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# Metabolism

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### PRELIMINARY REPORT

#### Are Patients With Hirschsprung's Disease Prediabetic?

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Hirschsprung's disease (HD) is considered a focal disease usually confined to the distal colon and rectum. However, autonomic dysfunction and dysmotility in the upper gastrointestinal tract have been reported, suggesting that this disease is not only confined to the distal gastrointestinal tract. This study examines the fasting and postprandial levels of glucose and insulin in adult patients with HD to elucidate whether there might also be an endocrine involvement in this disease. Sixteen patients with surgically treated HD during early childhood and 17 healthy subjects were studied. All subjects ingested a caloric liquid meal containing glucose, lactose, maize oil, and water (2,020 kJ) after an overnight fast. Blood samples were collected at regular intervals for insulin and glucose analyses. Fasting levels of both glucose ( $P < .05$ ) and insulin ( $P < .02$ ) were significantly higher in patients compared with healthy controls. Peak concentration of insulin following meal intake was significantly higher in the patient group ( $P < .05$ ), and peak concentration of glucose tended to be higher in patients compared with controls ( $P = .06$ ). There was no correlation between body mass index and serum levels of glucose or insulin. The present study shows that adult patients treated for HD during childhood have an impaired glucose and insulin homeostasis, indicating a mild degree of insulin resistance. This may imply susceptibility towards development of non-insulin-dependent diabetes mellitus.

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**H**IRSCHSPRUNG'S DISEASE (HD) is a focal aganglionosis usually confined to the rectum and distal colon. However, abnormalities in other parts of the nervous system<sup>1</sup> and the gastrointestinal tract<sup>2,3</sup> have been reported, suggesting that this disease is not only confined to the distal gastrointestinal tract. This study examines the fasting and postprandial levels of glucose and insulin in adult patients with HD to show whether there also might be an involvement of the endocrine function in this disease.

#### SUBJECTS AND METHODS

Sixteen patients (15 men and 1 woman) surgically treated for HD during early childhood were identified in the medical records of the Norwegian National Hospital. Their median age was 21 years (range, 16 to 26) and body mass index 24 (range, 20 to 37). Only 1 of the patients had gastrointestinal symptoms significantly affecting the general quality of life. The main symptom of this patient was meteorism. Seventeen healthy subjects (15 men and 2 women) with median age of 25 years (range, 22 to 30) and body mass index 23 (range, 19 to 26) served as controls. There was no significant difference in body mass index between patients and controls. All subjects gave their written informed consent, and the study protocol was approved by the regional ethics committee for medical research.

Both patients and controls ingested a caloric liquid meal containing glucose (45.0 g), instant milk (44.4 g), maize oil (15.6 g), and water after overnight fasting. Caloric load of the meal was 2,020 kJ (57%

carbohydrate, 30% fat, 13% protein). Blood samples were drawn from a venous cannula in the fasting state and 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, and 120 minutes after meal intake. Serum glucose was analyzed by the hexokinase method and insulin by a radioimmunoassay. Results are given as mean and 95% confidence intervals. Two sample *t* test and correlation technique were applied. The level of statistical significance was set at  $P < .05$ .

#### RESULTS

The fasting serum concentration of glucose was 5.1 mmol/L (4.9 to 5.4) in patients and 4.7 mmol/L (4.5 to 5.0) in controls ( $P < .05$ ) (Fig 1A). Corresponding values for insulin were 146 pmol/L (118 to 175) and 105 pmol/L (87 to 122) ( $P < .02$ ) (Fig

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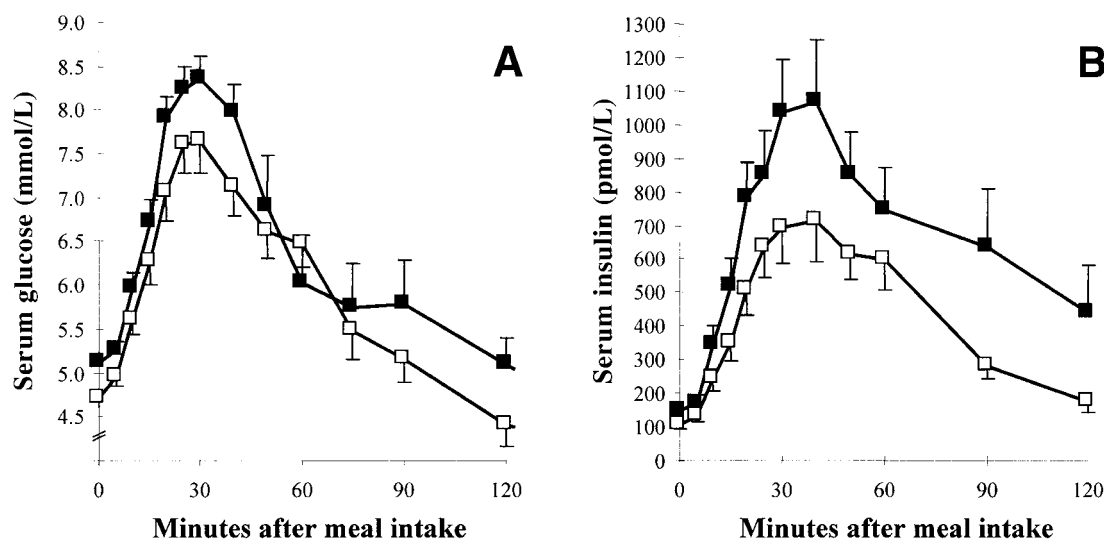
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**Fig 1.** Mean serum glucose (A) and insulin (B) following ingestion of a caloric liquid meal in adult patients with HD (■;  $n = 16$ ) and controls (□;  $n = 17$ ). Error bars denote standard error of the mean. The fasting levels of glucose ( $P < .05$ ) and insulin ( $P < .02$ ) were higher in the patient group than in the control group. The peak concentration of glucose tended to be higher in the patients than in the controls ( $P = .06$ ), whereas the higher level of insulin persisted after meal intake with peak concentration of insulin being higher in the patients than in the controls ( $P < .05$ ).

1B). Fasting glucose to insulin ratio ( $[\text{glucose}]/([\text{insulin}] \times 10^6)$ ) was 39 (32 to 45) in patients and 52 (39 to 64) in controls ( $P = .06$ ). Peak concentration of glucose after the meal was 9.2 mmol/L (8.4 to 10.0) in patients and 8.4 mmol/L (7.9 to 8.9) in controls ( $P = .06$ ). Corresponding values for insulin were 1,281 pmol/L (913 to 1,649) and 819 pmol/L (589 to 1,049) ( $P < .05$ ). Ratio of peak concentration of glucose to insulin was 8.8 (6.8 to 10.8) in patients and 12.4 (9.7 to 15.0) in controls ( $P < .05$ ). The increase in concentration of glucose from baseline to peak was 4.1 mmol/L (3.4 to 4.8) in patients and 3.6 mmol/L (3.2 to 4.1) in controls ( $P = .26$ ). Corresponding values for insulin were 1,134 pmol/L (788 to 1,481) and 715 pmol/L (493 to 936) ( $P < .05$ ). There was no correlation between body mass index and serum levels of glucose or insulin. Excluding the patient with body mass index of 37 did not influence the results of the statistical tests.

## DISCUSSION

The present study shows that HD is associated with increased serum concentrations of glucose and insulin. In the fasting state, the increase amounted to 40% for insulin and 8% for glucose compared with the controls. Meal stimulation resulted in a 40% excess increase of serum insulin in the patients with HD compared with the controls, whereas there was no excess increase in serum glucose.

The increased serum concentrations of insulin postprandially may be due to a general neuroendocrine dysfunction, and the excess increase may, in addition, be the result of altered gastric emptying in patients with HD. The increased serum concentrations of both glucose and insulin in the fasting state, however, indicate a degree of insulin resistance in this patient population. Accordingly, a previous report demonstrated a tendency towards increasing incidence of diabetes mellitus in the families of patients with HD.<sup>4</sup> The present findings raise the question

whether patients with HD have a predisposition to non-insulin-dependent diabetes mellitus.

Before modern surgical treatment of HD was introduced about 40 years ago,<sup>5</sup> most patients with severe HD did not survive. Few patients with the same severity of disease as the present patient group have yet reached the age in which non-insulin-dependent diabetes mellitus should be expected to occur.

Bias due to age and body mass index was accounted for by matching the control group with the patients. The magnitude of the differences between these moderately-sized study groups indicates that the findings may be of clinical importance.

In conclusion, the present study shows that adult patients treated for HD during childhood have an abnormal glucose and insulin homeostasis of yet unclear origin and significance. This may indicate susceptibility towards the development of non-insulin-dependent diabetes mellitus, which suggests that blood glucose levels should be monitored in patients with HD during aging.

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