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Effect of interferon treatment on glucose metabolism in children with chronic hepatitis B infection

Kronik hepatit B enfeksiyonlu çocuk hastalarda interferon tedavisinin glukoz metabolizması üzerine etkileri

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Background/aims: *Interferon is known to have some effects on glucose metabolism, but this issue has not been investigated in children with chronic hepatitis B infection. The aim of this study was to investigate the impact of interferon on glucose metabolism and to investigate whether autoimmunity has a role in the pathogenesis.* ***Methods:*** *Fourteen patients (9 male, 6.3±2.7 years) with children with chronic hepatitis B infection were prospectively evaluated. They received interferon 10 MU/m^2 for six months. Vral glucose tolerance test, fasting insulin and C-peptide, postprandial insulin and C-peptide, anti-GAD antibody, HOMA-IR and glucose / insulin ratio were measured before and after treatment.* ***Results:*** *Before interferon, oral glucose tolerance test showed glucose intolerance in two patients (14.5%) and hypoglycemia in one patient (7.1%). One patient had hyperinsulinemia and insulin resistance (7.1%), and four patients had hypoinsulinemia and insulin hypersensitivity (28.5%). After interferon, oral glucose tolerance test was normal in 13 patients (92.8%). Abnormal oral glucose tolerance test persisted in the same patient, but no difference was found in insulin resistance. Hypoinsulinemia and insulin hypersensitivity were present in five patients (35.7%). DM related autoantibodies were negative in all patients before interferon; however, one patient, whose glucose metabolism was within normal limits, developed anti-GAD antibody after interferon.* ***Conclusions:*** *Children with children with chronic hepatitis B infection were shown to have hypoinsulinemia and insulin hypersensitivity. These children may have risk of progresssing to insuline dependent drabetes mellitus. We demonstrated that interferon did not seem to worsen glucose metabolism, but it had minimal positive impact on it. These results should be supported with other studies and interferon should be used carefully, especially in children with decreased β cell reserve.*

Keywords: Children, chronic hepatitis B infection, interferon, glucose metabolism

Amaç: *interferon -α'nın glukoz metabolizması üzerine etkileri olduğu bilinmekle birlikte kronik hepatit Bvirüs'lü çocuk hastalarda bu konu araştırılmamıştır. Çalışmamızda kronik hepatit Bvirüslü enfeksiyonu olan çocuk hastalarda İFN tedavisinin glukoz metabolizması üzerine etkisinin belirlenmesi amaçlandı.* ***Yöntem:*** *Yaş ortalaması 6.3±2.7yıl olan kronik hepatit Bvirüslü enfeksiyonlu 14 hastaya (5 kız, 9 erkek) 10 MU/m2 İFN-a 6 ay süre ile verildi. Tedavi öncesi ve tedavi sonrası, açlık-tokluk insülin ve C-peptid düzeyi, oral glukoz tolerans testi, anti-GAD ve anti-insülin antikor , Glukoz/insülin oranı ve HOMA-IR bakıldı.* ***Bulgular:*** *Tedavi öncesi 11 hastada glukoz metabolizması normal (%78.5), iki hastada glukoz intoleransı (%14.2), bir hastada hipoglisemi (%7.1), bir hastada hiperinsülinemi (%7.1), 4 hastada hipoinsülinemi ve insülin duyarlılığında artış (%28.5) saptandı. Tedavi sonrası 13 hastanın (%92.8) glukoz toleransı normal olarak değerlendirildi. Önceden glukoz intoleransı olan bir hastanın patolojisinin açlık glukoz intoleransına (%7.1) gerilediği, ancak hastada tedavi öncesi mevcut olan hiperinsülinemi ve insülin direncinde bir değişiklik olmadığı görüldü. Beş hastada hipoinsülinemi ve insülin duyarlılığında artış (%35.7) olduğu görüldü. Diabet ile ilişkili otoantikorlar tedavi öncesinde tüm hastalarda negatif iken, tedavi sonrası 1 hastada anti-GAD pozitifliği (%7.1) gelişti. Bu hastanın glukoz metabolizması ile ilgili incelemeleri normaldi. Tedavi sonrası oral glukoz tolerans testi 30. ve 60. dakika kan şekeri ortalamaları tedavi öncesine göre anlamlı olarak düşük bulundu ($p<0.05$). Sonuç: Tedavi öncesi kronik hepatit Bvirüs'lü hastalarımızda hipoinsülinemi ve insülin duyarlılığında artış olduğu saptanmıştır. Bu hastaların insülin bağımlı diabetes mellitus gelişimi yönünden risk altında olduklarını düşünmekteyiz. Ancak uyguladığımız interferon tedavisi kronik hepatit Bvirüs'lü hastalarda var olan β hücre rezervini olumsuz yönde etkilememiştir. Çalışmamız, interferon tedavisinin glukoz toleransı üzerinde olumlu etkisinin olduğunu düşündürmektedir.*

Anahtar kelimeler: Çocuk, kronik hepatit B enfeksiyonu, interferon, glukoz metabolizması

INTRODUCTION

Interferon (IFN)-oc is regarded as the most effective treatment modality for chronic childhood hepatitis B virus (HBV) infection (1). In recent years, however, attention has been drawn to the possible

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effects of interferon-α on glucose metabolism. There have been arguments regarding whether this effect is positive or negative (2,3,4). Some studies claim that interferon either stimulates autoimmunity, thus triggering type 1 diabetes mellitus (DM) development, or impairs insulin sensitivity and glucose tolerance, which initiates glucose intolerance and type 2 DM. Other studies, on the other hand, have reported positive effects of interferon treatment on glucose homeostasis (3,5,6,7). The majority of these studies have involved patients with chronic hepatitis C infection and adults. To our knowledge, no study exists which investigates the effects of interferon on glucose metabolism in chronic hepatitis B infection of childhood (5, 8, 9). This study aimed to investigate the effect of IFN treatment on glucose metabolism in patients with chronic hepatitis B virus (CHBV) in childhood and to determine the role of islet cell autoantibodies in this issue.

MATERIALS AND METHODS

The study involved 14 pediatric patients (5 female, 9 male; age range: 2-9.6 years, mean age: 6.3±2.7 years) who were followed by the Department of Pediatric Gastroenterology of Ankara University, School of Medicine, between January 2002 and December 2003. The patients were HBsAg and HBeAg positive for at least six months and had alanine aminotransferase (ALT) of 1.5 times the reference values, HBV DNA > 5 pg/ml, liver histopathology compatible with chronic active hepatitis, Knodell hepatitis activity index (HAI) >5, and no underlying disease.

All the patients were administered subcutaneous 10 MU/m^2 interferon-α three days a week for six months. Before and after the treatment, the patients were subjected to oral glucose testing and evaluated for fasting -postprandial insulin and C-peptide levels, anti-glutamic acid decarboxylase (GAD) antibody and anti-insulin antibody. Insulin resistance was evaluated by glucose/insulin ratio and Homeostasis Model Assessment (HOMA).

Fasting C-peptide and insulin levels were studied after 12 hours of fasting, and postprandial C-peptide and insulin levels were studied in the serum obtained at the second hour of oral glucose testing. C-peptide level was studied with DSL-7000 kit (Diagnostic Systems Laboratories USA; reference values: 0.8-4 ng/ml), and serum insulin level was studied with Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, CA, USA, reference values: 3-15 mIU/ml) by radioimmunoassay (RIA) method. (10,11). Fasting insulin levels <3 mIU/ml were considered as hypoinsulinemia, while fasting insulin levels over 15-20 mIU/ml or postprandial insulin levels >100 mIU/ml were considered as hyperinsulinemia (12). Anti-glutamic acid decarboxylase antibody (Anti-GAD) was studied with Glutamic Acid Ab RIA/DA kit (CIS-Biointernational, USA; reference values: 0-1 U/L) by IRMA method, and anti-insulin antibodies were studied with Anti-insulin Ab RIA/CT kit (Biosource, USA; reference values: 4-10%) by semiquantitative RIA method (13,14). Oral glucose tolerance test (OGTT) was started after baseline (0 minute) glucose level was measured following 12 hours of fasting. Glucose was orally administered with 1.75 g/kg (maximum 50 g) doses, and glucose levels at 30th, 60th, 120th, and 180th minutes were studied in the serum samples. OGTT evaluation is presented in Table 1 (15). Insulin resistance was evaluated through glucose/insulin ratio and Homeostasis Model Assessment-insulin resistance (HOMA-IR). Glucose/insulin ratio was calculated by fasting serum glucose/insulin level, which is generally expected to be above 6-7 (16,17). HOMA-IR was calculated by the formula provided below and the value is generally expected to be under 2.5 (18):

HOMA-IR= (fasting glucose level/18 x fasting insulin) / 22.5.

Table 1. Evaluation of oral glucose tolerance test

		Criteria
Hypoglycemia	FPG	<70 mg/dl
Normal OGTT	FPG	< 110 mg/dl
	2-h PG during an OGTT	<140 mg/dl
Fasting glucose intolerance	FPG	110-126 mg/dl
	2-h PG during an OGTT	<140 mg/dl
Glucose intolerance	FPG	<126 mg/dl
	2-h PG during an OGTT	140 mg/dl
Type II DM	FPG	>120 mg/dl

OGTT: Oral glucose tolerance test, FPG: Fasting plasma glucose, PG: Plasma glucose 110-126 mg/dl

Informed consent was obtained from each patient's family, and Ankara University School of Medicine Ethics Committee approved the study protocol conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

All the values were calculated as mean ± standard deviation. The significance of intergroup differences was studied with SPSS 11.0 computer program by Wilcoxon-signed rank and McNemar tests. A value of $p < 0.05$ was considered significant.

RESULTS

The mean values before the treatment were as follows: ALT, 96.5±82.5 U/L; HAI, 6.9±2.1; and HBV DNA, 3220.3± 2224 pg/ml. The mean body mass index (BMI) of the patients before the treatment was 16.6±2.2. None of the patients was obese. There were no differences between the values of BMI before and after the treatment ($p>0.05$). After IFN treatment, the mean ALT and HBV-DNA values were significantly lower than before the treatment. ($p<0.01$) (Table 2).

Table 2. The comparison of mean ALT, HBV-DNA and BMI of the patients before and after interferon treatment

	Before treatment	After treatment	P
ALT (U/L)	96.5±82.5	43.7±17.9	<0.01
HBV DNA (pg/ml)	3220.3± 2224	7±8.7	<0.01
BMI	16.6±2.2	15.9±2.37	>0.05

Data are expressed as mean±SD

Glucose metabolism

The pre- and post-treatment OGTT results, insulin and C-peptide response upon oral glucose administration, glucose/insulin ratio and HOMA-IR values, anti-GAD, and anti-insulin antibodies are been presented in (Tables 3 and 4).

Glucose metabolism was normal in 11 patients before treatment (78.5%); two patients had glucose intolerance (14.2%) and one patient had hypoglycemia (7.1%). Glucose intolerance was accompanied by insulin resistance and hyperinsulinemia in one of the two patients with glucose intolerance (patient 10). The patient was not obese. However, the family history revealed type 2 DM. The insulin level of the second patient with glucose intolerance (patient 7) was within reference values. Fasting insulin level of the patient with hypoglycemia (patient 11), however, was significantly low; HOMA-IR was suppressed, and glucose/insulin ratio was significantly high, indicating increased sensitivity. Euglycemic hypoinsulinemia was detected in three patients (patients 1, 2, and 14). In these patients, despite normal results of OGTT, there was a striking increase in insulin sensitivity. In summary, before the treatment, four patients had hypoinsulinemia and increased insulin sensitivity (28.5%), and one patient had hyperinsulinemia and insulin resistance (7.1%). Fasting C-peptide levels of all the patients were within reference values except for two patients (patients 13 and 14). None of the patients had anti-GAD or anti-insulin antibody positivity before treatment.

Post-treatment glucose tolerance tests of 13 patients (92.8%) were normal. The pre-treatment glucose intolerance (7.1%) of one patient (patient 10) persisted after the treatment. However, the pathology had regressed to glucose intolerance level. The pre-treatment hyperinsulinemia and insulin resistance of this patient persisted (7.1%). In another patient with glucose intolerance before treatment (patient 7), however, post-treatment OGTT results were found to be normal. The serum glucose level of the hypoglycemic patient (patient 11) was 70 mg/dl, which was borderline, and hypoinsulinemia persisted. There were no changes in pre-treatment hypoinsulinemia of euglycemic patients (patients 1, 2, and 14). In addition to these patients, another patient (patient 13) also had hypoinsulinemia. In the patients with hypoinsulinemia, HOMA-IR was suppressed, and glucose/insulin ratio was high enough to indicate increased sensitivity. To summarize, five patients had increased hypoinsulinemia and sensitivity (35.7%) after treatment. Post-treatment fasting C-peptide levels of all patients except one were within reference values. In one patient (patient 9), anti-GAD positivity (7.1%) was detected after treatment. The glucose tolerance test results of this patient were normal and there was no increase in the insulin resistance or sensitivity. HLA typing of this patient was HLA A2, B5, B51, BW4, BW1, DR11, DR14, DR52, DQ5 and DQ7.

The levels of glucose, insulin and C-peptide before and after interferon treatment during OGTT

In the comparison of pre- and post-treatment glucose responses, post-treatment serum glucose levels at the 30th and 60th minutes were significantly

Table 3. OGTT results before interferon treatment and insulin and C-peptide responses to oral glucose administration, anti-GAD, and anti-insulin antibody levels

Patient No	Plasma glucose (mg/dl)					Insulin (mIU/ml)		C-peptide (ng/ml)		G/I	HOMA-IR	Anti-GAD (U/L)	Anti-insulin antibody
	Fasting		30th min	60th min	120th min	180th	Fasting	120th min	Fasting	120th min			
1	84	141	135	91	67	0.85	2.2	1.5	3.3	98.8	0.17	0.10	6.9
2	83	175	145	123	83	1.7	55	2.9	19.5	48.8	0.34	0.30	6.6
3	87	151	108	88	54	14.1	21.1	2.6	8.7	6.10	3	0.01	6.6
4	90	130	104	74	125	7.3	8	1.3	1.8	13.4	1.76	0.20	6.7
5	94	130	127	117	97	5.4	34.7	2.6	7.7	17.4	1.25	0.84	4.9
6	83	175	145	123	83	6.7	18.2	1	3.2	12.3	1.37	0.60	4.4
7	114	153	96	140	102	3.4	16	2.5	7	33.5	0.95	0.30	7
8	83	109	110	109	99	12.8	26.6	1.9	1.7	6.4	0.77	0.32	5.5
9	89	172	104	100	79	8.8	14.2	2.1	3.6	10.1	1.93	0.06	7
10	111	220	276	189	68	20	133	2.2	19	5.35	5.28	0.34	3.4
11	51	165	108	75	81	2.8	2	0.88	1.9	18.2	0.35	0.11	5.6
12	91	195	124	132	91	3	33.4	1.8	5.1	30	0.67	0.50	7
13	76	156	94	117	69	4.7	72.6	0.71	8.7	16.1	0.88	0.30	6.6
14	89	142	112	101	95	0.28	8.8	0.53	2.1	317	0.06	0.10	6.3

Table 4. OGTT results after interferon treatment, the insulin and C-peptide responses of the patients to oral glucose administration, and anti-GAD, and anti-insulin antibody levels

Patient No	Plasma glucose (mg/dl)					Insulin (mIU/ml)		C-peptide (ng/ml)		G/I	HOMA-IR	Anti-GAD (U/L)	Anti-insulin antibody
	Fasting		30th min	60th min	120th min	180th	Fasting	120th min	Fasting	120th min			
1	70	132	113	86	*66*	2.3	6.5	0.63	2.4	28.6	0.37	0.22	6.9
2	88	142	86	71	49	1	22	2.94	7.9	88	0.21	0.30	6
3	83	110	116	95	69	6.1	42.7	2	7.2	13.6	1.25	0.15	5.80
4	93	99	94	88	78	11.5	17	1.4	1.7	8.1	2.60	0.50	4
5	83	114	122	98	118	6.5	36.4	1.8	6.2	12.7	1.33	0.60	6
6	79	159	122	138	143	11.8	41.4	3.9	5.6	6.6	2.30	0.10	6.5
7	80	106	79	84	88	4.1	5.9	0.99	2.4	19.5	0.80	0.45	6
8	77	85	98	89	81	4.2	30.6	2.8	1.6	18.4	0.37	0.10	4.4
9	75	120	93	90	74	6.3	47.7	1.2	8.2	11.9	1.16	1.41	4.5
10	113	175	204	116	66	18.6	11.7	4.5	17.4	6	5.18	0.03	6.20
11	70	122	88	83	71	1.5	7.2	0.93	3.2	46.6	0.25	0.50	4.80
12	89	124	101	104	82	34	70.3	6.2	11	2.67	7.47	0.20	5.5
13	91	135	131	100	57	0.18	6.7	1	2.6	505.5	0.04	0.10	5
14	89	125	74	91	94	0.10	3.6	0.87	2.2	890	0.02	0.10	4.1

lower than those of pre-treatment values ($p<0.05$) (Table 5). Before and after treatment, fasting (0 minute) and OGTT at 120th minute with respect to mean insulin and C-peptide levels did not significantly differ ($p>0.05$) (Table 5).

Anti-GAD and anti-insulin antibodies before and after interferon treatment

None of the patients had anti-insulin antibody and anti-GAD antibody positivity before treatment. After treatment, one patient (patient 9) developed anti-GAD antibody (7.1%) ($p>0.05$) (Table 5).

DISCUSSION

The liver has an important role in the regulation of blood glucose levels. It has close encounters with hormones such as insulin and glucagon through which it facilitates the regulating of blood glucose (19). Glucose metabolism disorders such as glucose intolerance and diabetes mellitus are common in chronic liver diseases (20, 21). The incidence and severity of these disorders are correlated with the severity and stage of the liver disease (22). It is reported that 10% of the patients with chronic hepatitis suffer from disorders of glucose

Table 5. Glucose metabolism before and after interferon-α treatment in children with chronic hepatitis B infection

	Before treatment	After treatment
Plasma fasting glucose (mg/dl)	87.7±14.6	84±11.5
Plasma glucose 30th minute (mg/dl)	158.1±28.5	124.8±23.3*
Plasma glucose 60th minute (mg/dl)	127.7±45.7	108.6± 32.4*
Plasma glucose 120th minute (mg/dl)	112.7±29.6	96.1±19.1
Plasma glucose 180th minute (mg/dl)	85.2±18.1	81.1±24.4
Fasting insulin (mIU/ml)	7.2±5.5	7.7±9.2
Insulin 120th minute (mIU/ml)	31.9±35.5	24.9±20.3
Fasting C-peptide (ng/ml)	1.7±0.7	2.2±1.6
C-peptide 120th minute (ng/ml)	6.6±5.9	5.6±4.4
Glucose/Insulin ratio	45.2±82	118.4±257
HOMA-IR	1.34±1.38	1.66±2.17
Normal (n)	12	13
Fasting glucose intolerance (n)	0	1
Glucose intolerance (n)	2	0
Hypoglycemia (n)	1	0
Hypoinsulinemia (n)	4	5
Hyperinsulinemia (n)	1	1
Insulin resistance (n)	1	1
Increased insulin sensitivity (n)	4	5
AIA antibody positivity (n) -		
Anti-GAD antibody positivity (n) -		1

metabolism such as hyperinsulinemia, impaired glucose tolerance and insulin resistance (21-23). The majority of these studies were performed in adult chronic hepatitis C patients and attention has been drawn to increased type 2 DM incidence (21, 24, 25, 26). The few studies investigating the glucose metabolism of adult patients with chronic hepatitis B infection reported that patients with genetic tendency to diabetes may eventually develop insulin resistance and diabetes (26,27). Custro et al. reported that the diabetes incidence of adults with chronic HBV and HCV infection is four times higher than that of the general population (21). In another study on adults with chronic hepatitis B infection, 8% of the patients with mild chronic active hepatitis, 44% of the patients with severe chronic active hepatitis, and 40% of the patients with cirrhosis had associated diabetes (26). Literature reveals studies claiming that diabetes incidence in chronic HBV and chronic HCV infections is varied, while some other studies argue that, as in the study of Custro et al., the effects of HCV and HBV infections on glucose homeostasis are similar (21,24). In the study of Custro et al., DM incidence in chronic HBV and chronic HCV infections was 22.5% and 25%, respectively (21). Glucose metabolism impairment in chronic hepatitis cases, particularly diabetes development, has been reported to be associated with hyperinsulinemia and insulin resistance. In these patients, hyperinsulinemia was shown to be due to decreased insulin catabolism rather than the increase of insulin secretion in the pancreas (28). In another study, however, the increased sensitivity of (3 cells to glucose was held responsible for hyperinsulinemia (29). Nevertheless, literature presents no studies on p cell functions and insulin resistance parameters of patients with hepatitis B infection.

In our study, two patients had glucose intolerance before treatment. One of these patients also had accompanying hyperinsulinemia and insulin resistance, although the patient was not obese and did not have acanthosis nigricans or hypertension, which are known to lead to insulin resistance. Nevertheless, there was a family history of type 2 DM. It is known that a family history of concomitant type 2 DM and acanthosis nigricans shows close association with the development of type 2 DM in children, and the incidence rate of this disease among children is known to increase (30). Thus, in the aforementioned patient, the glucose metabolism impairment has been attributed to the patient's genetic tendency for type 2 DM. The glucose metabolism improved after treatment in the other patient who had glucose intolerance before treatment. Although this suggests that glucose intolerance in this patient may have been associated with chronic hepatitis B, it is hard to make definite interpretations due to the limited number of our patients.

The most striking result of our study was that increased insulin sensitivity was found before treatment in four of our patients (28.5%). Furthermore, in all of these patients, insulin sensitivity was accompanied by hypoinsulinemia. On the other hand, low or borderline levels of C-peptide in these four patients are suggestive of (3 cell hypofunction rather than increased insulin catabolism. Type 1 DM is a disease characterized by progressive immune-mediated β cell destruction and, in the early diagnosis of the disease, demonstration of autoantibodies against islet cells is of great value (31). Anti-GAD and anti-insulin antibodies were negative in our patients with hypoinsulinemia. In the light of these findings, we can say that these patients developed (3 cell hypofunction and had impaired insulin secretion. It has been demonstrated that diabetes is frequently seen in chronic viral hepatitis. However, these studies have emphasized the association of chronic viral hepatitis with type 2 DM. There have been no studies on whether or not chronic viral hepatitis is also a risk factor for type 1 DM development. Before clinical findings emerge in type 1 DM, the first anomaly that could be demonstrated is the loss of acute insulin response during intravenous glucose testing in addition to the presence of autoantibodies (31). Therefore, we plan to investigate the acute insulin responses of our patients with increased insulin sensitivity and to determine HOMA-β cell function in comparison with the healthy controls.

Recent studies have reported the effect of interferon treatment on glucose metabolism, however, the process by which this effect could develop has not been completely understood (2, 3, 7, 9, 33). There are three hypotheses on this issue: the first states that interferon stimulates the immune system, through which autoimmune reaction to pancreas (3 cells begins and type 1 DM develops (33, 34). Interferon-α has been held responsible for both the stimulation of autoimmunity and type 1 DM development in patients with chronic HBV or HCV (2, 3, 4, 8, 35). Tai et al. studied 28 patients with HBV and HCV infection and reported that after interferon treatment, there was no positivity for anti-insulin, anti-GAD and ICA 512 antibodies, which are highly essential in type 1 DM diagnosis (36). In our study, none of our patients had anti-insulin or anti-GAD positivity before treatment. However, only one patient developed anti-GAD antibody after interferon treatment. Although there was no statistically significant difference, the presence of immunologic β cell destruction triggered in one patient by interferon is suggestive of a potential risk of interferon for the development of such an effect. Therefore, wide-scale studies should be conducted, keeping in mind that interferon may induce autoimmune diseases and trigger DM; thus, it should be carefully used as a treatment modality.

The second hypothesis puts forward that interferon, by increasing the direct or free radicals, destroys pancreas β cells and induces diabetes development. The last of the three hypotheses suggests that interferon may have an effect on insulin sensitivity, thus triggering the development of diabetes. Interferon has also been reported to cause glucose intolerance by inducing peripheric and hepatic insulin resistance (5).

Contrary to the adverse effects of interferon on glucose metabolism mentioned above, some studies have shown its positive effect on peripheric insulin sensitivity by clearing HBV and HCV from the liver and improving liver function (7, 22, 26, 32, 37, 38). In our study, interferon treatment did not have any adverse effect on insulin sensitivity and/or glucose tolerance. Decreased levels of blood glucose in OGTT, resolution of glucose intolerance in one patient and improvement in glucose intolerance in another patient after interferon treatment are all suggestive of the positive effect of interferon on glucose metabolism. Furthermore, patients in whom hypoinsulinemia and increased insulin sensitivity were present before interferon treatment continued to show the same pattern after treatment.

In conclusion, the results of our study indicate that children with chronic hepatitis B infection are prone to decreased insulin secretion and increased insulin sensitivity and have a risk of developing insulin dependent DM. Interferon treatment did not have any positive or negative effect on the low β cell reserve of these patients. In addition, the results showed that interferon treatment did not lead to insulin resistance or glucose intolerance in children with hepatitis B infection; on the contrary, it improved necroinflammation and, though slightly, positively affected glucose metabolism. Further detailed studies on β cell reserve involving larger numbers of children with chronic hepatitis B infection are needed.

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