# Glucagon secretion in response to hypoglycemia in patients with congenital hyperinsulinism

**Yi Wang, Chunxiu Gong, Chang Su,Di Wu, Yi Gu, Min Liu,Wenjing Li**

**Beijing Children's Hospital, Capital Medical University.**

**Introduction** Hypoglycemia triggers the secretion of counter-regulatory hormones such as cortisol, growth hormone(GH), and glucagon, all of which are protective mechanisms to restore euglycemia. Congenital hyperinsulinism (CHI) is a group of genetic diseases with abnormal insulin secretion. The clinical phenotype of CHI is characterized by severe hypoglycemia. It has been suggested that CHI patients have abnormal glucagon secretion during hypoglycemia, but the data is limited.

**Methods** In this study, twogroups of patients with CHI (n=79) and ketosis hypoglycemia (KH, n=25) were reviewed retrospectively. All patients were admitted to the Department of Endocrinology at the Beijing Children's Hospital. Blood was collected during hypoglycemia, serum glucagon was measured by radioimmunoassay, and insulin was measured by electrochemiluminescence immunoassay.

**Results** CHI patients had more severe hypoglycemia than patients with KH. The mean glucose levels in CHI patients were 1.81±0.54 mmol/L, and the levels were 2.13±0.50 mmol/L(p<0.050.01) in KH patients. This severe hypoglycemia in CHI was the result of abnormal insulin secretion. Insulin levels of CHI patients were 9.20(5.71,16.95)(median (Interquartile)) IU/ml, whereas KH patients had very low insulin levels( 0.35 range0.20,0.10)IU/ml. However, glucagon secretion in response to hypoglycemia in CHI patients was not low: the median glucagon value in CHI patients was 222(range 165,355)pg/ml compared to153(range 116,215)pg/ml in KH patients (p< 0.05). We also compared the hormones secretion when blood glucose levels of the two groups had no significant difference, the results showed that Insulin levels of CHI patients were(13.05±12.30) IU/ml, but KH patients still had low insulin levels(0.58±0.47) IU/ml.Whereas glucagon levels of CHI patients were 216（174,262）pg/ml, which was higher than that of KH patients (142 range 114,197,p< 0.05).For CHI patients ,cortisol secretion was lower than that in KH patients, but growth hormone levels had the reverse result. Besides, we choosed three different glucose levels in order to discover the law of glucagon secretion, but the result suggested that glucagon had no obvious secretion peak in CHI patients.

Table1Hormones secretion between CHI and KH patients

| | CHI（n=79） | KH（n=25） | P value |
|---|---|---|---|
| | | | CHI vs KH |
| Blood Glucose(mmol/L) | 1.81±0.54 | 2.13±0.50 | 0.011 |
| Blood Insulin(IU/ml) | 9.20(5.71,16.95) | 0.35(0.20,0.10) | 0.000 |
| Insulin/Glucose Ratio | 5.73(3.27,10.07) | 0.17(0.09,0.46) | 0.000 |
| Blood Glucagon(pg/ml) | 222(165,355) | 153(116,215) | 0.021 |
| Glucagon/Glucose Ratio | 116.23(83.20,216.23) | 73.21(49.39,113.60) | 0.006 |
| Glucagon/Insulin Ratio | 24.87(12.50,41.81) | 471.79（151.03,792.50） | 0.000 |

| | | | |
|---|---|---|---|
| Blood ACTH（pg/ml） | 21.20（11.90,45.01） | 25.65（20.50,48.90） | 0.133 |
| Blood GH（ng/ml） | 3.34（1.34,7.32） | 1.54（0.46,3.84） | 0.011 |
| Blood Cortiol（ug/dl） | 10.35（5.78,17.43） | 28.70（21.30,33.30） | 0.000 |

Table 2 Hormones secretion between CHI and KH patients at similar glucose level

| | CHI（n=31） | KH（n=19） | P value |
|---|---|---|---|
| | | | CHI vs KH |
| Blood Glucose(mmol/L) | 2.34±0.22 | 2.33±0.23 | 0.899 |
| Blood Insulin(IU/ml) | 13.05±12.30 | 0.58±0.47 | 0.000 |
| Insulin/Glucose Ratio | 5.76±5.85 | 0.24±0.19 | 0.000 |
| Blood Glucagon(pg/ml) | 216（174,262） | 142（114，197） | 0.017 |
| Glucagon/Glucose Ratio | 92.40（70.76,110.20） | 64.09（46.99,87.64） | 0.032 |
| Glucagon/Insulin Ratio | 24.87（12.70,55.11） | 520.90（142.41,828.75） | 0.000 |
| Blood ACTH（pg/ml） | 20.05（11.98,61.65） | 24.70（20.50,43.83） | 0.460 |
| Blood GH（ng/ml） | 6.26±8.10 | 2.74±2.79 | 0.046 |
| Blood Cortiol（ug/dl） | 11.90（6.87,20.75） | 29.40（20.15,32.45） | 0.000 |

Table3 Hormones secretion in CHI patients at different glucose levels

| | CHI1（n=24） | CHI2（n=31） | CHI3（n=24） | P value | P value | P value |
|---|---|---|---|---|---|---|
| | | | | CHI1 vs CHI2 | CHI1 vs CHI3 | CHI2 vs CHI3 |
| Blood Glucose(mmol/L) | 1.19±0.35 | 1.83±0.17 | 2.42±0.18 | 0.000 | 0.000 | 0.000 |
| Blood Insulin(IU/ml) | 10.69（7.11,21.60） | 8.20（4.27,14.00） | 8.68（5.70,16.86） | 0.507 | 0.436 | 0.869 |
| Insulin/Glucose Ratio | 8.69（6.15,21.17） | 4.48（2.26,8.75） | 3.70（2.27,6.74） | 0.026 | 0.014 | 0.687 |
| Blood Glucagon(pg/ml) | 204（161,266） | 236（172，408） | 213（151,262） | 0.965 | 0.628 | 0.579 |
| Glucagon/Glucose Ratio | 173.20（117.52,261.97） | 125.48（86,221.58） | 89.57（54.51,109.17） | 0.028 | 0.002 | 0.314 |
| Glucagon/Insulin Ratio | 20.53（11.09,29.73） | 39.83（18.90,60.70） | 22.33（12.47,31.52） | 0.057 | 0.299 | 0.353 |
| Blood ACTH（pg/ml） | 19.25（11.18,28.70） | 23.40（11.90,47.18） | 18.90（11.75,62.40） | 0.768 | 0.301 | 0.431 |
| Blood GH（ng/ml） | 5.87±8.61 | 5.72±5.67 | 6.00±8.09 | 0.941 | 0.956 | 0.897 |
| Blood Cortiol（ug/dl） | 7.35（4.41,19.40） | 12.65（6.61,18.28） | 10.35（6.93,16.50） | 0.254 | 0.819 | 0.379 |

CHI1：Blood Glucose<1.6mmol/L, CHI2:1.6≤Blood Glucose<2.2mmol/L,CHI3:2.2≤Blood Glucose<2.8mmol/L

Furthermore, we compared the subgroups of CHI patients, grouped by sensitivity to Diazoxide, which is a frontline insulin secretion inhibitor, by targeting the KATP channel. The number of Diazoxide-sensitive CHI patients was 52, the others were Diazoxide-unresponsive. Insulin and glucagon secretion and glucagon/insulin ratio in these two groups of CHI patients were similar. There were 14 cases of CHI carry mutations at KATP channel gene (ABCC8 or KCNJ11).Glucagon secretion in response to hypoglycemia in patients with KATP channel mutations was similar to the patients with negative mutations for known CHI genes.

**Conclusion** The data suggests that in response to hypoglycemia, glucagon secretion in the CHI patients of the Chinese population is not impaired. Under similar circumstances of severe hypoglycemia, glucagon secretion in CHI patients is significant higher than that in KH patients, indicationg α cells of CHI patients have better responsive to hypoglycemia. Although the pricise regulation mechanism of glucagon secretion remains unclear, it is well known that islet β cells is an important factor in the regulation of α cells secreting glucagon[1]. Insulin released from β cells have been shown to inhibit α-cell electrical activity and glucagon secretion in isolated islets[2]. But High level insulin doesn't inhibit glucagon secretion in CHI patients, suggesting that paracrine between β cells and α cells occurs obstacle.

References

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