Interferon- α reduces insulin resistance and β -cell secretion in responders among patients with chronic hepatitis B and C

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Abstract

This study aimed at elucidating the effects of interferon (IFN)- α on glucose metabolism in patients with chronic hepatitis B and C infections. Twenty-eight biopsy-proven patients with chronic hepatitis B (ten cases) and hepatitis C (18 cases) were given IFN- α for a total of 24 weeks. The patients received a 75 g oral glucose tolerance test (OGTT), glucagon stimulation test, tests for type 1 diabetes-related autoantibodies and an insulin suppression test before and after IFN- α therapy. Ten of the 28 patients responded to IFN- α therapy. Steady-state plasma glucose of the insulin suppression test decreased significantly in responders (13.32 ± 1.48 (S.E.M.) vs 11.33 ± 1.19 mmol/l, $P=0.0501$) but not in non-responders (12.29 ± 1.24 vs 11.11 ± 0.99 mmol/l, $P=0.2110$) immediately after completion of IFN- α treatment. In the oral glucose tolerance test, no significant difference was observed in

plasma glucose in either responders (10.17 ± 0.23 vs 10.03 ± 0.22 mmol/l) or non-responders (10.11 ± 0.22 vs 9.97 ± 0.21 mmol/l) 3 months after completion of IFN- α treatment. However, significant differences were noted in C-peptide in both responders (2.90 ± 0.13 vs 2.20 ± 0.09 nmol/l, $P=0.0040$) and non-responders (2.45 ± 0.11 vs 2.22 ± 0.08 nmol/l, $P=0.0287$) before vs after treatment. The changes of C-peptide in an OGTT between responders and non-responders were also significantly different ($P=0.0028$), with responders reporting a greater reduction in C-peptide. No case developed autoantibodies during the treatment. In patients who were successfully treated with IFN- α , insulin sensitivity improved and their plasma glucose stayed at the same level without secreting as much insulin from islet β -cells.

Journal of Endocrinology (2003) **178**, 457–465

Introduction

Glucose intolerance and diabetes mellitus are often seen in patients with chronic liver disease (Megeysi *et al.* 1967, Petrides *et al.* 1994). The phenomena are claimed to result from insulin resistance of muscle and a relatively lower insulin secretory response to nutrient stimulation (Kruszynska *et al.* 1991). Recently, interferon (IFN)- α has been extensively applied to the treatment of chronic viral hepatitis. The effective amelioration rate of the liver function was about 30 and 40% respectively, in chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections (Moriyama *et al.* 1993, Poynard *et al.* 1996). On the one hand IFN- α has been reported to induce type 1 diabetes (Foulis *et al.* 1987, Fabris *et al.* 1992, Waguri *et al.* 1994, Cesare *et al.* 1996, Eibl *et al.* 2001) and acute insulin resistance (Koivisto *et al.* 1989, Ishigami *et al.* 1994, Imano *et al.* 1998) in patients with chronic HCV infection, and on the other hand some

studies claim that long-term IFN- α treatment for patients with HCV infection, instead of causing deterioration of insulin sensitivity and glucose tolerance, is capable of improving glucose tolerance (Ito *et al.* 1999, Konrad *et al.* 1999, 2000). In short, the role IFN- α plays in glucose homeostasis for patients with HCV infection remains to be elucidated. Little information is available except for one report addressing the beneficial effect of IFN- α on glucose homeostasis in patients with HBV infection (Tanaka *et al.* 1997), although exacerbation of type 2 diabetes during IFN- α therapy for HBV has also been reported (Lopes *et al.* 1994).

Custro *et al.* (2001) reported that the prevalence of diabetes associated with virus-related chronic hepatitis is on average four times higher than in the general population. Moreover, HBV and HCV infections do not appear to have a different impact on glucose homeostasis (Custro *et al.* 2001). Nevertheless, HCV-infected patients have also been reported to have a higher incidence of diabetes

than patients with HBV infection (Fraser *et al.* 1996, Mason *et al.* 1999), suggesting a link between HCV infection and diabetes mellitus. In spite of the controversies, the unsuitability of insulin-related parameters to represent insulin resistance and islet β -cell function in patients with chronic hepatitis has been neglected in previous studies. Hyperinsulinemia in chronic active hepatitis has been reported to be associated with impaired insulin removal rather than pancreatic hypersecretion (Bonora *et al.* 1984), rendering C-peptide that is not degraded significantly by the liver more suitable to represent pancreatic responsiveness to glucose load in patients with chronic hepatitis (Iwasaki *et al.* 1978). Another study reports that hyperinsulinemia is the consequence of increased β -cell sensitivity to glucose (Greco *et al.* 2002). Furthermore, previous studies seem unable to answer the question whether responses to IFN- α therapy can affect insulin resistance and islet β -cell function in patients with chronic HBV and HCV hepatitis. Our study endeavored to investigate the respective impacts of IFN- α and the responses to it on glucose metabolism-related parameters, with reference to the grading and staging of liver disease and to the contribution of the two main responsible viruses.

In this report, serial work-ups were executed to observe the glucose tolerance, insulin resistance, endogenous insulin release and type 1 diabetes-related autoantibodies in response to IFN- α therapy on 28 biopsy-proven chronic HBV- and HCV-infected hepatitis patients.

Materials and Methods

Patients

Twenty-eight biopsy-proven chronic viral hepatitis patients, ten with HBV and 18 with HCV infection, were enrolled to our study. Liver biopsy was performed before starting the therapy and scored by histological activity index (HAI) (Knodell *et al.* 1981) to determine the severity of the HBV and HCV infections. All met the following inclusion criteria: (i) elevated serum alanine aminotransferase (ALT) levels at least twice the upper limit of the normal standard as documented on three occasions within 6 months before enrollment; (ii) positive serum HBV antigen (HBeAg) or HCV mRNA; and (iii) a histological diagnosis of chronic hepatitis without cirrhosis. They were all regularly followed up at the out-patient clinics of gastroenterology at National Taiwan University Hospital (NTUH) from 1998 to 1999, with the following exclusion criteria: (i) reporting a known history of diabetes mellitus with or without receiving hypoglycemic agents; (ii) having major concomitant diseases, such as hypertension, stroke, cardiac or renal disease, or abnormal serum albumin and bilirubin levels; or (iii) taking medications known to affect glucose tolerance or insulin secretion.

Informed consent was obtained from each patient, and the NTUH Ethics Committee approved the study protocol conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

Treatments

A diagram presenting the study protocol is given in Fig. 1. The doses of IFN- α (α -2B interferon; Schering-Plough Co.) were 5×10^6 IU and 3×10^6 IU respectively for HBV- and HCV-infected patients for each s.c. administration. They were given three times a week for a total duration of 24 weeks. Serum HBV DNA or HCV mRNA, ALT, and clinical examinations were performed immediately before and within 1 week after completion of IFN- α therapy, as well as 12 weeks after termination of IFN- α therapy.

Four patients were found to have mild diabetes while nine showed impaired glucose tolerance (IGT) at the baseline evaluation according to an oral glucose tolerance test (OGTT) as based on the revised (1997) diagnostic criteria of the American Diabetes Association (Anonymous 1997). Although being informed of the diagnosis of diabetes, they received no dietary or pharmacological treatments for their mild diabetes during the study. Thus none of them was excluded from the study.

Identification of treatment responses

Serum ALT was measured by an autoanalyzer (Hitachi 7250, Special; Hitachi, Tokyo, Japan), HBeAg by an enzyme immunoassay (Murex HBeAg kit; Abbott Laboratories, Dartford, Kent, UK), HBV DNA by a nucleic acid hybridization microplate test (Hybrid Capture II HBV DNA test; Digene, Gaithersburg, MD, USA) and HCV mRNA by RT-PCR. In patients with HBV infection, response to IFN- α therapy was defined as serum HBeAg and HBV DNA turning to negative after treatment. In patients with HCV infection, response to IFN- α was defined as negative serum HCV mRNA after treatment.

Assays of glucose homeostasis

The standard 75 g OGTT, glucagon stimulation test (GST), glycosylated hemoglobin (HbA_{1c}) and insulin autoantibodies anti-GAD65 and ICA512 were conducted immediately before and 12 weeks after termination of the therapy. Plasma glucose was determined by an autoanalyzer (Hitachi 7250, Special; Hitachi), serum insulin and C-peptide by immunometric assay and chemiluminescent enzyme immunoassay (Immulite; Diagnostic Products Co., Los Angeles, CA, USA) respectively. HbA_{1c} was measured with a DCA 2000 (Bayer Sankyo, Tokyo, Japan), and insulin antibody titer by a radioimmuno-metric method (Tai 1980). Anti-GAD65 and ICA512

Figure 1 Flowchart of the study protocol.

antibodies were detected simultaneously by radioligand methods as previously reported (Gianani *et al.* 1995).

The OGTT was performed after an overnight fast, and blood samples for plasma glucose, serum insulin and C-peptide were taken at 0, 30, 60, 90 and 120 min following glucose ingestion. For the GST overnight-fasted patients in a recumbent position received an i.v. bolus of 1 mg glucagon (Novo Nordisk Co., Copenhagen, Denmark). Serum insulin and C-peptide levels were determined from the blood sampled before, 3 and 6 min after the glucagon injection.

The insulin resistance of the peripheral tissue was determined twice by a modified insulin suppression test as reported (Pei *et al.* 1994). The first one was immediately before initiation, and the second one after completion of the 24-week IFN- α therapy. For patients with an over-

night fast, glucose at 240 mg/m² of body surface area/min, insulin at 25 mIU/m² of body surface area/min and Sandostatin (somatostatin analogue; Sandoz) at 0.5 μ g/min were infused immediately after an i.v. bolus injection of 25 μ g Sandostatin. Venous blood samples were obtained for measurement of plasma glucose and insulin at time 0 and every 10 min from 150–180 min to represent the steady-state plasma glucose (SSPG) and insulin (SSPI). The SSPI levels were rendered comparable in all subjects during the test.

To assess the insulin resistance and islet β -cell function, data were analyzed by homeostasis model assessment (HOMA-IR and HOMA-B) (Matthews *et al.* 1985, Haeflén 1998, Levy *et al.* 1998) and quantitative insulin sensitivity check index (Quicki) (Katz *et al.* 2000) from fasting plasma glucose and insulin concentrations.

Table 1 Demographic characteristics and glucose tolerance of patients with and without response to IFN therapy. Data are expressed as means ± S.D.

	Age	Sex (M/F)	IFN-α therapy	BMI (kg/m ²)	HbA _{1c} (%)	IGT <i>n</i> (%)	Diabetes <i>n</i> (%)
Non-responders (<i>n</i> =18)	40.4 ± 11.7	13/5	Before	24.24 ± 2.92	5.07 ± 0.38	6 (33.3)	3 (16.7)
			After (<i>n</i> =15)	23.65 ± 2.52	4.89 ± 0.24	3 (16.7)	2 (13.3)
Responders (<i>n</i> =10)	37.6 ± 15.8	9/1	Before	24.26 ± 3.49	5.08 ± 0.79	3 (30)	1 (10)
			After	23.96 ± 3.32	4.86 ± 0.60	2 (20)	1 (10)

The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Statistical analysis

A chi-square test for heterogeneity was applied to assess whether or not there was a difference in the proportion of IGT and diabetes mellitus cases for HBV- and HCV-infected patients. The other data are presented as means ± S.E.M., and normal distribution was assumed for analysis. Repeated-measures ANOVA based on linear mixed models was used to compare the results of glucose metabolism-related parameters before and after IFN-α therapy between subgroups, i.e. responders and non-responders, HBV- and HCV-infected patients. Comparisons at multiple time points were adjusted by adding a linear and a quadratic term of measurement time in the linear mixed models. Subgroup analysis was applied to compare the results of selected parameters within each subgroup because the parameters compared exhibited a significant difference after IFN-α therapy or a significant difference can be observed between the aforementioned subgroups. The differences of HAI scores between responders and non-responders to IFN-α were determined by a two-tailed, unpaired Student's *t*-test. Results were considered statistically significant at $P < 0.05$.

Results

Basic characteristics

The demographic characteristics of the patients are presented in Table 1. Ten (four HBV-infected and six HCV-infected) of the 28 patients showed responses to IFN-α therapy according to the aforementioned criteria. None of the treated patients had positive insulin auto-antibodies, anti-GAD65 and ICA512 antibodies, during or after the therapy. The HAI scores of responders to IFN-α therapy betrayed no significant difference from that of non-responders (7.25 ± 0.92 vs 6.71 ± 1.52 , $P = 0.7523$). Neither did the HAI scores between HBV- and HCV-infected patients differ significantly (6.22 ± 1.24 vs 7.8 ± 0.99 , $P = 0.3298$).

SSPG

SSPG data, as shown in Table 2, exhibited an overall significant decrease after IFN-α therapy (12.81 ± 0.79

vs 11.22 ± 0.98 mmol/l, $P = 0.0411$). Subgroup analysis revealed no significant change after therapy among non-responders to IFN-α therapy (12.29 ± 1.24 vs 11.11 ± 1.00 mmol/l, $P = 0.2110$), but a borderline significant decrease in SSPG was observed among responders (13.32 ± 1.48 vs 11.33 ± 1.19 mmol/l, $P = 0.0501$) after IFN-α therapy. When HBV- and HCV-infected patients were analyzed separately, no statistically significant differences in SSPG could be observed.

OGTT

Nine of the 28 patients (32.1%) had IGT (plasma glucose between 7.8 and 11.1 mmol/l, 2 h after a 75 g oral glucose load), and another four patients (14.3%) had diabetes mellitus (2 h plasma glucose ≥ 11.1 mmol/l during an OGTT). Twelve weeks after termination of IFN-α therapy, the number of cases with IGT declined to 5 of 25 patients (20%), and that with diabetes declined to three (12%). All had HCV infection except for one patient. The only HBV-infected patient who had IGT initially was found to have normal glucose tolerance after IFN-α therapy. The chi-square test for heterogeneity revealed that there was a significant difference in the proportion of IGT and diabetes mellitus cases for HBV- and HCV-infected patients ($P = 0.016$).

The plasma glucose, serum insulin and C-peptide values at each time point during OGTT before and after the treatment are illustrated in Fig. 2 and their mean ± S.E.M. values are presented in Table 3. By repeated-measures ANOVA based on linear mixed models, the differences in plasma glucose and serum insulin in both responders and non-responders after IFN-α therapy were not statistically significant after treatment. The mean values of plasma glucose seemed slightly decreased at any time point in responders but had no statistical significance. However, the overall serum C-peptide dropped significantly (2.67 ± 0.09 vs 2.21 ± 0.08 nmol/l, $P < 0.0001$) after IFN-α therapy in both responders (2.90 ± 0.13 vs 2.20 ± 0.09 nmol/l, $P = 0.0040$) and non-responders (2.45 ± 0.11 vs 2.22 ± 0.84 nmol/l, $P = 0.0287$) in subgroup analysis. In addition, the change in C-peptide after IFN-α therapy was significantly different between the responders and non-responders ($P = 0.0028$), with the responder group registering a greater reduction of C-peptide after IFN-α

Table 2 Metabolic parameters including SSPG and those derived from fasting plasma glucose and serum insulin of the patients before and after IFN- α treatment. Data are expressed as means $\pm$ S.E.M.

	Responders (n=18)		Non-responders (n=10)		HBV (n=10)		HCV (n=18)	
	Before	After	Before	After	Before	After	Before	After
SSPG (mmol/l) ^a	13.32 $\pm$ 1.48	11.33 $\pm$ 1.19 ^a	12.29 $\pm$ 1.24	11.11 $\pm$ 0.99	11.61 $\pm$ 1.55	9.51 $\pm$ 1.25	14.00 $\pm$ 1.19	12.94 $\pm$ 0.95
HOMA-IR	3.67 $\pm$ 0.51	3.93 $\pm$ 0.89	3.36 $\pm$ 0.43	3.94 $\pm$ 0.74	2.71 $\pm$ 0.54	3.16 $\pm$ 0.93	4.32 $\pm$ 0.41	4.70 $\pm$ 0.71
Quicki	0.3214 $\pm$ 0.0062	0.3198 $\pm$ 0.0087	0.3248 $\pm$ 0.0052	0.3220 $\pm$ 0.0073	0.3333 $\pm$ 0.0065	0.3274 $\pm$ 0.0091	0.3129 $\pm$ 0.0050	0.3144 $\pm$ 0.0070
HOMA-B	159.32 $\pm$ 19.65	158.19 $\pm$ 33.75	141.46 $\pm$ 16.47	153.47 $\pm$ 28.30	138.85 $\pm$ 20.58	137.28 $\pm$ 35.35	161.93 $\pm$ 15.72	174.37 $\pm$ 27.00

OGTT-PG, OGTT-Insulin, OGTT-C-peptide: area under curve of plasma glucose, serum insulin and C-peptide during oral glucose tolerance test; GST-Insulin, GST-C-peptide: area under curve of serum insulin and C-peptide glucagon stimulation test. ^a $P < 0.05$ after vs before IFN treatment.

therapy (Fig. 1 and Table 3). When HBV- and HCV-infected patients were analyzed separately in subgroup analysis, a statistically significant decrease in C-peptide after treatment could be observed in HBV (2.47 ± 0.09 vs 1.84 ± 0.09 nmol/l, $P = 0.0014$) but not in HCV (2.47 ± 0.22 vs 2.33 ± 0.22 nmol/l, $P = 0.5578$) patients, and the differences between the two types of hepatitis were statistically significant ($P = 0.0080$).

Glucagon stimulation test

The serum insulin and C-peptide during glucagon stimulation tests among responders and non-responders after treatment were compared by repeated ANOVA (Table 3). Similar to OGTT, only the serum C-peptide showed an overall significant decrease (2.12 ± 0.11 vs 1.88 ± 0.10 nmol/l, $P = 0.0187$) after IFN- α therapy. The differences in change of C-peptide after treatment between responders (2.37 ± 0.19 vs 1.93 ± 0.20 nmol/l, $P = 0.0005$) and non-responders (1.86 ± 0.13 vs 1.83 ± 0.11 nmol/l, $P = 0.8806$) were also significant ($P = 0.0346$). However, when HBV- and HCV-infected patients were assessed separately in subgroup analysis, no statistically significant decrease in C-peptide after treatment was observed in HBV- and HCV-infected patients.

Other parameters of glucose homeostasis

The data of HOMA-IR, Quicki and HOMA-B failed to show significant difference between responders and non-responders to IFN- α therapy before and after treatment (Table 2). They remained insignificant when HBV- and HCV-infected patients were separately studied.

Discussion

Among the 28 subjects with chronic HBV and HCV infections, the prevalence of diabetes and IGT was 14.3 and 32.1% respectively. Three months after completion of IFN- α treatment, the prevalence declined to 12 and 20% respectively. The results were similar to those of previous reports (Ito *et al.* 1999, Konrad *et al.* 1999, 2000) and indicated a minor beneficial long-term effect of IFN- α therapy on glucose homeostasis. Moreover, all except one of them had HCV infection, suggesting that HCV, rather than HBV, may play an important role in the development of diabetes mellitus. This too was a result echoing previous reports (Fraser *et al.* 1996, Mason *et al.* 1999). However, it should be noted that in this study the only patient with HBV infection had IGT initially but reported normal glucose tolerance after IFN- α therapy, a finding opposed to the statement that IFN- α might have adverse effects on glucose homeostasis of patients with HBV infection. In brief, our data support the view that administration of IFN- α *per se* is not associated with an impairment of glucose homeostasis in HBV- and HCV-infected patients.

Figure 2 Plasma glucose (upper panels), serum insulin (middle panels) and serum C-peptide (lower panels) in 75 g OGTTs before and after IFN- α treatment. Mean values are plotted with S.E. bars.

On the contrary, it might even help improve glucose homeostasis.

Since IFN- α is able to induce autoantibodies related to type 1 diabetes (Foulis *et al.* 1987, Fabris *et al.* 1992, Waguri *et al.* 1994, Cesare *et al.* 1996, Eibl *et al.* 2001), insulin autoantibodies, anti-GAD65 and ICA512 antibodies, were measured in our patients. However, fasting blood glucose levels of all 28 patients remained below 7.0 mmol/l without any intervention, and none of them

developed antibodies throughout the course of observation, suggesting that IFN- α -induced immunological destruction of islet β -cells was unlikely to occur in our patients. However, the absence of IFN-induced type 1 diabetes in these patients might result from the small sample size. Based on previous reports, we recommended that IFN- α should still be used with caution in patients with a predisposition to autoimmune disease and diabetes mellitus.

Table 3 Metabolic parameters in OGTTs and glucagon stimulation tests (GSTs) of the patients before and 12 weeks after termination of IFN- α treatment. Data are expressed as means $\pm$ S.E.M.

	Responders (n=15)		Non-responders (n=10)		HBV (n=9)		HCV (n=16)	
	Before	After	Before	After	Before	After	Before	After
OGTT								
Glucose (mmol/l)	10.17 $\pm$ 0.23	10.03 $\pm$ 0.22	10.11 $\pm$ 0.22	9.97 $\pm$ 0.21	10.19 $\pm$ 0.23	9.86 $\pm$ 0.23	10.10 $\pm$ 0.22	10.14 $\pm$ 0.21
Insulin (pmol/l)	476.68 $\pm$ 25.08	481.74 $\pm$ 29.70	465.48 $\pm$ 24.53	488.34 $\pm$ 27.58	459.34 $\pm$ 25.08	466.76 $\pm$ 29.70	482.82 $\pm$ 24.53	503.32 $\pm$ 27.58
C-peptide ^a (nmol/l)	2.90 $\pm$ 0.13	2.20 $\pm$ 0.09 ^b	2.45 $\pm$ 0.11	2.22 $\pm$ 0.08 ^{a,d}	2.81 $\pm$ 0.12	2.15 $\pm$ 0.09 ^b	2.53 $\pm$ 0.11	2.27 $\pm$ 0.09 ^d
GST								
Insulin (pmol/l)	416.72 $\pm$ 82.83	396.69 $\pm$ 3.98	241.07 $\pm$ 9.44	244.26 $\pm$ 5.25	257.63 $\pm$ 6.76	240.35 $\pm$ 56.54	400.16 $\pm$ 6.26	400.60 $\pm$ 3.18
C-peptide ^a (nmol/l)	2.37 $\pm$ 0.16	1.94 $\pm$ 0.16 ^b	1.86 $\pm$ 0.14	1.81 $\pm$ 0.13 ^c	1.81 $\pm$ 0.17	1.54 $\pm$ 0.16	2.42 $\pm$ 0.13	2.22 $\pm$ 0.13

^a $P < 0.05$, ^b $P < 0.01$ after vs before IFN treatment. ^c $P < 0.05$, ^d $P < 0.01$ comparing the differences of pre- and post-IFN treatment values between subgroups, i.e. responders vs non-responders, HBV- vs HCV-infected patients.

Although IFN- α has been reported to induce acute insulin resistance in patients with chronic active HCV infection (Koivisto *et al.* 1989, Ishigami *et al.* 1994, Imano *et al.* 1998), long-term IFN- α treatment seems to produce no detrimental effect on insulin sensitivity and glucose tolerance (Ito *et al.* 1999). One study even suggests that IFN- α can improve glucose tolerance in diabetic and non-diabetic patients with HCV-induced liver disease (Konrad *et al.* 1999, 2000). Our results showed that peripheral insulin sensitivity, as measured by SSPG, improved in responders but not in non-responders immediately after completion of the 6 month IFN- α therapy, indicating that clearance of HBV and HCV and amelioration of liver function might have a beneficial effect on peripheral insulin sensitivity. The degree of liver injury before treatment, as measured by HAI score on liver histology, did not differ between responders and non-responders and was unlikely to bias the results of glucose metabolism-related parameters. Furthermore, the presence of lower mean HbA_{1c} and a decreased number of cases of diabetes and IGT 3 months after completion of IFN- α therapy (Table 1) is consistent with the favorable long-term effect of IFN- α on glucose homeostasis. However, the statistically significant differences in SSPG in responders after 6 months of IFN- α therapy disappeared as HBV- and HCV-infected patients were separately studied, which might be caused by the small case number in our study.

Hyperinsulinemia of chronic active hepatitis is believed to result from either impaired insulin removal (Kasperska-Czyzykova *et al.* 1983, Bonora *et al.* 1984) or pancreatic hypersecretion (Greco *et al.* 2002). The liver is the primary organ of insulin clearance, in which about 50% of the hormone secreted by the pancreas is broken down at one single passage (Johnston *et al.* 1978). C-peptide and insulin are secreted in equimolar quantities. However, liver does not degrade C-peptide like it does insulin, and in patients with chronic hepatitis the peripheral C-peptide concentration is a better index of insulin secretion than that of insulin (Johnston *et al.* 1978, Bonora *et al.* 1984). Based on the above concept, any parameters derived from insulin (such as HOMA-IR, HOMA-B, Quicki) may not be suitable to be used to represent insulin resistance or β -cell function in patients with chronic hepatitis.

In our study, C-peptide serves better to represent the pancreatic response to glucose load in patients with liver diseases. Although the mean plasma glucose in OGTTs of responders 3 months after completion of IFN- α therapy was only slightly decreased, the overall C-peptide values during OGTT dropped significantly. Although the C-peptide values during OGTTs in non-responders decreased significantly after IFN- α therapy, too, their reduction is much smaller in amplitude than those in the responder group. According to the combined data on SSPG and C-peptide in OGTTs, it was presumable that islet β -cells in responders have no need to secrete as much insulin to compensate the glucose load during OGTT as

before IFN- α therapy. In other words, insulin sensitivity improved much more greatly in responders to IFN- α therapy as compared with non-responders. The latter might also explain why there is a lesser degree of C-peptide release in IFN- α responders during glucagon stimulation tests after IFN- α therapy.

Furthermore, one study has suggested that hyperinsulinemia, at least in Child's disease grade B cirrhotic patients, is the consequence of increased β -cell sensitivity to glucose, while hepatic insulin extraction does not seem to play a significant part (Greco *et al.* 2002). Therefore another possible explanation is that, in responders to IFN- α therapy, β -cell sensitivity to both glucose and glucagon was decreased. However, the defect was compensated by the improved peripheral insulin sensitivity, and as a whole led to a slight reduction of glucose area under the curve in OGTT and the decrease in case numbers of diabetes and IGT after IFN- α therapy. We propose that the down-regulation of insulin receptors in the hyperinsulinemic state and the consequent insulin resistance is at least partially reversed in responders to IFN- α therapy.

In summary, peripheral insulin sensitivity measured by SSPG improved significantly in patients who were successfully treated with IFN- α . Furthermore, in responders to IFN- α therapy, plasma glucose stayed at the same level or even slightly decreased without secretion of as much insulin from islet β -cells in OGTT and glucagon stimulation tests 3 months after completion of IFN- α therapy, indicating a beneficial long-term effect of IFN- α on insulin sensitivity and β -cell load.

Acknowledgements

The technical assistance of Ms J P Wang and Ms T M Chen and the statistical assistance of Prof. C Hsiung and Dr J M Chiou are sincerely appreciated. The study was supported by grant NSC87-2314-B-002-092 from the National Science Council, Executive Yuan, Republic of China.

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Received in final form 20 May 2003

Accepted 23 May 2003