Beta-cell function improves with intensive insulin therapy in patients with NIDDM

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It has been reported that high concentrations of circulating glucose have desensitizing and, in long-term, toxic effects on (i-cells. These adverse effects lead to impaired insulin secretion. We investigated p-cell function in five patients with newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM). p-cell function was investigated by C-peptide response to glucagon before and after 3-month intensive insulin treatment period during which tight glycemic control was made. At the end of 3 months, the glycosylated hemoglobin levels decreased from 9.5±1.6% to 7.1±0.8 (p<0.05) indicating to improved glycemic control. Meanwhile, significant increments in stimulated C-peptide levels were demonstrated with intensive insulin therapy (0.93±0.2 nmol/l vs 1.50±0.6 nmol/l; p<0.05). Daily insulin requirements declined gradually in all patients and insulin was discontinued within one month after the completion of intensive insulin therapy. These preliminary data suggest that tight glycemic control should be aimed in newly diagnosed NIDDM to overcome the deleterious effects of hyperglycemia on p-cells and to restore initially impaired insulin secretory function.
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Key Words: p-cell function, Non-insulin dependent diabetes mellitus, Insulin

Insulin secretion is altered in human diabetes. Selective loss of the p-cell response to glucose has been described in both non-insulin-dependent (NIDDM) (1-3) and early insulin-dependent-diabetes mellitus (IDDM) (4,5). High glucose concentrations have been shown to cause reductions in insulin content and impairment of glucose-induced insulin secretion in cultured p-cells (6,7). It has also been shown that |3-cell function improves upon culturing with lower glucose concentrations (6,7). To a certain extent, these observations may have reflected decreased insulin stores and (3-cell exhaustion as a result of repeated, short-term exposure to high concentrations of glucose (8).

We conducted the present study to determine the clinical validities of these observations in NIDDM. Therefore, we investigated the p-cell function at diagnosis and after restoration of glycemic control with intensive insulin therapy in non insulin dependent diabetic patients with relatively short duration of symptoms.

MATERIALS AND METHODS

Patients: Five male patients with NIDDM with a mean age of 33±7 (range: 25-44) years were enrolled in the study. Mean symptom duration was 2.8±1.9 (range: 1-6) months and mean body mass index was 25.9+3.5 (range: 22.2-31.2) kg/m2. None of them had taken any oral hypoglycemic drugs (sulfonylureas of biguanides) before attending to our clinic. All patients had high glycosylated hemoglobin (HbA1c) (9.5±1.6%; range: 8.2-10.6%), fasting (16.1±3.2 mmol/l; range: 12.2-19.5 mmol/l) and 2-hour postprandial plasma glucose levels (23.0±3.5 mmol/l; range: 19.8-29.0 mmol/l) indicating to poor glycemic control. Ketosis was absent in all patients. Informed written consent was obtained from each patient.

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Procedures: To determine p-cell reserve, all patients underwent C-peptide stimulation tests with glucagon. After an over-night fast, they received 1 mg glucagon by intravenous route at 08:00 a.m. and samplings for C-peptide determinations were obtained 6 minutes afterwards. Islet cell antibody (ICA) determinations were also performed at diagnosis.

To achieve tight glycemic control, intensive insulin therapy was initialized and continued for 3 months in each patient. Our goal was to maintain fasting glucose levels between 3.3-5.0 mmol/l and 2-hour postprandial glucose levels below 7.7 mmol/l. For initial therapy, 0.6 U/kg/d human insulin was given, 25% intermediate acting (NPH) and 75% regular. NPH insulin was given at bedtime (22HOO) and changed every 48 hours solely on the basis of the fasting blood glucose level. In the initation phase, the regular insulin dose for each meal was based on the postprandial glucose value from the previous day. Once the therapeutic plan was developed, alterations in

the daily insulin dose were based on immediate preprandial glucose levels. Regular insulin was injected immediately before each meal. Changes in insulin doses were made according to the schedule which has been recommended by Schriffin et al (9). The patients self-monitored their blood glucose levels and recorded them with insulin doses during the entire treatment period. The consultant physician (AG) checked these records weekly. Besides, the patients gave information about their records in they had any problem regarding to the insulin dose adjustments.

At the end of the 3 months, conventional twice-daily insulin therapy (mixture of regular and intermediate acting human insulin before breakfast and dinner) replaced the intensive therapy regimen. Meanwhile, C-peptide stimulation tests, glycosylated hemoglobin (HbA1c) and fasting/2-h postprandial plasma glucose (FPG) determinations were repeated.

Assay procedures: Plasma glucose concentrations were determined by glucose-oxidase method using a spectrophotometer. Glycosylated hemoglobin levels (HbA1c) were measured by cation-exchange chromatography using a commercial kit (BIO-RAD, Richmond, CA, USA; normal range: 6-8%). Serum C-peptide concentrations were measured with a commercial radioimmunoassay kit (INCSTAR, Stillwater, MN, USA). Normal range for the assay was 0.33±1.20 nmol/l. Intraassay and interassay coefficients of variation were 5.7 and 15.3 percent, respectively. The minimum detectable amount was 0.02 nmol/l. Islet cell antibodies (ICAs) were determined by a qualitative microwell/ELISA test (ISLETEST, Biomerica, CA, USA) using highly purified mixture of pancreatic antigens as proposed by Boitard et al (10).

Statistical analysis: Data are presented as means±standart deviation (SD). Wilcoxon Signed-Rank test was used to check the significance of differences between variables which have been determined before and after intensive insulin therapy period.

RESULTS

Glycemic control was improved in all patients with 3-month intensive insulin therapy. Glycosylated hemoglobin levels (HbA1c) decreased from 9.5±1.6% to 7.1±.0.8% (range: 6.1-8.1%) ($p<0.05$). Fasting and 2-hour postprandial glucose levels improved significantly with respect to the values measured at diagnosis (fasting; 16.1+3.2 mmol/l vs 5.4±0.6 mmol/l; $p<0.05$, postprandial; 23.0±3.5 mmol/l vs 6.0±1.4 mmol/l; $p<0.05$). Meanwhile, daily insulin requirements decreased from 45.7±7.5 U to 39.6±15.3 U, but the difference was not statistically significant ($p=0.46$). All patients gave negative reactions with respect to ICAs. After tight glycemic control, significant increments in stimulated C-peptide levels were observed (initial; 0.93±0.2 nmol/l vs final; 1.5±0.6 nmol/l; $p<0.05$) (Figure 1).

At the follow-up period, daily insulin requirements gradually declined in all patients after intensive therapy period (data not shown). Insulin therapy was discontinued within one month in all patients and normoglycemia (i.e. FPG between 3.8-6.1 mmol/l; 2-hour postprandial glucose <7.7 mmol/l) was maintained with only diet up to the time this paper has been delivered for publication (i.e. 6 months after diagnosis).

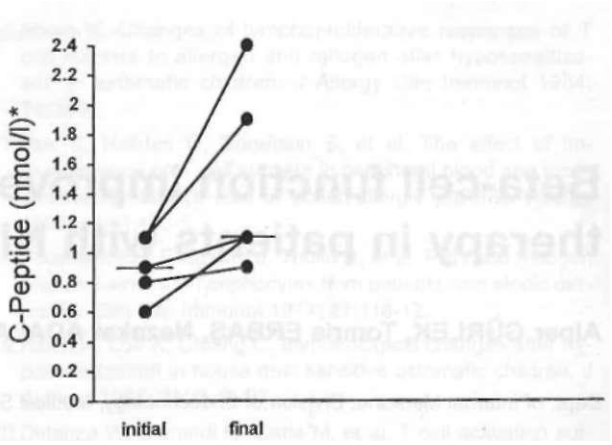

Figure 1. Serum C-peptide levels before and after intensive insulin therapy. The median values (horizontal lines) were significantly different ($p<0.05$ by Wilcoxon test).
'Stimulated C-peptide level 6 min after 1 mg glucagon

DISCUSSION

It has previously been remonstrated that high circulating glucose levels can cause deleterious effects on p-cell function (11-13). The adverse effects of glucose on p-cell function for prolonged periods (e.g. years) are known as glucose toxicity, and these are inherently irreversible (8). However, the term glucose desensitization implies a temporary, readily induced, physiological and reversible state of cellular refractoriness due to repeated exposure to an agonist (i.e. glucose) (8). In human islet experiments, Eizirik et al (7) have used culture medium containing 5.6, 11 or 28 mM glucose for seven days. Insulin content and glucose-induced insulin secretion has been shown to decrease when high glucose concentrations were used. These changes were partially reversible when the glucose concentration was lowered. Smilarly, Vague et al (14) have reported that normalization of hyperglycemia by 20-hour insulin infusion restored glucose-induced insulin secretion. These data provided important evidence about the concept "glucose desensitization". Of note, exposure to hyperglycemia was in terms of weeks.

In this preliminary study, we examined the clinical applicability of these experimental observations. We determined the C-peptide responses to glucagon in NIDDM patients at diagnosis. This is an easy and useful test which shows the p-cell insulin secretory function (15). We diagnosed our patients as NIDDM since they have retained a relatively preserved p-cell function with glucagon-stimulated C-peptide responses above 0.6 nmol/l (16), and had negative reactions with respect to the ICAs at diagnosis (17), Furthermore, they were nonketotic at initial presentation. Although these data strong-

IV suggest that our patients had NIDDM, they do not exclude the occasional patient with atypical-onset IDDM with negative ICAs, who will eventually deteriorate into an insulin-deficient state (18,19). We selected patients with relatively short duration of symptoms, assuming that high circulating glucose levels have desensitized their (3-cells. Our expectation was that, upon restoration of normoglycemia during 3 months, the p-cells would exhibit an improved response to stimulation with glucagon. Indeed, the results of our study demonstrated that p-cell function is impaired in newly diagnosed NIDDM, possibly due to high circulating glucose levels, p-cell function was improved with tight glycémie control in our patients, suggesting the reversibility of this phenomenon.

Previously, Garvey et al (20) have reported that mean 24 h integrated serum insulin and C-peptide concentrations have increased significantly with 3-week intensive insulin therapy in NIDDM. They have also demonstrated that post-treatment C-peptide responses to intravenous glucagon have improved when glucose infusion was made. Our results support their observations, but we observed significantly improved C-peptide responses to glucagon without glucose infusion. Andrews et al (21) have shown that 1-month rigorous insulin therapy increased the glucose-induced insulin secretion 2.5-fold, and this effect has been maintained for 2 weeks after the withdrawal of insulin therapy. Interestingly, normoglycemia was maintained with only diabetic diet after the discontinuation of insulin therapy for at least two months in our patients.

In conclusion, the results of the present study suggest that we should intensify our efforts to achieve tight glycémie control in newly diagnosed patients with NIDDM. This approach would lead the patients to better and easier glycémie control with an improved p-cell function and prevent toxic effects of glucose on p-cells in long term. However, since the whole-time follow-up is limited with 6 months and the patient number is small in this study, further studies with larger patient groups and longer follow-up periods are essential.

insüline bağımlı olmayan diabetli hastalarda yoğun insülin tedavisi p-hücre fonksiyonunu düzeltiyor.

Yüksek konsantrasyonlarda glukozun p hücreleri üzerinde kısa vadede desensitizan, uzun vadede ise toksik etkileri olduğu bildirilmiştir. Bu zararlı etkiler insülin sekresyonunun bozulmasına neden olabilmektedir. Bu çalışmada yeni tanı almış olan 5 adet insüline bağımlı olmayan diyabetik hastanın p hücre fonksiyonları incelenmiştir, p hücre fonksiyonu, sıkı glisemik kontrolün sağlanmaya çalışıldığı 3 aylık yoğun insülin tedavisi döneminin öncesinde ve sonrasında glukagona C-peptid yanıtları ölçülerek değerlendirilmiştir. 3 aylık dönem sonunda, glikozile hemoglobin düzeylerinin %9.5±1.6'dan %7.1±0.8'e düşmesi ve bunun istatistiksel olarak anlamlı olması (p<0.05), glisemik kontrolün sağlandığını göstermiştir. Yoğun insülin tedavisi döneminin sonunda glukagonla uyarılmış ortalama C-peptid düzeyinin 0.93±0.2 nmol/l'den 1.5±0.6 nmol'ye (p<0.05) yükselmesi, p hücre fonksiyonunun düzeldiğini göstermiştir. Yoğun insülin tedavisinin bitiminden sonra 1 ay içinde hastaların günlük insülin. ihtiyaçları giderek azalmış ve tayın sonunda insülin tedavisi kesilmiştir. Bu ön veriler, insüline bağımlı olmayan diyabetlilerde, hipergliseminin p hücreleri üzerindeki olumsuz etkilerini gidermek ve glukoz desensitizasyonu nedeniyle bozulan p hücre fonksiyonunu yeniden tesis etmek için sıkı glisemik kontrolün amaçlanması gerektiğini düşündürmektedir. [Türk J Med Res 1996; 14(2):63-66]

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