Comparative study of blood insulin levels in breast and endometrial cancer patients

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Blood insulin level was measured in 113 breast cancer (BC) patients, 18 endometrial cancer (EC) patients, and 35 women with benign breast disease (BBD), after fasting and after 120 min of oral glucose tolerance test (OGTT). A significant increase in reactive insulin level was shown in postmenopausal BC patients with abdominal obesity (waist/hip ratio > 0.85) and no differences in insulin level were found between BC and BBD patients. Menstrual status and overweight (Quetelet index) did not influence significantly blood insulin concentration in BC patients, but the basal insulin level was lower in those patients who had been moderate smokers. In EC patients, the level of insulin after fasting and following 120 min OGTT was much higher than in BC and BBD patients although they had a similar body mass to these groups of patients. The effect of age on insulin secretion in BC patients is discussed as well as the possible causes and consequences of hyperinsulinemia developing in EC and BC patients.

Key words: Insulin, breast cancer, endometrial cancer, benign breast disease, aging, upper type of obesity, smoking.

Insulin may directly or indirectly promote somatic cell division, enhance the activity of lipoprotein lipase, increase body fat concentration, and take part in modification of cellular immunity and metabolic immunodepression (for review see [8, 11]). In a case-control study of 223 women, Bruning et al. [5] have concluded that hyperinsulinemia and insulin resistance are risk markers for breast cancer and are independent of general obesity and body fat distribution. These authors found increased C-peptide concentration in the serum of breast cancer patients (higher in postmenopausal than premenopausal women) compared to that of patients with other types of cancer (melanoma, cervical cancer, malignant lymphoma). Del Giudice et al. [6] also report hyperinsulinemia to be a risk factor for premenopausal breast cancer development but details are not available. It has been suggested that overrich diet and insufficient physical exercise may favor the development of hyperinsulinemia and increase the risk of breast cancer in women, especially in those with genetic susceptibility to neoplastic development [15]. Hyperinsulinemia has also been noted in women with early cancer of the endometrium or ovary but levels fell to normal after surgery or in advanced disease [18].

In earlier studies [3, 4, 7, 8, 17] we have reported that hyperinsulinemia is a key element leading to hyperlipidemia, obesity, and age-associated disturbances in tolerance to carbohydrates and it was postulated that in breast and endometrial cancer patients, the changes in blood insulin and glucose levels might promote stimulation of tumor growth, or modifications in immune defence mechanisms. The present work reports the insulin response to the oral glucose tolerance test (OGTT) in patients with early breast cancer and relates it to menstrual status, body mass (Quetelet index), type of fat topography and smoking. Patients with endometrial cancer or benign breast disease were investigated as control groups.

Subjects and methods

113 patients with breast cancer, 18 patients with early endometrial cancer, and 35 women with benign breast disease were investigated at our Institute between 1992 and 1995. None had received any therapy before the examination and their ages ranged from 25 to 77. Of 113 breast can-

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Table 1. Blood glucose and insulin levels (M ± m) in breast cancer (BC), endometrial cancer (EC) and benign breast disease (BBD) patients

Group	Age (y)	Body weight (kg)	Glucose (mg%)		Insulin (μU/ml)	
			0 min	120 min	0 min	120 min
BC $n = 113$	52.1 ± 0.5	69.7 ± 1.2	90.5 ± 1.6	111.7 ± 3.8	7.9 ± 0.5	36.5 ± 3.1
BBD $n = 35$	50.0 ± 2.1	71.8 ± 2.5	94.6 ± 3.3	118.1 ± 6.4	9.0 ± 1.8	32.7 ± 3.9
EC $n = 18$	60.1 ± 2.2	70.0 ± 3.5	100.5 ± 2.9[b]	134.9 ± 9.8[a]	14.3 ± 2.0[b,c]	67.1±10.9[b,d]

a – Difference from BC group is significant ($p < 0.05$), b – difference from BC group is significant ($p < 0.01$), c – difference from BBD group is significant ($p < 0.05$), d – difference from BBD group is significant ($p < 0.01$).

cer (BC) patients (all of them at an early clinical stage), 57 patients aged from 25 to 52 were premenopausal, and 56 patients aged from 47 to 77 were postmenopausal for more than 12 months. Among 18 patients with early endometrial cancer (EC), 3 women were premenopausal and 15 women postmenopausal for at least a year. The third group consisted of 35 women with either diffuse or nodular benign breast disease (BBD) and comprised 22 premenopausal and 13 postmenopausal women. The total number of cases was 166 and none had a history or evidence of overt diabetes mellitus, thyroid or liver disease.

Blood insulin and glucose levels were determined after night fasting and during oral glucose tolerance test - peroral glucose load (40 g/m^2 of body surface). Glucose concentration in serum sampled from the cubital vein was measured by enzymo-colorimetrical method using special kits (Boehringer Mannheim Gmbh, FRG). Commercial RIA kits (Nonorganic Chemistry Institute, Minsk, Belarus) were used for insulin determination. Intraassay coefficients of variation for insulin and glucose concentrations were 5.0% and 4.3%, respectively. Also Quetelet index (weight, kg/height (m^2)) was calculated, and as a criterion of fat distribution, the waist/hip ratio was measured. Differences between the studied groups were evaluated by Student's *t*-test. Besides mean values (M), standard deviations (σ) and standard errors (m), linear correlation coefficients (γ) were also calculated. The computerized statistical analysis was used for estimation of the results.

Results

Table 1 shows the results of blood glucose and insulin measurement in BC, EC and BBD patients after night fasting, and 120 min following the oral glucose load. It is seen from the table, that glucose and insulin levels in BC patients are similar to those in BBD patients and their mean values of body weight and age are practically the same. Average values of body weight in EC patients were similar to those in BC and BBD patients. In EC patients, blood insulin concentrations sampled following night fasting and by the 120-min of OGTT were significantly higher than those in BC and BBD patients, while their levels of basal and reactive glycemia exceeded those of BC patients only.

When the data were analyzed according to whether the patients were pre- or postmenopausal (Table 2), blood insulin and glucose levels after night fasting and 2 h following the glucose load were found to be similar in pre- and postmenopausal BC patients. Mean values of body weight of these patients were also similar. Postmenopausal BBD patients showed a significant rise in glycemia level after 120 min OGTT as compared to premenopausal BBD patients. Postmenopausal BBD patients also demonstrated a tendency to a larger body mass and an enhanced reactive insulin level. However, an increased blood insulin concentration was most pronounced in postmenopausal EC patients although they did not differ sig-

Table 2. Blood glucose and insulin levels (M ± m) in pre- and postmenopausal BC, EC and BBD patients

Group	Menstrual status	Age (y)	Body weight (kg)	Glucose (mg%)		Insulin (μU/ml)	
				0 min	120 min	0 min	120 min
BC	premenopausal $n = 57$	44.4 ± 0.7	68.7 ± 1.8	89.7 ± 2.1	108.1 ± 4.9	8.0 ± 0.7	35.3 ± 4.7
	postmenopausal $n = 56$	60.0 ± 0.8	70.7 ± 1.4	91.4 ± 2.4	115.3 ± 6.0	7.9 ± 0.6	37.8 ± 4.1
BBD	premenopausal $n = 22$	42.4 ± 1.4	68.6 ± 3.1	90.3 ± 3.9	103.0 ± 5.2	8.6 ± 1.6	28.9 ± 4.5
	postmenopausal $n = 13$	62.7 ± 2.4	77.1 ± 3.9	101.9 ± 5.5	143.6 ± 12.2[a]	9.9 ± 4.3	40.6 ± 7.3
EC	premenopausal $n = 3$	43.0 ± 2.5	63.7 ± 3.1	103.0 ± 3.7	115.3 ± 10.7	10.3 ± 4.2	41.7 ± 16.7
	postmenopausal $n = 15$	63.5 ± 1.5	71.3 ± 4.1	100.0 ± 3.4	139.1 ± 11.4	15.1 ± 2.2[a,b]	73.5 ± 12.4[a,b,c]

a – Difference from BBD group of reproductive age is significant ($p < 0.02$), b – difference from BC group of reproductive and postmenopausal age is significant ($p < 0.02$), c – difference from BBD group of postmenopausal age is significant ($p < 0.05$).

Table 3. Blood glucose and insulin levels (M ± m) in BC patients with different Quetelet index values and different types of fat topography

Parameter	Group	Value of parameter	Age (y)	Body weight (kg)	Glucose (mg%)		Insulin (μU/l)	
					0 min	120 min	0 min	120 min
Quetelet index	premeno-pausal	< 30 n = 48	44.2 ± 0.9	64.3 ± 1.3	89.3 ± 4.9	104.9 ± 5.7	7.7 ± 0.9	31.8 ± 5.1
		> 30 n = 9	45.1 ± 2.0	90.1 ± 4.2	90.4 ± 3.7	126.2 ± 14.7	9.4 ± 1.7	51.7 ± 15.6
	postmeno-pausal	< 30 n = 40	59.6 ± 0.9	65.8 ± 1.1	86.5 ± 2.2	109.7 ± 5.4	7.4 ± 0.7	34.8 ± 4.3
		> 30 n = 16	61.8 ± 1.5	83.5 ± 1.5	100.2 ± 5.2[a]	129.8 ± 14.0	9.1 ± 1.1	44.7 ± 7.0
W/H ratio	premeno-pausal	< 0.85 n = 34	43.0 ± 1.0	64.5 ± 2.1	87.8 ± 2.6	105.0 ± 5.6	8.5 ± 0.9	33.7 ± 5.5
		> 0.85 n = 23	47.3 ± 1.8	77.6 ± 3.4	93.4 ± 3.8	112.0 ± 7.4	6.9 ± 0.9	37.9 ± 8.8
	postmeno-pausal	< 0.85 n = 30	58.3 ± 2.7	64.3 ± 1.5	85.6 ± 2.8	100.9 ± 5.9	7.5 ± 0.8	29.4 ± 4.1
		> 0.85 n = 26	61.6 ± 1.3	76.6 ± 1.6	97.7 ± 3.7[b]	130.2 ± 9.9[b]	8.2 ± 0.9	44.1 ± 5.8[b]

a – Difference from postmenopausal patients with Quetelet index <30 is significant ($p < 0.05$), b – difference from postmenopausal patients with waist/hip (W/H) ratio <0.85 is significant ($p < 0.05$).

nificantly in their body mass and glycemia level from the EC patients of reproductive age (Table 2).

Table 3 shows that an increase of Quetelet index over 30 was not accompanied by a significant rise in blood insulin concentration either in premenopausal or in postmenopausal BC patients. However, postmenopausal BC patients with the abdominal (or android) type of fat topography (waist/hip ratio > 0.85) demonstrated a pronounced hyperinsulinemia by 120 min OGTT as compared with patients with a waist/hip ratio < 0.85.

Correlation analysis in breast and endometrial cancer patients (Table 4) shows that anthropometric parameters exert a greater effect on insulin levels in EC patients than in BC patients. In postmenopausal BC patients, the correlation between insulin level and age was stronger than that between insulin level and body size parameters.

Among BC patients, 35 women (31.0%) were moderate smokers (they smoked on the average 7 cigarettes per day). When the relationship between the studied parameters and smoking habits was analyzed (Table 5), blood insulin levels were found to be lowest in postmenopausal BC patients who had smoked over 5 cigarettes a day, whereas glucose concentrations were practically identical in all other groups.

Discussion

Our study shows that blood insulin levels in BC patients are similar to those in BBD patients and are not affected by menstrual status or by overweight (Quetelet index). However, only postmenopausal women with the abdominal obesity (waist/hip ratio > 0.85) show a higher level of hyperinsulinemia by 120 min of OGTT, than those with lower body type of obesity (Tables 1–3). Many authors [3, 12, 16] have noted that hyperinsulinemia and insulin resistance are associated with abdominal obesity, a decreased blood level of sex hormone-binding globulin (SHBG) and corresponding increase of free blood estradiol concentrations.

Table 4. Coefficients of linear correlation between basal and reactive (120 min after glucose load) blood insulin level and some indices in breast and endometrial cancer patients

Group	Breast cancer				Endometrial cancer	
parameter	premenopausal		postmenopausal			
	insulin 0 min	insulin 120 min	insulin 0 min	insulin 120 min	insulin 0 min	insulin 120 min
Body weight (kg)	0.089	0.234	0.262	0.248	0.291	0.348
Quetelet index	0.069	0.273	0.252	0.237	0.476*	0.289
W/H ratio	-0.047	0.096	0.153	0.280	0.254	0.586*
Age (y)	-0.321*	0.151	0.372*	0.304*	0.166	0.170

*$p < 0.05$.

Table 5. Blood glucose and insulin levels (M ± m) in pre- and postmenopausal smoking and non-smoking BC patients

Menstrual status	Group	Glucose (mg%)		Insulin (μU/ml)	
		0 min	120 min	0 min	120 min
Premenopausal	non-smoking $n = 33$	90.0 ± 2.7	112.6 ±7.1	7.4 ± 0.9	38.9 ± 7.6
	smoking $n = 24$	89.2 ± 3.5	100.5 ±5.7	8.9 ± 1.4	29.0 ± 3.5
	>5 cig/day $n = 10$	88.2 ± 6.5	101.3 ±9.4	7.9 ± 2.7	32.8 ± 5.6
Postmenopausal	non-smoking $n = 45$	93.9 ± 2.5	116.5 ±6.6	7.9 ± 0.7	37.6 ± 3.9
	smoking $n = 11$	82.2 ± 6.6	113.7 ±16.1	8.2 ± 1.6	32.3 ± 12.3
	>5 cig/day $n = 7$	84.1 ± 9.5	100.2 ± 24.9	5.8 ± 0.5*	23.0 ± 10.0

*Difference from non-smoking patients of the same group is significant ($p < 0.05$).

In our study we failed to observe any differences in blood insulin concentrations between patients with early stage BC, and BBD cases of the same age group and the same menstrual status (Table 2). The progression of hyperin-

sulinemia and insulin resistance in BC patients with age was noted in our earlier work [4, 8]. In this study, the age-dependent character of insulinemia in BC patients is most clearly demonstrated in the group of postmenopausal patients (Table 4).

Of a special interest is the level of hyperinsulinemia found in the group of EC patients (Tables 1, 2). In these patients, basal blood insulin concentration is more than 1.5 times that of BC and BBD patients. According to the average data, in EC patients, hyperinsulinemia was not related to the excess of body mass (just as in BC and BBD patients). However, the correlation between insulin level determined after fasting and the Quetelet index, and also between insulin concentration by 120 min of OGTT and waist/hip ratio, was higher in patients with EC than in those with BC (Table 4).

In postmenopausal patients with EC Nagamani et al. [10] reported the levels of hyperinsulinemia which were more than 3 times the control figures, and also luteinization of the ovarian stroma, while their glycemia levels did not differ from those in the control group. The cause of such pronounced hyperinsulinemia in EC patients is unclear and needs further research. According to recent data, hyperinsulinemia suppresses the expression of insulin-like growth factor binding protein-1 and thus may lead to the excessive and continuous stimulation of endometrium by IGFs [13]. On the other hand, it should be taken into account that giving birth to a large baby (as an early sign of development of the lowered carbohydrate tolerance and of resistance to insulin) is much more frequent in case histories of patients with EC than in those of BC patients [2], and therefore, the factors promoting hyperinsulinemia development may be formed long before the disease is detected.

It has been reported that in people smoking more than 20 cigarettes a day, the basal and the reactive insulin levels were elevated in response to glucose load [19], although this was not observed in people who smoked moderately [9]. Nicotine infusion to rats during 2–14 days, has led to the decline of blood insulin level [14]. These findings may be relevant to our data concerning the decrease of basal blood insulin levels in BC patients who smoke moderately (Table 5). Since, as a rule, BC patients smoke more often than EC patients [1], it cannot be excluded that in BC patients, smoking may influence the incidence of hyperinsulinemia.

Confirmation is needed that hyperinsulinemia is a marker of increased risk to hormone-related cancers such as those of breast and endometrium. Our observations suggest that hyperinsulinemia is as common in BBD as in BC cases and therefore, that it does not merely reflect the presence of cancer but is an antecedent condition.

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