Non-islet-cell tumor hypoglycemia (NICTH)

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Approach

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a: Interpretation of laboratory tests*

Glucose (mg/dL)/(mmol/L)	Insulin (microU/mL)/(pmol/L)	C-peptide (nmol/L)/(ng/mL)	Proinsulin (pmol/L)	Beta-hydroxybutyrate (mmol/L)	Glucose increase after glucagon (mg/dL)/(mmol/L)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
<55/3	<3/20.8	<0.2/0.6	<5	>2.7	<25/1.4	No	No	Normal
<55	>>3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
<55	>>3	>>0.2 ¶	>>5 ¶	≤2.7	>25	No	Pos	Insulin autoimmune
<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF Δ
<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

: positive; NIPHS: noninsulinoma pancreatogenous hypoglycemia syndrome; PGBH: post-gastric bypass hypoglycemia; IGF: insulin-like growth factor.
gs during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (ie, Whipple's triad not documented) and in individuals with
r IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms.
d proinsulin concentrations are low.
F-2, free IGF-2, IGF-2/IGF-1 ratio.

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Non islet cell tumor

- **Non-islet-cell tumor hypoglycemia (NICTH)**

  syndrome of hypoglycemia produced by or associated with any neoplasm which increase overproduction of IGF-2
- The initial recognition of this syndrome dates to 1929 in patients with hepatocellular carcinoma
- **Most common** : solid tumors → mesenchymal or epithelial origin
- **Incidence** : unknown, male predominate

Yevgeniya Dynkevich. Endocrine reviews,2013,34(6):798-82.

Non islet cell tumor

- Tumors are quite large at the time of diagnosis: weighing ≥ 3 kg
- Tumors arise in thorax, retroperitoneum, or pelvis: usually clinically silent and tend to reach a significant size before diagnosis
- Tumors are located in extremities are detected much earlier due to signs and symptoms related to mass

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Non islet cell tumor

- **Clinical presentation** :
  - hypoglycemia as the initial manifestation of the tumor (48%)
  - often occur in the fasting state
  - confusion, lethargy, diaphoresis or progressive somnolence
  - weight loss, abdominal mass, pain or detection on routine radiologic examination

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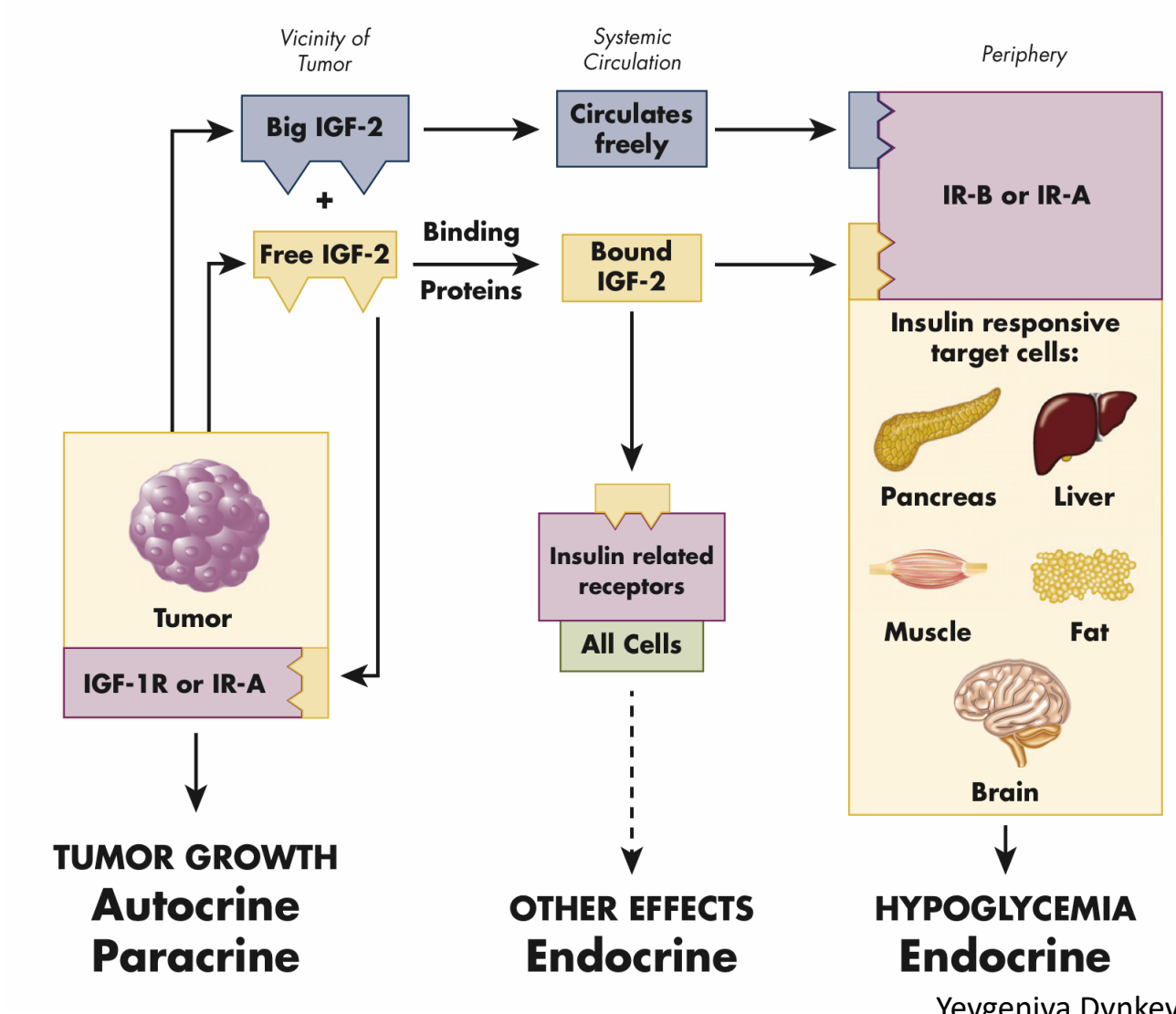
Autocrine, paracrine, and endocrine effects of IGF-2



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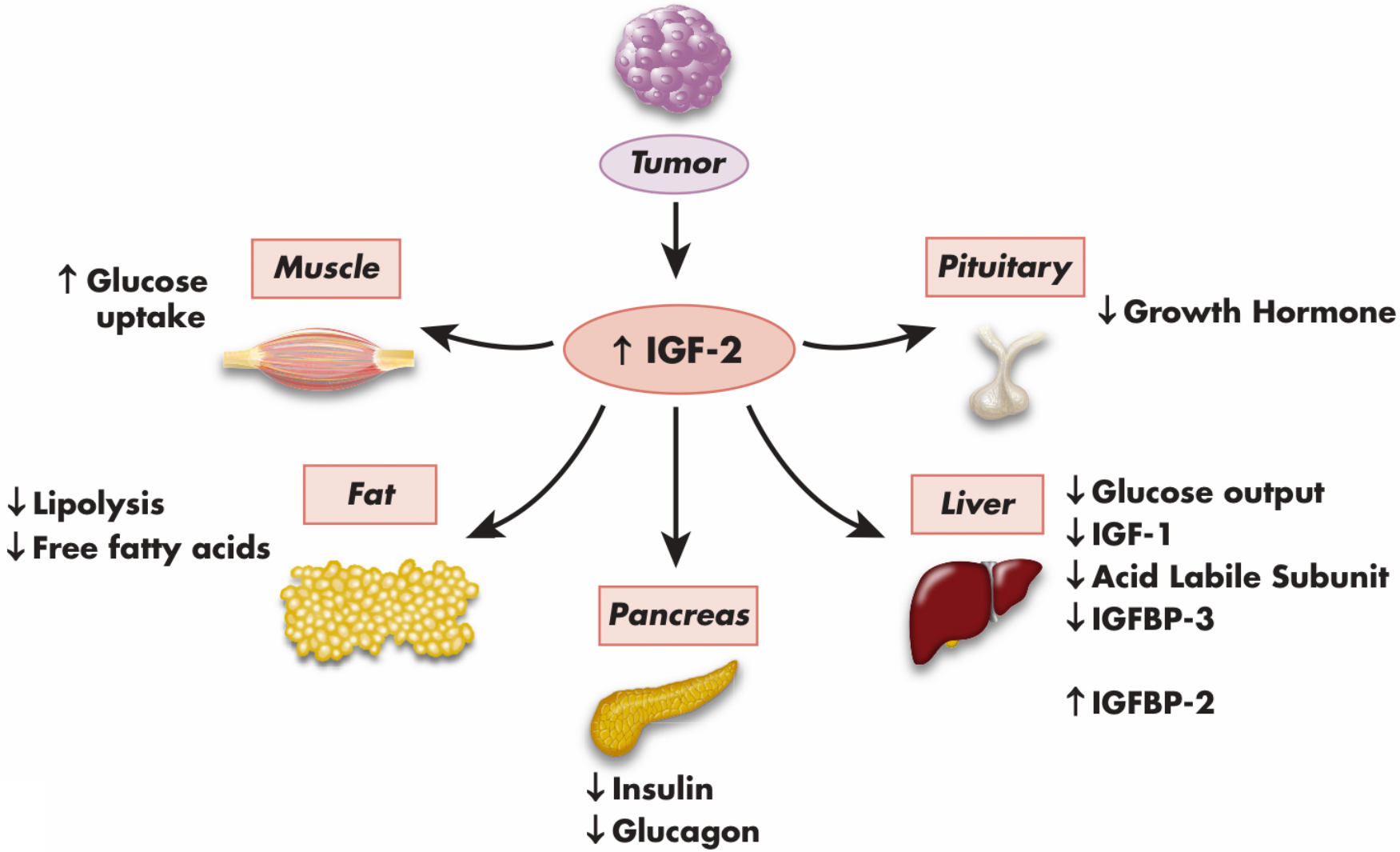
Major biological effects of excess IGF-2



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Approach

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Table 1. Tumors Associated With IGF-2–Induced Hypoglycemia[a]

Tumor Type	Prevalence, %
Epithelial origin	45
Hepatocellular carcinoma	20
Adrenocortical carcinoma	5
Stomach	4
Pancreas (non-islet cell)	4
Lung	3
Colon, rectum, esophagus	3
Carcinoid, neuroendocrine, medullary thyroid	2
Breast, ovary, prostate	1
Others: seminoma, pseudomyxoma, sarcomatous teratoma, melanoma, Wilms' tumor, dysgerminoma of the ovary, cervix, bladder, uterus, cholangioma	3
Mesenchymal origin	42
Fibrosarcoma, fibroma	23
Mesothelioma	8
Hemangiopericytoma, hemangioendothelioma, hemangiosarcoma	7
Hematologic: lymphoma, leukemia, lymphosarcoma, myeloma	1
Others: rhabdomyosarcoma, liposarcoma, neurofibroma, neurofibrosarcoma, histiocytoma, neuroblastoma, mesoblastic nephroma, neurilemmoma, meningioma, reticulum cell sarcoma, pelvic clear cell sarcoma	3
Unknown etiology	13

melanoma, Wilms' tumor,
dysgerminoma of the ovary,
cervix, bladder, uterus,
cholangioma

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Investigation

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- Confirm hypoglycemia with simultaneous measurement of levels for insulin, proinsulin, C-peptide, β-hydroxybutyrate
- Typical pattern for NICTH
  - low glucose (serum glucose < 55 mg/dL)
    - low insulin/proinsulin/C-peptide/B - hydroxybutyrate levels
    - absence of positive results on an oral hypoglycemic agent screen
    - levels of total IGF-2 may be elevated or normal
    - elevated ratio of IGF-2 to IGF-1 > 3:1 may be helpful in the diagnosis (patient with recurrent hypoglycemia, ratios of 10:1 are virtually diagnostic for IGF-2–linked hypoglycemia

Bodnar et al. J Clin Endocrinol Metab, March 2014, 99(3):713–722.

Investigation

- Abnormally high IGF-2 to IGF-1 ratios can also occur in patients with sepsis and severe cachexia but both IGF-2 and IGF-1 levels are subnormal
- IGF binding protein (IGFBP)-1 and IGFBP-2 levels are increased
- Low GH levels lead to reduction in synthesis of IGFBP-3 and of the acid-labile subunit (ALS)

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IGF2 specimen collection

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- **Method :**

  Name Blocking Radioimmunoassay (RIA) after acid-alcohol extraction

- **Specimen Type** :

  Serum

- **Specimen Required**

  Draw blood in a plain, red-top tube(s)

  Separate within 1 hour of collection, freeze immediately

  Send 0.5 mL serum frozen

Treatment

- Immediate correction of hypoglycemia
- Treatment directed at the underlying malignancy
- Prevention of recurrent hypoglycemia if the tumor cannot be controlled

Acute management : similar to the management of hypoglycemia

- unconscious or unable to ingest carbohydrate → requires a subcutaneous or intramuscular injection of glucagon (0.5 to 1.0 mg)
- 25 g of 50 percent glucose (dextrose) intravenously

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Treatment

Treatment of the tumor : The mainstay of therapy for NICTH

- If the tumor is not resectable, palliative tumor debulking is usually performed Depending upon the tumor type, chemotherapy, radiation, cryoablation, radiofrequency ablation, or selective embolization of tumor feeding blood vessels may be used to control the tumor and improve hypoglycemia

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Treatment

Medical therapy :

Case series and reports

- Glucocorticoids (ex. prednisolone 40 mg daily), ★
- Glucagon
- Recombinant human growth hormone (rhGH)
- Somatostatin analogues and diazoxide have not been effective

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Treatment

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Initial medical therapy

Glucocorticoids (30 to 60 mg daily) are a reasonable initial therapy

Refractory hypoglycemia

glucagon (eg. hypoglycemia due to big IGF-2) : long-term intravenous glucagon infusion (0.06 to 0.30 mg/hour)

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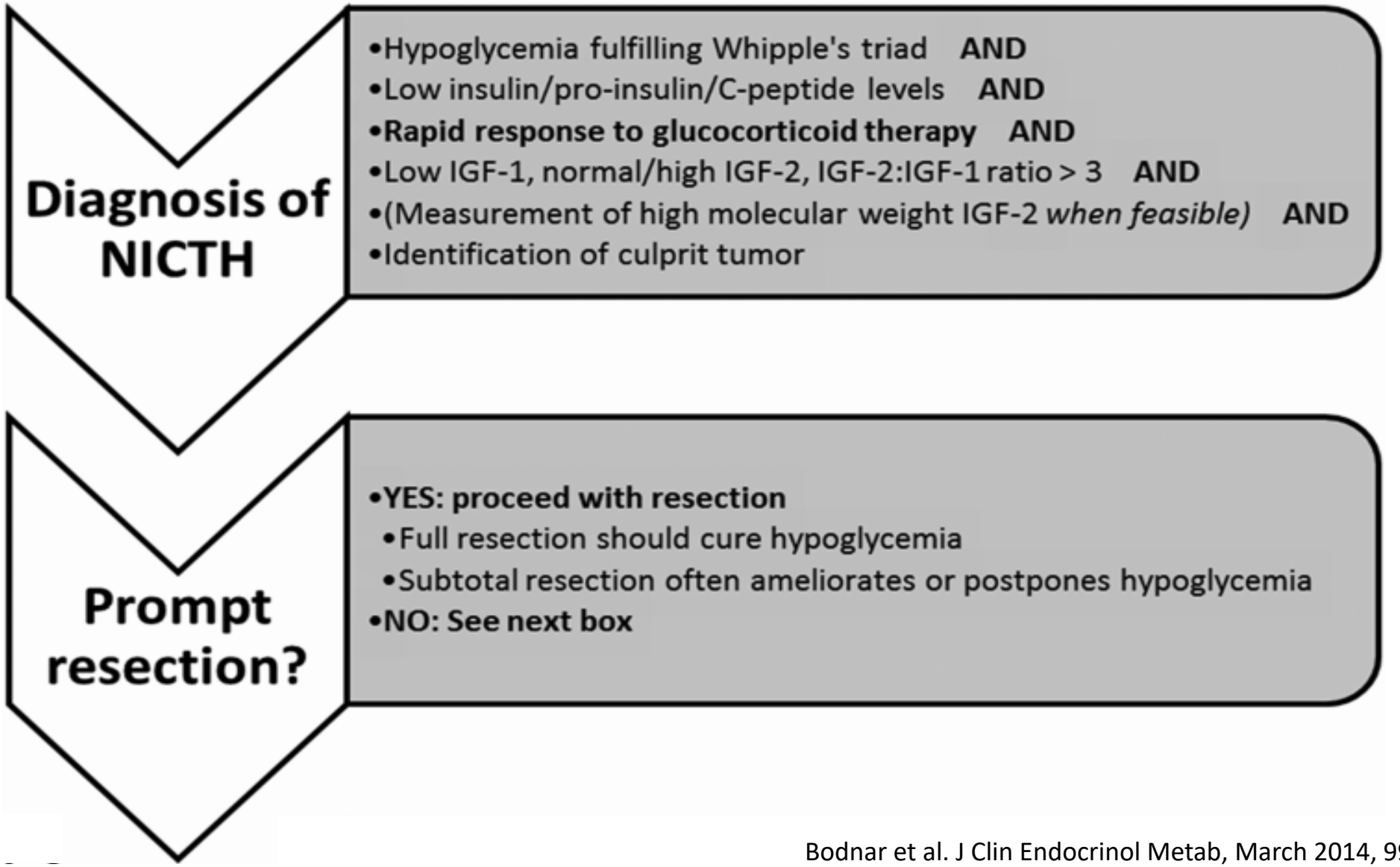
Non islet cell tumor



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Non islet cell tumor

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Not feasible?

- Alternate anti-tumor modalities available? (e.g., tumor embolization, radiation therapy, chemotherapy)
- Increase frequency or volume of caloric intake
  - Increased frequency of meals and snacks
  - Increased total calories
  - Enteral tube feeds or parenteral nutrition

Refractory to above?

- **Glucagon infusion** (best for short-term, inpatient/monitored situations, e.g., bridge to surgery or for palliation)
- **Glucocorticoids** (easy and inexpensive, but with potential for detrimental short-term and long-term adverse effects)
- **Recombinant hGH** (expensive, may have more favorable adverse effect profile compared to glucocorticoids, possible tumor growth?)
- *Octreotide, diazoxide have no role*

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