Insulin and Glucagon Secretion by Renal Adenocarcinoma

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A patient with histologically verified renal adenocarcinoma had dramatic increases in glucagon and insulin levels in plasma and in tumor tissue.

Cancer **48:98–100, 1981.**

RECENTLY WE DESCRIBED tumor-dependent synthesis of insulin and glucagon activity in diabetic mice.[7,8] The results of this research prompted us to screen 70 patients with malignancies (mammary carcinoma, lymphoproliferative tumors, abdominal tumors) for the levels of immunoreactive glucagon (IRG) and immunoreactive insulin (IRI). Here we describe a patient with histologically verified adenocarcinoma which was accompanied by dramatic increases in glucagon and insulin levels in blood and tumor tissue. On the basis of the present data it can be assumed that blood glucagon and insulin levels might become a relevant parameter in the diagnosis and treatment of abnormalities in glucose metabolism associated with certain tumors.[6,11,14]

Materials and Methods

We were following glucose, IRI and IRG levels in blood of our patient. The blood was being taken when the patient was still fasting. It was aliquoted for separate determinations of levels of three substances.

Blood glucose was determined by the Hyvarinen and Nikkila method.[1] IRI in sera and tumor tissue was determined by the Morgan and Lazarow two-antibody method[3] with the use of porcine (^{125}I) insulin and crystalline rat insulin standards (Sorin, Saluggia, Italy). Glucagon was determined by the Shima and Foa method.[13]

Tumor tissue or healthy organs were homogenized in 0.9% NaCl solution (50 mg tissue per ml of medium) using an all-glass Potter-Elvehjem homogenizer. The homogenate was centrifuged at 75,000 × *g* for 1 hour at 4 C.[6] The supernatant was decanted and used for insulin and glucagon determination.[14]

Results

The patient was a 59-year-old woman admitted to the Military Medical Academy, Belgrade, on September 17, 1979, because of pains in the left lumbal region and in the left side of the abdomen. The lumbal region of the spine was painfully sensitive. A solid tumorous formation could be easily felt on the left side of the abdomen. The size of the liver had increased by 3 cm. A roentgenogram of the native abdomen revealed a large retroperitoneal tumorous formation on the left side. Intravenous urography and scintigraphy did not reveal the left kidney. A massive pathologic vascularization of the left kidney was revealed by renovasography. Liver scintigraphy showed an enlarged liver and "cold regions" around the haepatic port. A chest x-ray examination revealed the existence of circular shades on the right hand side of the aortal arch. These shades were believed to be metastases. The second lumbal vertebra was pathologically fractured with osteolytic changes.

Laboratory investigations revealed a high rate of erythrocyte sedimentation (145/160), hypochromic anaemia, hypoalbuminemia, elevated levels of alkaline phosphatase (165 mU/ml compared with the normal values of 30–85 mU/ml) and of urea (70 mg/dl as compared with the upper level of normal of 40 mg/dl). All these features indicated the existence of an expansive process in the kidney accompanied by metastases in the liver, lungs and second lumbal vertebra.

After embolisation of art. renalis the tumor was removed on October 9, 1979. The dimensions of the tumor tissue were 25 × 15 × 8 cm. Histopathologic analysis showed that it was an adenocarcinoma. In spite of intensive postoperative treatment (Depo-Provera, x-ray irradiation of the second lumbal

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The authors thank Dr. S. Vuk-Pavlović for his help in preparing the manuscript, Professor R. Mićić for helpful suggestions, and Mrs. B. Slijepčević for technical assistance.

Accepted for publication July 2, 1980.

0008–543X/81/0701/98/$0.70

vertebra) the patient died on November 23, 1979, five weeks after the operation.

Since her admission to the hospital, the patient's blood glucose levels had been displaying extreme variations between 50 and 200% of the normal, although she was not given any drug known to affect sugar metabolism. Therefore on the 21st day before the operation we also began to record the levels of IRG and IRI in blood. The results of these tests as a function of time are displayed in Figure 1. It can be noted that the initial high level of blood glucose is accompanied by a high glucagon/insulin ratio. Four days later, the subnormal sugar level was paralleled by a low glucagon/insulin ratio; this sugar level persisted for the next few days. A change towards high sugar in the blood can be seen one week before the operation. At the time of the operation (day 0 in Figure 1) the sugar level was normal, while glucagon and insulin were up. Following the removal of the tumor all three parameters stabilized at near-normal levels.

We also determined the respective hormone levels in the extracted tumor tissue homogenate. While the mean level of IRI in homogenates of three healthy kidney preparations were 0.3 ± 0.2 mU/g, the corresponding value of the homogenized tumor was 29.2 mU/g. Similarly, the normal IRG values were 0.02 ± 0.01 μg/g, and the level in the tumor was 0.51 μg/g.

Discussion

Tumor-dependent insulin[6,7] and glucagon[8] secretion has been described both in diabetic/tumorous animals and in humans.[2,4,10,11] In this paper we have demonstrated that glucagon activity can also be tumor-dependent. The interplay of supranormal hormone concentrations induces dramatic variations in blood glucose levels. Removal of the tumor in our patient was followed by normalization of all three parameters (glucose in the blood, IRG and IRI). However, the persistence of slightly elevated IRG and IRI levels after surgery can be connected with numerous metastases.

There is probably no need for surprise at the data that the renal carcinoma has a high insulin and glucagon activity. It is a well-known fact that renal tumors cause a whole series of nonspecific symptoms and can often have an endocrinal function.

In conclusion, we wish to present these findings as circumstantial evidence that glucagon activity can also be secreted by tumorous tissues, along with insulin for which substantial experimental and clinical evidence already exists.[2,5–7,9,12,14] Investigation of tumor growth parameters of insulin and glucagon is now under way.

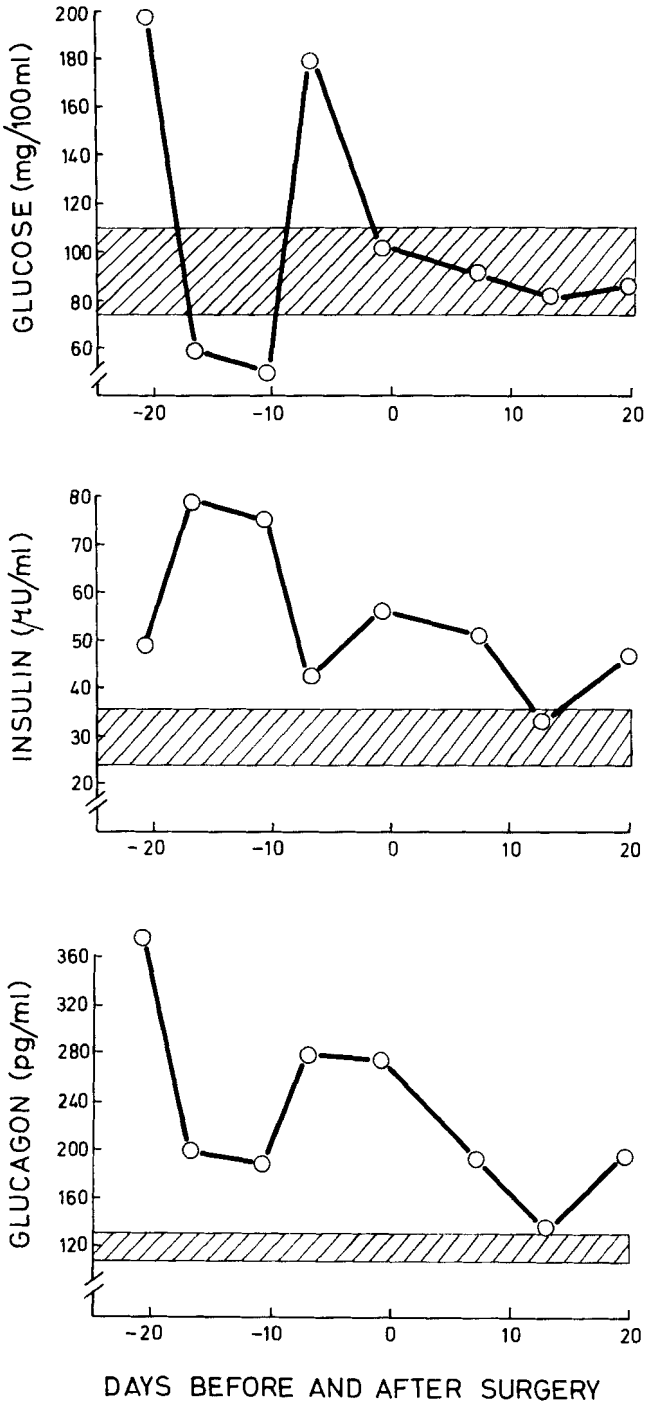

FIG. 1. The levels of blood glucose, immunoreactive insulin and immunoreactive glucagon in blood of patient with renal adenocarcinoma. The adenocarcinoma was extracted on day 0.

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