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Original Article

Incidence of diabetes mellitus requiring insulin treatment after renal transplantation in patients with hepatitis C

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Abstract

Background. Hepatitis C virus (HCV) infection has been associated with an increased incidence of diabetes mellitus, both in the general population and among transplant patients.

Methods. To test this hypothesis, we reviewed the records of 1614 patients who had undergone renal transplant at six Spanish centres between 1992 and 1998. We established the rate of onset of diabetes mellitus requiring >1 month of treatment with insulin (insulin-treated diabetes mellitus, I-TDM) among the 177 patients showing HCV antibody seropositivity at the time of transplant (HCV+ group). As controls, 177 HCV patients were selected who had received a kidney allograft immediately before or after the study patients at the same centre.

Results. The HCV+ patients were well matched with controls in terms of characteristics (except a longer time on dialysis) and immunosuppressive treatment. After a mean follow-up of 44 months, 28 cases of I-TDM were diagnosed (9.6% in HCV+ and 6.2% HCV−, not significant (NS); odds ratio 1.6; 95% confidence interval 0.75–3.50). The onset of I-TDM was somewhat later in HCV+ patients (467 days *vs* 292 days in HCV− patients, NS). Multivariate analysis identified the following prognostic factors for I-TDM onset: age and BMI at the time of transplant, and polycystic kidney disease as the underlying cause of chronic renal insufficiency. No correlation was found with HCV positivity or time on dialysis.

Conclusions. We were unable to confirm a greater incidence of post-renal transplant insulin-requiring diabetes in association with HCV infection. However, the observed tendency towards such an association suggests that the follow-up period would need to be extended.

Keywords: diabetes mellitus; hepatitis C; polycystic kidney disease; renal transplant

Introduction

Hepatitis C virus (HCV) has been associated with diabetes mellitus in two types of study. The first shows that among diabetes mellitus patients there is a higher prevalence of HCV infection compared with the non-diabetic population [1], and the second demonstrates that patients with chronic liver disease due to HCV show an increased incidence of diabetes mellitus [2–4]. The issue is, however, controversial [5] and the findings of several studies question this association [6].

In the organ transplant setting, data on this putative association is scarce. Nevertheless, a greater incidence of diabetes mellitus has been reported in patients undergoing liver transplant due to HCV-induced cirrhosis [7]. A significantly higher incidence of insulin-dependent diabetes mellitus following renal transplant has also been described in patients with HCV infection [8], as has an increased frequency of diabetes mellitus and vascular complications during the late post-operative period [9].

The present retrospective, multicentre study was designed to explore this association between renal transplant, I-TDM and HCV infection in a large series of cadaveric kidney allograft recipients.

Subjects and methods

A review was made of all renal transplantations performed at six Spanish centres over the period 1 January 1992 to 30 June 1998, according to their situation on 31 December 1998

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(follow-up was at least 6 months post-renal transplantation) (1614 cases). Patients were excluded if: (i) diabetes mellitus was known before renal transplant; (ii) they had undergone the simultaneous transplant of another organ; (iii) they had lost their graft before 3 months; or (iv) they had presented unknown or doubtful HCV serology. We established a study group (HCV+; $n=177$) by selecting from the remaining patients those with a positive HCV blood test (determined by the presence of HCV antibodies by 2nd–3rd generation enzyme immunoassay) immediately before, or during the first 3 months after, renal transplant. The control group (HCV−; $n=177$) was formed from patients who had undergone transplant immediately before or after each study patient at the same centre and who showed a negative HCV blood test (during dialysis and post-transplantation). The number of HCV+ patients from each centre varied notably as a proportion of all renal transplants performed over the period examined (7.4–15.5%).

Initial immunosuppressive treatment for the entire patient series included corticosteroids. Cyclosporin was used for maintenance immunosuppression in 96.6% of patients, and was given in combination with azathioprine in 29.9%, with mycophenolate in 7.9%, and was accompanied by induction with poly- or monoclonal antibodies (with or without azathioprine) in 48.3%. Tacrolimus, with or without azathioprine, was used in 3.4% of the patients. Immunosuppression varied considerably in terms of the combination of drugs given, both over the entire length of the study period and in the different centres. The proportion of patients free from steroids at 1 year post-transplantation or at the close of the study was very small (3%).

The following data were obtained: age, sex, causal aetiology of chronic renal failure (CRF), weight and height at the time of renal transplant, date and cause of graft loss or patient death, immunosuppressive therapy during the early post-transplant period, at the end of the first year and at the end of the study, and onset of post-transplantation insulin-treated diabetes mellitus (I-TDM). The latter was defined as the requirement for continuous use of insulin over $\geqslant 1$ month, irrespective of subsequent glycaemic control without insulin. The following additional data were considered in cases of I-TDM: duration of renal transplant, liver biochemistry (TGO/TGP, GGT, total billirubin) and immunosuppressive agents used at the time of diagnosis. In a complementary manner, data regarding the use of oral antidiabetic agents were also recorded.

Statistical analysis was performed using SPSS 9.0 software. Student's *t*-test, χ^2 (Pearson) and odds ratio (OR) methods were used in the univariate comparisons. Logistic regression was used for the multivariate analysis entering the following as covariables: age, sex, body mass index (BMI) at renal transplant, time on dialysis, HCV status and adult polycystic kidney disease (APKD).

Results

Patient characteristics

No differences were observed between the HCV+ and HCV− (control) group in age, sex, CRF aetiology or time of post-transplant follow-up (Table 1). Body weight, but not the BMI, at renal transplant was significantly lower than in the HCV− group. Mean time on dialysis was almost triple in the HCV+ compared with the HCV− group. There were no significant differences in the basic immunosuppressive regimen employed in terms of pharmacological agents or combinations of these between the study and the control group.

Table 1. Patient characteristics

	HCV+	HCV−	*P* value
Age at renal transplant (years)	42.3 ± 12	40.5 ± 13	NS
Sex (% male)	57.1	62.7	NS
Weight at renal transplant (kg)	61.7 ± 11	65.7 ± 14	0.003
BMI at renal transplant	23.9 ± 4.1	24.7 ± 4.5	0.10
Time on dialysis (months)	93.3 ± 34	37.8 ± 37	0.000
Post-renal transplant follow-up (months)	43.0 ± 23	44.5 ± 22	NS

Table 2. Diabetic patient characteristics

	Diabetes ($n=28$)	Remaining cases ($n=326$)	*P* value
Age at renal transplant (years)	51.2 ± 10	40.6 ± 12	0.000
Sex (% male)	46.4	61.0	0.13
Weight at renal transplant (kg)	66.6 ± 11	63.5 ± 13	NS
BMI at renal transplant	26.6 ± 4.3	24.1 ± 4.3	0.04
Polycystic kidney disease, *n* (%)	10 (35.7)	32 (9.0)	0.01
HCV+, *n* (%)	17 (60.7)	160 (49.1)	NS
Time on dialysis (months)	65.9 ± 58	65.7 ± 59	NS
Post-renal transplant follow-up (months)	44.4 ± 21	43.7 ± 23	NS

The number of patients diagnosed with I-TDM was 28 (7.9%). These patients were older and showed a higher BMI than non-I-TDM patients (Table 2), but did not differ in terms of sex, time on dialysis, post-transplant follow-up or initial immunosuppressive therapy. I-TDM patients showed a 4-fold higher frequency of APKD as the underlying cause of CRF.

All patients were receiving steroids when I-TDM was diagnosed; in two patients, cyclosporin had been replaced with tacrolimus as rejection rescue therapy. Time of post-transplant follow-up until diagnosis was 396 ± 532 days and tended to be longer in the HCV+ group (467 ± 598 *vs* 292 ± 423 days; not significant (NS)). Only four out of 17 HCV+ patients with I-TDM showed normal liver biochemical variables (transaminases and γ-glutamyl-transpeptidase less than double the normal upper limit), compared with seven out of 11 in the control group.

Occurrence of I-TDM

The frequency of HCV+ was somewhat greater, although not significantly different, among diabetics (Table 2). Expressed in another way, I-TDM occurred in 9.6% of the HCV+ group compared with 6.2% in the HCV− group, with no statistical difference

between these proportions. The resultant OR was 1.60 (95% confidence interval (CI) 0.73–3.50).

Only two patients were treated with oral antidiabetics (one in each study group). By the end of our study, insulin treatment had been withdrawn in six of the 28 patients with I-TDM: in two patients this followed the complete withdrawal of steroids, and in a further two it followed a reduction in the steroid and/or tacrolimus dose. Five of these six patients were HCV+.

Patients with APKD showed a 23.8% rate of I-TDM, compared with 5.8% for the remaining aetiologies, with an OR of 5.1 (95% CI 2.17–11.99). It should be noted that polycystic patients showed different characteristics to the remaining patients: greater age (50.55 ± 8.3 *vs* 40.19 ± 12.5 years, $P = 0.000$), shorter time on dialysis (50.3 ± 45 *vs* 67.7 ± 60 months, $P = 0.031$), and a tendency towards a higher BMI at renal transplant (25.2 ± 3.3 *vs* 24.1 ± 4.5, $P = 0.07$).

The frequency of I-TDM was also very different at the different centres and ranged from 2.0% to 15.6% of all patients included in the study (HCV+ and controls). No relationship was found between the basic combination of immunosuppressive agents used at each centre and the incidence of I-TDM, although there were no data available on the doses used (particularly cumulative steroid doses) or on the type of anti-rejection therapy employed.

Multivariate analysis

Logistic regression using the covariables described previously only identified age, BMI and APKD as significant prognostic factors for developing I-TDM. APKD presented a relative risk of 3.36 compared with the remaining aetiologies. The resultant model is shown in Table 3.

Discussion

In the present study, an I-TDM frequency that tended to be greater in HCV+ than HCV− patients who had undergone kidney transplant was shown, yet this increase was not statistically significant over the follow-up period considered. Thus, we were unable to confirm the previously reported association between HCV and diabetes mellitus presentation following renal transplant.

Table 3. Logistic regression model for risk of I-TDM

	β coefficient	P value	Odds ratio	95% confidence interval
Age (per year)	0.064	0.003	1.066	1.022–1.112
BMI (/1)	0.090	0.052	1.095	0.999–1.199
Polycystic kidney disease	1.216	0.008	3.36	1.37–8.32

Post-renal transplant diabetes mellitus is a relatively common complication, although its incidence according to published reports ranges from 2% to >40% [10,11], depending on the definition used, recipient characteristics and, in some cases, the immunosuppressive treatment. Both resistance to insulin and diminished insulin secretion appear to play a role in the physiopathology of post-renal transplant diabetes mellitus [12]. As far as predisposing factors [10,11,13,14] are concerned, there is general consensus with regard to age, and certain reports also specify race, obesity and cadaveric donor, although opinions are divided. Other factors have generated much dispute and include sex, HLA phenotype, underlying cause of CRF, and the immunosuppressant and its cumulative dose. Steroids have traditionally been considered an important factor for the genesis of post-renal transplant diabetes mellitus, since they show clear discompensatory effects when used in high doses for the treatment of rejection [13,14].

Several authors have suggested that HCV infection is highly prevalent among diabetes mellitus patients [1,2,15]. In a recent investigation, the presence of HCV even showed an accelerating effect on the diabetic nephropathy that progressed more quickly to CRF [15]. This idea has not been clearly confirmed and several authors have questioned its veracity or suggested its dependence on local factors (virus strain or patient ethnicity) [16].

There are also numerous descriptions of a greater incidence of diabetes mellitus in patients with HCV-induced hepatopathy compared with other aetiologies [2–4]. The findings of some of these studies point towards an association with cases that have already progressed to cirrhosis [3], while others extend it to all degrees of liver pathology [4]. Also in this setting, discordant contributions have led to controversy that has not yet been fully resolved [6]. According to those who dispute a direct causal nature for this association, the fibrous lesion caused by HCV (and other aetiological factors such as alcohol) is the factor specifically implicated in the genesis of diabetes mellitus. This theory may find support in studies that establish a correlation between changes in glucose metabolism and the degree of fibrosis shown on biopsy [17].

The mechanism for this hypothetical diabetogenic action of HCV remains unclear. It has not been possible to detect a greater rate of anti-islet or anti-insulin antibodies, thus an autoimmune explanation, identified in extrahepatic diseases such as thyroid disorders or cryoglobulinaemia, is unlikely [18]. As an alternative, a direct injuring effect of the virus on pancreatic beta cells has been proposed as for other viruses, although this theory has little experimental back-up.

Several studies have already shown an increased incidence of diabetes mellitus following liver transplant in patients with HCV with respect to control patients with hepatitis B or no viral infection [7]. In a group of longstanding renal transplant patients, HCV-positive recipients presented higher rates of diabetes mellitus and mortality, including that due to myocardial

infarction [8]. Recently, a greater incidence of I-TDM has been reported in renal transplant recipients with HCV antibodies [9]. This finding was confirmed by another team, but only in patients not treated with interferon [19].

In the present study, we observed a frequency of I-TDM that tended to be higher in kidney allograft recipients with HCV antibodies, but it was far from showing statistical significance. Thus, our initial hypothesis could not be confirmed in principle. However, given the relatively short post-transplant follow-up period, it cannot be ruled out that owing to the slow nature of HCV disease, a positive relationship might emerge in the longer term. Moreover, our study was limited to considering diabetes mellitus of prolonged insulin dependence and it is therefore not possible to unequivocally exclude the appearance of significant differences related to milder forms of carbohydrate intolerance. A further limitation is that there were no data available on virus replication or liver histopathological status. It is possible that predisposition to diabetes mellitus is more related to the presence of active infection or to a particular degree of liver fibrosis than simply to the presence of antibodies.

Our review did not include background data on the functional capacity of beta pancreatic cells nor the relative contribution of peripheral resistance to insulin. Nevertheless, it should be highlighted that at least some of the patients were able to stop taking insulin once their steroid and anticalcineurin doses had been reduced. This might indicate a considerable component of increased resistence to insulin due to steroids and/or anticalcineurin agents. Alternatively, it could be attributable to a decrease in a hypothetical direct effect of the virus on the pancreas due to diminished viral replication as immunosuppression is decreased.

The present study did not intend to determine the frequency of, or the factors involved in diabetes mellitus in the general transplant population. However, given that the patients included may be considered to be fairly representive of this population (except in the frequency of HCV and time on dialysis), we judge it admissible to evaluate possible prognostic factors. Well known factors such as age and excess weight (on the limit of statistical significance) were identified as prognostic factors for the onset of post-renal transplant diabetes mellitus, but surprisingly APKD was also found to be associated with diabetes mellitus. This relationship has already been described in a single-centre analysis [20] that suggested a cell membrane defect present in patients with APKD or simply a greater duration of pre-renal transplant CRF in this pathology as possible explanations. In our patient series, the time on dialysis was not a significant factor for the appearance of diabetes mellitus, and patients with APKD in fact presented a shorter dialysis period. However, the total time of renal insufficiency is methodologically hard to establish in retrospective studies. On the other hand, patients with APKD presented factors predisposing to diabetes mellitus, such as greater age and weight. The results of the multivariate analysis seem to suggest that this is not the reason for the greater frequency of diabetes mellitus. It is clear that a specifically designed study is required before this association may be confirmed.

We failed to establish an association between diabetes mellitus and any of the different combinations of immunosuppressive agents employed, which always included steroids. Nonetheless, this question was not precisely addressed here and we cannot rule out the effects of variations in immunosuppression (especially the cumulative dose of steroids or the use of boluses) to explain the differences found between centres.

In conclusion, it was not possible to confirm the hypothetical association between HCV and diabetes following renal transplant. Further work is required, perhaps on larger patient series and considering a longer follow-up period, to unequivocably clarify this issue.

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