

**Glucose-dependent Insulinotropic Polypeptide (GIP) Resistance and  $\beta$ -cell Dysfunction Contribute to Hyperglycaemia in Acromegaly**

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**Supplementary Table 1: Δ Change in glycaemic status after surgery**

<b>Parameters</b>	<b>Acromegaly Cured (n = 8) Mean± S.D. (Mean Rank )</b>	<b>Acromegaly Not Cured (n = 12) Mean± S.D. (Mean Rank)</b>	<b>Man Whitney U test Chi square (P value)</b>
<b>FPG (mg/dl)</b>	<b>-35.4± 52.4 (9)</b>	<b>-13.9± 20.6 (11.50)</b>	<b>0.857(0.355)</b>
<b>FPI (μU/ml)</b>	<b>-14.8±8.9 (8.75)</b>	<b>-11.4±8.7 MR=11.67</b>	<b>1.167(0.280)</b>
<b>Fasting C-peptide (ng/ml)</b>	<b>-2.0±1.6 (9.88)</b>	<b>-1.6±1.2 (10.92)</b>	<b>0.149 (0.700)</b>
<b>HOMA-IR</b>	<b>-1.8± 1.2 (9.13)</b>	<b>-1.2±1.0 (11.42)</b>	<b>0.720 (0.396)</b>
<b>HOMA- IS</b>	<b>27.5±15.4 (12.75)</b>	<b>25.9±44.8 MR=9</b>	<b>1.929(0.165)</b>
<b>Matsuda Index</b>	<b>4.9±2.9 (14.25)</b>	<b>2.0±1.9 (8)</b>	<b>1.168 (0.021*)</b>
<b>HOMA-β</b>	<b>-9.4±89.5 (11.50)</b>	<b>-13.8±37.7 (9.83)</b>	<b>0.381 (0.537)</b>
<b>Insulinogenic index</b>	<b>-2.2±3.9 (8.75)</b>	<b>-0.5±1.9 (11.67)</b>	<b>1.168 (0.280)</b>
<b>Hyperinsulinemic Euglycemic Clamp(HEC)</b>			
<b>GDR (mg/kg/min)</b>	<b>1.7±1.5 (11.38)</b>	<b>1.3±1.2 (9.92)</b>	<b>0.292 (0.589)</b>

<b>IS (mg/kg/min/uU/ml)</b>	<b>5.3,3.2 (13.31)</b>	<b>2.9,2.8 (8.63)</b>	<b>3.016 (0.082)</b>
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\* Significant difference between the groups

FPG- Fasting plasma glucose; FPI- Fasting plasma insulin; FPC- Fasting plasma c-peptide; HOMA-IR- Homeostatic model assessment of insulin resistance; HOMA- $\beta$  -Homeostatic model assessment of  $\beta$  cell function; HOMA-IS- Homeostatic model assessment of insulin sensitivity; GDR: Glucose disposal rate; and IS- insulin sensitivity.

**Supplementary Table 2 :  $\Delta$  Change in glycaemic status and incretin parameters after surgery during MMT**

<b>Parameters</b>	<b>Acromegaly Cured (n = 8) Mean<math>\pm</math>S.D. (Mean Rank )</b>	<b>Acromegaly Not Cured (n = 12) Mean<math>\pm</math> S.D. (Mean Rank )</b>	<b><i>Man Whitney U test</i>  <i>Chi square</i> (P value)</b>
<b>AUC-glucose (mg/dl <math>\times</math> min)</b>	<b>-8586.0<math>\pm</math>15515.5 (11.13)</b>	<b>-7762.5<math>\pm</math>9220.7 (10.08)</b>	<b>0.149 (0.700)</b>
<b>AUC-Insulin (<math>\mu</math>U/ml<math>\times</math>min)</b>	<b>-22551.9<math>\pm</math>21332.1 (7.50)</b>	<b>-8313.3<math>\pm</math>9521.9 (12.50)</b>	<b>3.429 (0.064)</b>
<b>AUC- C- peptide (ng/ml x min)</b>	<b>-1019.9<math>\pm</math>486.4 (8.25)</b>	<b>-765.5<math>\pm</math>877.3 (12.00)</b>	<b>1.929 (0.165)</b>
<b>Fasting GIP(pmol/L)</b>	<b>-18.0<math>\pm</math>24.1 (10.25)</b>	<b>-12.3<math>\pm</math>26.1 (10.67)</b>	<b>0.024 (0.877)</b>
<b>AUC-GIP (pmol/L <math>\times</math> min)</b>	<b>-9654.1<math>\pm</math>5919.1 (7.75)</b>	<b>-4335.9<math>\pm</math>7440.2 (12.33)</b>	<b>2.881 (0.090)</b>
<b>Fasting GLP-1 (pmol/L)</b>	<b>0.2<math>\pm</math>3.7 (9.88)</b>	<b>-1.4<math>\pm</math>9.1 (10.92)</b>	<b>0.149 (0.700)</b>
<b>AUC-GLP1 (pmol/L <math>\times</math> min)</b>	<b>731.3<math>\pm</math>1826.2 (11.38)</b>	<b>-887.5<math>\pm</math>3066.3 (9.92)</b>	<b>0.292 (0.589)</b>
<b>Fasting Glucagon (pmol/L)</b>	<b>-8.1<math>\pm</math> 5.8 (11.75)</b>	<b>-12.2<math>\pm</math>12.4 (9.67)</b>	<b>0.595 (0.440)</b>
<b>AUC Glucagon (pmol/L<math>\times</math> min)</b>	<b>-1295.3<math>\pm</math>1554.1 (11.63)</b>	<b>-2101.2<math>\pm</math>2094.3 (9.75)</b>	<b>0.482 (0.487)</b>
<b>M<sub>0</sub> x10<sup>-7</sup> (1/min)</b>	<b>-33.8<math>\pm</math>87.8</b>	<b>-1.8<math>\pm</math>39.6</b>	<b>1.006</b>

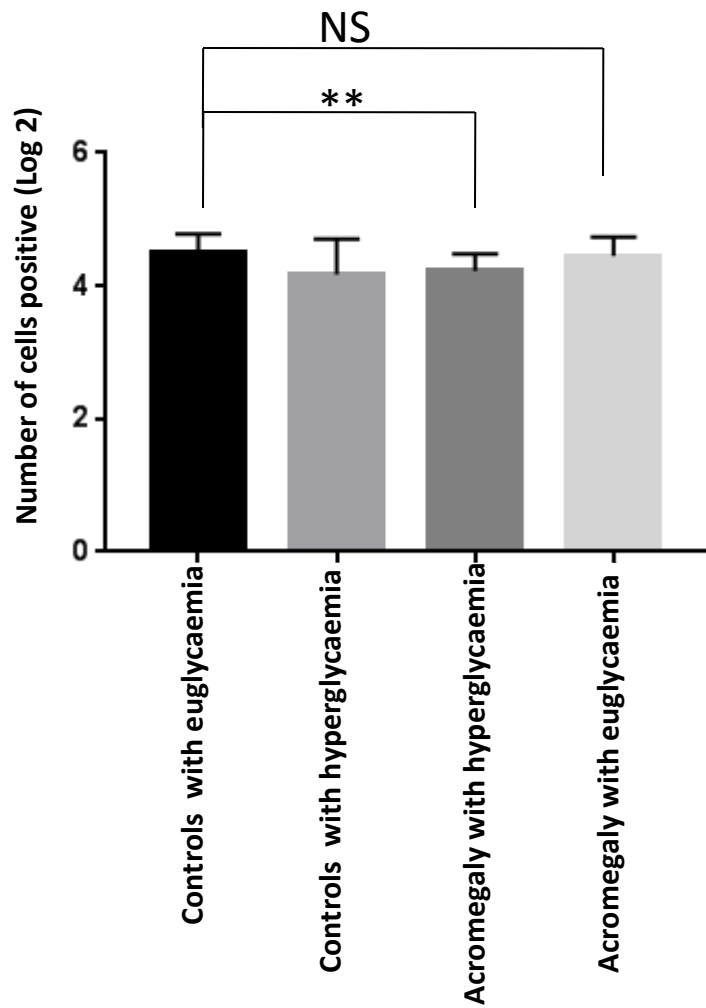
	<b>MR=12.63</b>	<b>MR=9.08</b>	<b>(0.316)</b>
<b>M<sub>1</sub> x10<sup>-7</sup> (1/min)</b>	<b>0.9±9.1</b> <b>(8.88)</b>	<b>-0.9±5.4</b> <b>(11.58)</b>	<b>1.720</b> <b>(0.190)</b>

\* Significant difference between the groups

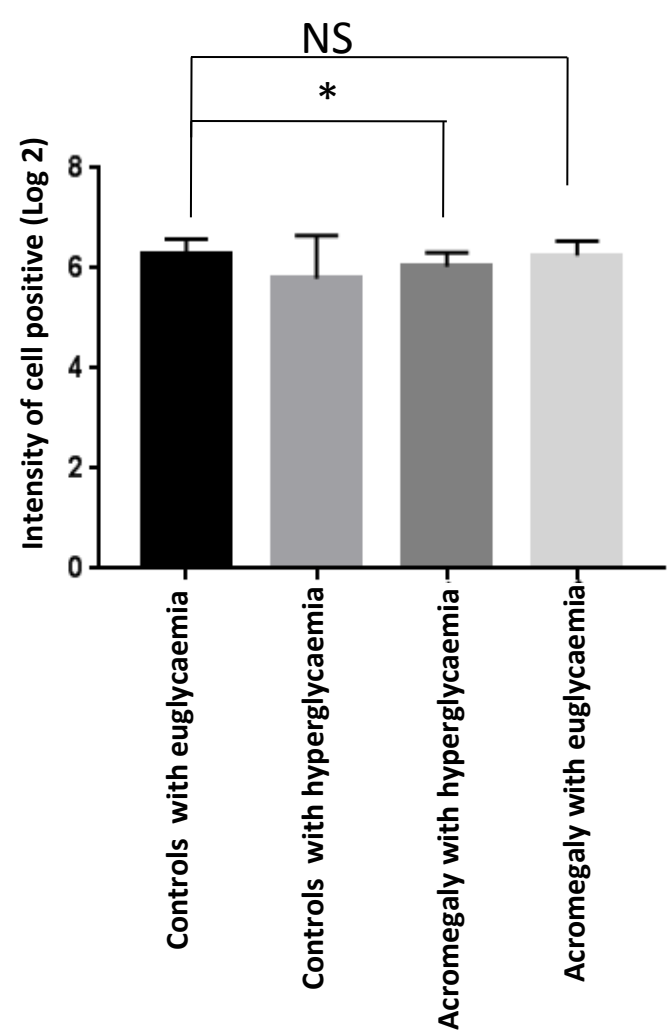
AUC- Area under curve; M<sub>0</sub> – Basal β-cell function; M<sub>1</sub>- postprandial β-cell function.

**Figure Legends:**

**Supplementary Figure 1:** The bar diagram showing a significantly lower number and intensity of GIP staining cells in patients of acromegaly with diabetes as compared to healthy controls.



Number of cell positive (Log2)		P-value
Controls with euglycaemia	Acromegaly with hyperglycaemia	0.009**
	Acromegaly with euglycaemia	0.4
Controls with hyperglycaemia	Acromegaly with hyperglycaemia	0.54
	Acromegaly with euglycaemia	0.75
Acromegaly with hyperglycaemia	Acromegaly with euglycaemia	0.09



Intensity of cell positive (Log 2)		P-value
Controls with euglycaemia	Acromegaly with hyperglycaemia	0.03*
	Acromegaly with euglycaemia	0.455
Controls with hyperglycaemia	Acromegaly with hyperglycaemia	0.6526
	Acromegaly with euglycaemia	0.5848
Acromegaly with hyperglycaemia	Acromegaly with euglycaemia	0.1406