for energy production, decreased glucose assimilation capacity, and decreased synthesis of proteins in skeletal muscle tissue (15).

This study was attempted to elucidate further the possible role of peripheral tissues for glucose uptake in cancer patients.

MATERIALS AND METHODS

Patients. The study group comprised 28 patients with cancer, 17 men and 11 women ages 45 to 80 years. The diagnosis and other pertinent data are listed in Table 1. Normal serum levels for liver tests were defined as follows: serum bilirubin, <21 mmol/liter; alkaline phosphatase, <5 μkat/μmol/liter; aspartate aminotransferase, <0.7 μkat/liter; and alanine aminotransferase, <0.7 μkat/liter. The histological grading of the tumor cells was performed by a pathologist and was given as high, medium, and low grades of differentiation. Besides the laboratory tests the examinations of the patients performed were radiography of the lungs and the bone system and, in most patients, aortography. The cancer patients were in a more or less advanced stage, but none was totally bedridden. In a randomized subgroup of 10 hospitalized patients, the caloric intake was estimated by a dietitian. The caloric intake in this group, which was considered representative for the study group, varied between 580 and 2250 kcal/day [1296 ± 520 (S.D.)]. All of the cancer patients reported weight loss amounting to 3 to 12 kg during the 6 months before admission to the hospital. Weight index according to Broca's formula was 0.85 ± 0.02 for cancer patients and 1.04 ± 0.02 for the controls ($p < 0.001$).

Twenty-seven patients who were appropriately matched with respect to age, diet, and daily activity served as controls in the study. These patients were admitted to the hospital for operation of uncomplicated gallbladder disease, peptic ulcer, varicose vein, or inguinal hernia.

None of the cancer patients or the controls had a history of diabetes. Informed consent was obtained from all patients.

Insulin Challenge and Glucose Tolerance Test. Ten representative cancer patients and 11 controls were subjected to insulin challenge and glucose tolerance test. In the morning after an overnight fast, arterial and venous blood samples were taken simultaneously for determination of the basal level of glucose (14), insulin (8), free fatty acids (26), acetoacetic acid (27), lactate (7), and glycerol (13). Thereafter 0.10 unit insulin (Novo Insulin, Copenhagen, Denmark) per kg body weight was injected into the right cubital vein. Arterial and venous blood samples were taken

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Table 1

Data of the total group of cancer patients (A) and of the subgroup subjected to insulin load and glucose tolerance test (B)

Diagnosis, the complete cancer material	No.	Sex	Age (yr)	Liver serum test		Grade of differentiation	Tumor spread			*In vitro* studies
				Normal	Not normal		No spread	Regional lymph nodes	Generalized	
A.										
Esophageal cancer	3		52–74	2	1	High-low	2	1		3
Gastric cancer	4		60–73	2	2	Medium-low		2	2	4
Pancreatic cancer	4		52–80		4	Medium-low		2	2	4
Hepatic cancer	1		50		1	Medium		Multiple location in the liver		1
Colon cancer	4		45–77	2	2	High-low		3	1	4
Rectal cancer	2		63, 68	2		Medium-low		1	1	2
Renal cancer	3		62–74	2	1	Medium-low	1	1	1	3
Liposarcoma	1		59	1		High		Local spread		1
Leiomyoblastoma	1		63		1	Low	1			1
Retroperitoneal sarcoma	1		61		1	Medium		Local spread		1
Uncertain origin	4		57–68		4	?			4	4
B.										
Hepatoma		M	50	Not normal		Medium		Multiple location in the liver		+
Pancreatic cancer		F	68	Not normal		Low		+		+
Gastric cancer		F	66	Not normal		Low			+	+
Gastric cancer		M	70	Normal		Low		+		+
Gastric cancer		M	65	Not normal		Low		+		+
Retroperitoneal sarcoma		M	60	Normal		Medium		Local spread		+
Uncertain origin		M	69	Not normal		?			+	+
Leiomyoblastoma		M	66	Normal		Low	+			+
Renal cancer		F	73	Normal		Low			+	+
Renal cancer		F	74	Normal		Medium	+			+

in the femoral artery and the left cubital vein after 6, 15, 30, 45, 60, 90, and 120 min for determination of insulin, glucose, and free fatty acids. Altogether about 150 ml of blood were drawn from each patient. Duplicate determinations were performed on each sample, and the mean was used for calculations.

An i.v. glucose tolerance test was performed 4 to 7 days later. In the morning, after an overnight fast, 25 g of D-glucose as 30% solution were injected into the right cubital vein. Within 3 min venous blood samples were taken in the contralateral cubital vein before and 10, 20, 25, 30, 40, 50, 60, 70, and 90 min after the glucose injection for determination of glucose and insulin. The glucose disappearance rate (k value in percentage/min) was calculated from the blood glucose concentrations at the sampling times after logarithmic transformation according to the equation

$$k = ({}^{e}\log C_{10} - {}^{e}\log C_{20\text{–}90}) \cdot 100/(t_{20\text{–}90} - t_{10})$$

Incubation Procedures. The preparation and incubation procedures for determination of the glucose incorporation into various metabolites were as described in detail previously (15, 16). In the morning after an overnight fast, the muscle biopsies for incubations were taken in local field anesthesia, which previously has been shown not to interfere with the *in vitro* determinations (4). The muscle biopsies were taken from the rectus abdominal muscle. Isolated muscle fibers were prepared from the biopsy specimen and incubated in Krebs-Ringer phosphate buffer solution, pH 7.4, at 37° in the presence of D-glucose (8.5 mmol/liter and [U-^{14}C]glucose (10^6 dpm). The incorporation rate of glucose carbon into glycogen and carbon dioxide was calculated from the specific activity of glucose in the incubation medium. In some experiments insulin was added to the incubation medium (25 units/liter).

For the determination of the incorporation rate of amino acids into total proteins, isolated muscle fibers were incubated in Krebs-Ringer bicarbonate buffer solution, pH 7.4, at 37° in the presence of [^{14}C]leucine and all amino acids at human plasma concentrations (16). The incubation procedures and preparation of proteins for radioactivity determination have been described previously (16). The incorporation rate of amino acids into proteins was calculated from the specific activity of leucine in the incubation medium. The specific activity of the incubation medium was used, since it has been shown that the precursor pool for protein synthesis in isolated muscle fibers equilibrated more rapidly with the extracellular pool than with the total intracellular precursor pool in this muscle preparation (18).

Statistical Methods. Nonparametric statistics according to the Mann-Whitney *U* test was used for comparison between 2 independent samples (25). Comparison between 2 dependent samples was performed by the Wilcoxon's test for matched pairs (25).

RESULTS

Glucose disappearance rate during glucose tolerance test was low both in cancer (k = 0.58 ± 0.08) and control patients (k = 0.66 ± 0.08), but not significantly different between the groups. Sum of insulin values during the test was 75 ± 11 and 137 ± 14 in the cancer and control groups, respectively ($p < 0.01$).

Statistically significant release of insulin from the forearm was registered between 15 and 45 min after insulin challenge (0.10 units/kg body weight) in cancer patients. In controls a corresponding release was found between 30 and 45 min after the injection (Table 2). The elimination of plasma insulin showed a good fit for first-order kinetics in both cancer patients and controls (r = 0.97 and 0.98, respectively) (Chart 1). The elimination rate did not differ significantly between the groups, but the arterial and venous concentration of insulin was slightly lower between 10 and 45 min after injection in cancer patients. The arterial and venous glucose concentration in plasma decreased significantly less in cancer patients than in controls between 15 and 45 min after the insulin injection (Table 2; Chart 2).

In the basal fasting state, neither cancer nor control patients showed a significant glucose uptake across the forearm. After the insulin challenge glucose was taken up, but there was no difference between the groups (Table 2). The arteriovenous difference of glucose across the forearm was not correlated to the arterial insulin concentration in any group, but it was significantly correlated to the arterial glucose concentration in controls (Spearman's rank correlation coefficient, 0.56; $p < 0.005$), although not in cancer patients.

The arterial and venous concentration of free fatty acid was significantly lower in cancer patients in the basal state but not different during the insulin challenge (Table 2).

The arterial and venous concentrations of acetoacetate, lactate, and glycerol did not differ between the groups. Glycerol was released in both cancer and control patients without showing significant difference. Only the cancer

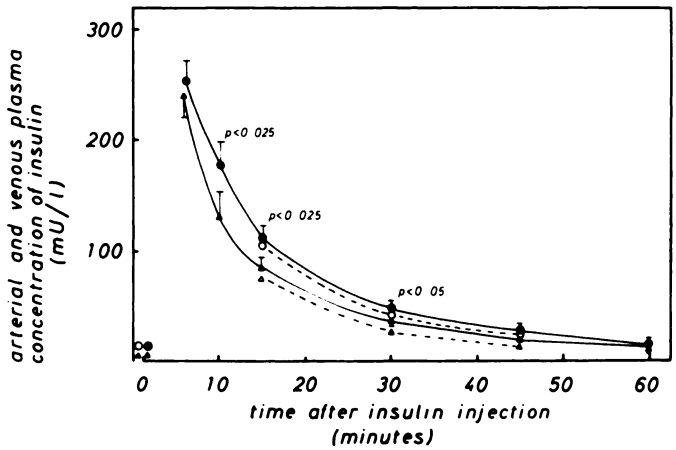

Chart 1. Disappearing rate of insulin in arterial and venous blood after i.v. injection of insulin in cancer patients and controls. Insulin (0.10 units/kg body weight) was injected i.v. as a single shot in the right cubital vein. Blood samples were thereafter simultaneously drawn from the femoral artery and the left cubital vein at various times for insulin determination. ▲, venous insulin concentration in cancer patients; △, arterial concentration in cancer patients; ●, venous insulin concentration in controls; ○, arterial concentration. p, statistical significance between concentrations of insulin in plasma from cancer and controls.

Table 2

Arterial and venous concentrations of insulin, glucose, and free fatty acids in 10 cancer patients and 11 controls at various conditions

For details see "Materials and Methods." Mann-Whitney *U* test was used for the statistical analysis of 2 independent groups, and Wilcoxon's pair test was used for the analyses of the arteriovenous differences.

Time (min) after insulin injection	Site of concentration	Concentration (0.10 unit/kg body wt)								
		Insulin			Glucose			Free fatty acids		
		Cancer	Control	p	Cancer	Control	p	Cancer	Control	p
0[a]	Arterial	11 ± 2[b]	16 ± 2	<0.05	5.1 ± 0.4	4.7 ± 0.2	NS[c]	699 ± 55	996 ± 126	<0.05
	Venous	9 ± 1	14 ± 2[d]	NS	5.1 ± 0.3	4.7 ± 0.1	NS	733 ± 60	1055 ± 124	<0.05
15	Arterial	76 ± 8	106 ± 9	<0.025	4.4 ± 0.3	3.4 ± 0.1	<0.01	431 ± 42	616 ± 109	NS
	Venous	83 ± 7[e]	115 ± 9	<0.025	4.1 ± 0.3[e]	3.0 ± 0.1[e]	<0.01	527 ± 52[f]	695 ± 109[e]	NS
30	Arterial	28 ± 3	42 ± 5	<0.025	3.2 ± 0.3	2.4 ± 0.1	<0.01	344 ± 33	496 ± 96	NS
	Venous	38 ± 3[e]	49 ± 4[e]	<0.05	3.1 ± 0.3[d]	2.1 ± 0.1	<0.01	409 ± 54[f]	483 ± 120	NS
45	Arterial	17 ± 2	24 ± 3	NS	3.2 ± 0.2	2.8 ± 0.2	<0.05	372 ± 78	495 ± 96	NS
	Venous	21 ± 2[e]	27 ± 3[e]	NS	3.0 ± 0.3[f]	2.2 ± 0.1	<0.05	344 ± 33	496 ± 96	NS
60	Arterial	14 ± 1			3.5 ± 0.3					
	Venous	17 ± 1	18 ± 2	NS	3.1 ± 0.4[d]	2.8 ± 0.01	NS	458 ± 50	614 ± 91	NS

[a] 0, basal state after 12 hr fast.
[b] Mean ± S.E.
[c] NS, not significant.
[d, e, f] Significance of arteriovenous difference indicated by $p < 0.05$ (Footnote *d*); $p < 0.025$ (Footnote *e*); $p < 0.01$ (Footnote *f*). The arteriovenous differences of glucose, insulin, and free fatty acids were not statistically significantly different between cancer patients and controls.

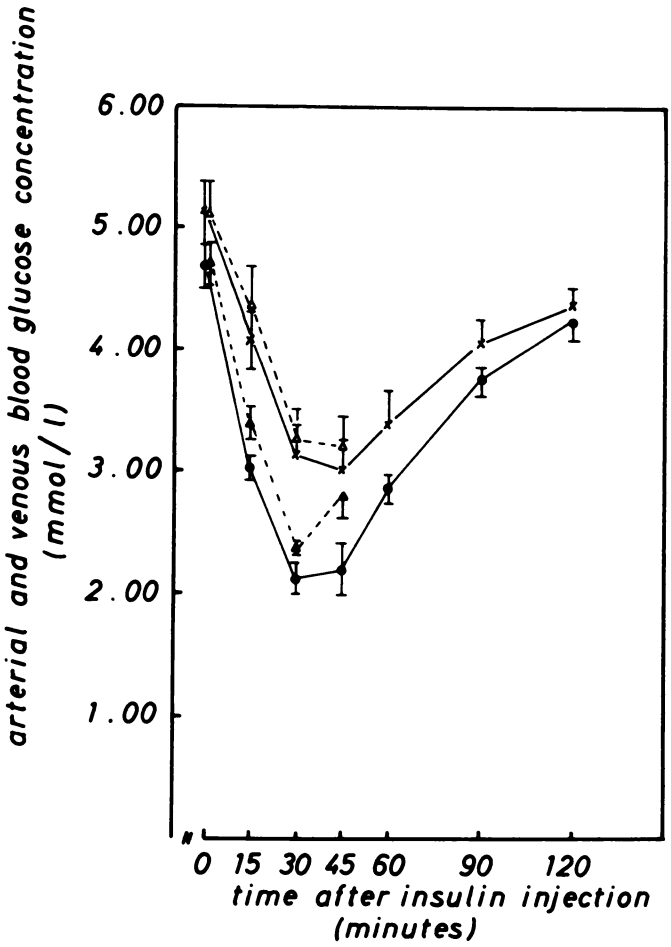

Chart 2. Arterial and venous concentration of glucose at various times after i.v. injection of insulin in 10 cancer patients and 11 controls. Insulin (0.10 units/kg body weight) was injected i.v. as a single shot at zero time. Blood samples were drawn simultaneously at various times thereafter from the femoral artery and the left cubital vein for glucose determination. ▲, venous glucose concentration in cancer patients; △, arterial concentration; ●, venous glucose concentration in controls; ×, arterial concentration.

patients showed a significant release of lactate in the forearm ($p < 0.01$).

Isolated skeletal muscle fibers from cancer patients incorporated glucose carbon into glycogen and carbon dioxide at a significantly lower rate than did fibers from controls. The oxidation rates of palmitate and of leucine were not significantly different between the 2 groups (Table 3).

Insulin (25 units/liter) stimulated the incorporation rate of glucose-carbon into glycogen significantly less in isolated muscle fibers from cancer patients than from controls (Table 4). However, the relative stimulatory effect of insulin on glucose incorporation rate into glycogen and on leucine incorporation rate into proteins was not statistically different in cancer patients.

DISCUSSION

The main positive finding in this study was a significantly smaller response of arterial and venous blood glucose to insulin challenge in cancer patients than in controls. The arterial and venous insulin concentrations after the insulin injection were slightly lower in cancer patients, but the elimination rate of plasma insulin was not different between the groups. The lower insulin concentrations in cancer patients might be dependent on a different distribution space or on a greater initial uptake of insulin in these patients. Both in cancer patients and controls, there was a small but significant insulin release from the forearm between 15 and 45 min (controls 30 min) after the insulin injection. The explanation for this finding is not known, but it may be related to rapid initial uptake of insulin followed by a later release. In a current study we found uptake of insulin across the forearm the first 6 min followed by a release from 10 to 60 min after insulin injection (unpublished observations). Displacement of insulin into the circulation from capillaries or tissues by arterial injection of insulin has been reported previously in dog experiments (20). Rasio *et al.* (21) also reported insulin release from the forearm after arterial injection of glucose.

The smaller glucose response to insulin in cancer patients implies a decreased insulin sensitivity. However, in line with previous findings (17), the cancer patients also had a glucose disappearance rate not significantly different from that of controls concomitant with a decreased insulin response during an i.v. glucose tolerance test. According to conventional interpretations this suggests an increased sensitivity to insulin. Our results thus seem to be contradictory.

The design of this study was directed towards evaluation of the role of peripheral tissues for insulin sensitivity in cancer. The main reason for this design was the previously reported decreased assimilation capacity of glucose and decreased activities of glycolytic and oxidative enzymes in isolated muscle fibers from cancer patients (15), *i.e.*, circumstantial evidence for an insulin resistance in muscles.

The fractional uptake of glucose across the forearm in cancer patients was not significantly different from that of controls. Unfortunately, it was not possible to determine the blood flow in forearm during the insulin challenge for calculations of the absolute uptake of glucose. The results from the studies of isolated abdominal muscle fibers, showing decreased incorporation rate of glucose carbon into glycogen and carbon dioxide as well as significantly smaller stimulation of insulin on the incorporation rate of glucose carbon into glycogen, suggest a decreased glucose uptake and a decreased insulin sensitivity of this tissue in the cancer patients. Besides, the *in vitro* results pointed to the possibility that the carbohydrate metabolism was specifically altered in cancer, since the oxidation rate of palmitic acid and leucine and the insulin stimulation of leucine incorporation rate into muscle proteins were not significantly different from those in controls. Tissue compartments generally are reduced in advanced cancer disease (28). A reduced tissue mass with decreased glucose assimilation capacity per unit of tissue concomitant with an increased plasma flow (12, 22) could explain the unchanged fractional uptake of glucose in the forearm of our patients with cancer.

Although the muscle tissue in cancer patients had decreased capacity for glucose metabolism, it cannot be postulated that this decrease is solely responsible for the smaller glucose response to insulin challenge in these patients. A decreased hepatic insulin sensitivity may be of

Table 3

Incorporation rate of glucose into glycogen and the oxidation rate of glucose, palmitic acid, and leucine in isolated human skeletal muscle fibers from cancer patients and appropriate controls

For details see "Materials and Methods." Mann-Whitney *U* test was used for the statistical analysis.

	Incorporation (μmol/hr/g wet wt)			
	Glucose into		Palmitic acid into	Leucine into
	Glycogen	Carbon dioxide	Carbon dioxide	Carbon dioxide
Cancer	0.079 ± 0.011[a] (28)[b]	0.242 ± 0.019 (20)	0.043 ± 0.004 (21)	0.0048 ± 0.0012 (19)
Controls	0.158 ± 0.022 (27)	0.333 ± 0.028 (27)	0.048 ± 0.005 (16)	0.0032 ± 0.0018 (15)
p	<0.0025	<0.005	NS[c]	NS

[a] Mean ± S.E.
[b] Numbers in parentheses, number of patients.
[c] NS, not significant.

Table 4

Influence of insulin on the incorporation rate of glucose into glycogen and on the incorporation rate of leucine into muscle proteins in isolated muscle fibers from cancer patients and appropriate controls

Muscle fibers isolated from a biopsy specimen were incubated with and without (basal) insulin in the incubation medium. For details see "Materials and Methods." Mann-Whitney *U* test was used for the statistical analyses of independent variables, and Wilcoxon's pair test was used for the analyses of the insulin effect. The cancer and control subjects comprising experiment of the glucose metabolism are included in corresponding studies shown in Table 3.

	Incorporation rate of glucose carbon into glycogen			Incorporation rate of leucine into muscle proteins		
	Insulin effect (μmol/hr/g wet weight)	Δ insulin stimulation (μmol/hr/g wet weight)	%	Insulin effect (μmol/hr/g protein)	Δ insulin stimulation (μmol/hr/g protein)	%
Cancer						
Basal	0.094 ± 0.020[a]	0.028 ± 0.007	37 ± 8 (13)[b]	0.088 ± 0.011	0.025 ± 0.010	26 ± 6 (18)
+ insulin	0.122 ± 0.021[c]			0.109 ± 0.017[c]		
Controls						
Basal	0.115 ± 0.014	0.060 ± 0.015	57 ± 16 (14)	0.098 ± 0.010	0.031 ± 0.006	32 ± 12 (14)
+ insulin	0.173 ± 0.022[c]			0.129 ± 0.011[c]		
p		<0.05	NS[d]		NS	NS

[a] Mean ± S.E.
[b] Numbers in parentheses, number of patients.
[c] $p < 0.005$.
[d] NS, not significant.

importance (23). Tumor-bearing animals have increased gluconeogenetic enzyme activities in the liver (6) and increased gluconeogenesis from amino acids (24). A combined effect of decreased insulin sensitivity in peripheral tissues and increased hepatic gluconeogenesis is consistent with higher fasting blood glucose level in cancer patients (17) and with these findings of a smaller response of blood glucose to insulin challenge and unchanged glucose disappearance (*k*) at an i.v. glucose tolerance test in the cancer patients.

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