Post-transplant diabetes mellitus after liver transplantation

Vicki Munslow

ARTICLE POINTS

1 Post-transplant diabetes mellitus (PTDM), characterised by insulin resistance and absent biphasic insulin secretion from pancreatic beta-cells, is common.

2 Evidence suggests that corticosteroid treatment, often used after organ transplant, is an important indicator for the onset of diabetes.

3 Commonly used immunosuppressive drugs are known to precipitate diabetes and accelerate atherosclerosis.

4 Complications of diabetes are likely to be worse in liver transplant patients.

5 It is vitally important that people with PTDM are monitored very closely to improve long-term outcome.

KEY WORDS

- **Post-transplant diabetes mellitus**
- **Drug-induced diabetes**
- **Corticosteroids**
- **Immunosuppressive drugs**
- **Monitoring**

Vicki Munslow is a Staff Nurse and Diabetic Link Nurse at Queen Elizabeth Hospital NHS Foundation Trust, Birmingham

Introduction

The following paper will explore the incidence and aspects of post-transplant diabetes mellitus (PTDM) in relation to immunosuppressive drug therapy and different types of liver disease. The focus of the discussion will be centred on PTDM and its incidence after liver transplantation. A critique of existing research findings and literature in this specific practice area will be offered. Gaps in the literature and any implications and ideas for further research will be identified.

Diabetes mellitus is frequently encountered in patients having received a solid organ transplant, with an estimated prevalence of 10–30% (Markell, 2001). Post-transplant diabetes (PTDM), characterised by insulin resistance and absent biphasic insulin secretion from pancreatic beta-cells, is commonly diagnosed after orthotopic liver transplant (Jindal, 1994; Navasa et al, 1996). In liver transplant recipients, new onset of diabetes mellitus is estimated to occur in 9–21% of recipients (John and Thuluvath, 2002).

Rates of post-transplantation diabetes are similar among liver, heart and kidney transplant recipients and it has been suggested that they share a common aetiology. Some authors have suggested that PTDM may be secondary to an impaired insulin secretion or decreased insulin sensitivity induced by drug therapy used to prevent graft rejection (Markell, 2001; Nieuwenhuis and Kirkels, 2001).

Post-transplant medication and complications

Treatment with corticosteroids

Corticosteroids are often used to treat patients after organ transplantation. Bialas and Routledge (1998) state that corticosteroids are used as part of an immunosuppressive therapy due to their wide range of anti-inflammatory and immunosuppressive effects. Prednisolone is usually the agent of choice if long-term immunosuppression is required. Corticosteroid treatment has an effect on carbohydrate and protein metabolism and can induce diabetes by increasing hepatic gluconeogenesis and decreasing the body's tissue responsiveness to insulin (Young and Koda-Kimble, 1995; Bialas and Routledge, 1998). Ariza-Andraca et al (1998) state that steroid-induced diabetes has been identified for as long as 30 years. This suggests that PTDM could be classified as drug-induced diabetes, i.e. secondary diabetes.

Drug- or chemical-induced diabetes is identified as being a rare type of diabetes (Belchetz and Hammond, 2003). There is evidence to suggest that the use of corticosteroids is the main indicator for the onset of diabetes related to drug-induced diabetes (Hardy, 1998; Graber and McDonald, 2000; Belchetz and Hammond, 2003). Young and Koda-Kimble (1995) agree and state that corticosteroids are one of the most common drug groups that may aggravate pre-existing diabetes or may produce hyperglycaemia or overt diabetes in individuals who are not otherwise predisposed.

Cosio et al (2001) and Rao and Anderson (1987) also support the view that PTDM is drug-induced and state that PTDM is a serious complication of transplantation caused by immunosuppressive drugs. In

Cosio et al's (2001) study, the patients were on a triple therapy of ciclosporin, azathioprine (Imuran) and prednisolone.

The majority of patients who have undergone liver transplantation at the liver unit in the West Midlands receive a triple therapy of immunosuppressive medication. This usually takes the form of tacrolimus (Prograf), azathioprine and prednisolone. Any episodes of acute rejection are treated with high-dose prednisolone. However, Cosio et al's (2001) findings cannot be directly applied to the liver unit patients as they researched patients following renal transplantation not liver transplantation. It has been observed by others that early steroid withdrawal has significantly reduced the incidence of PTDM (Ramirez et al, 1998; Everson et al, 1999; Reding, 2000).

In a more recent study, Aldosary et al (2002) found that 24% of patients studied developed PTDM but that steroid dosage was not predictive of PTDM. In fact, they found that patients who were taking tacrolimus had a greater incidence of PTDM. This suggests that it is not only steroid treatment that leads to PTDM: other immunosuppressant medication can also lead to PTDM. A further study by Tueche (2003) supported these findings.

Treatment with tacrolimus and ciclosporin

It seems then, that it is not only the use of prednisolone that can precipitate diabetes. The use of both tacrolimus and ciclosporin have also been associated with an incidence of diabetes mellitus of up to 40% (Fernandez et al, 1999). Much concern has been expressed regarding the diabetogenic potential of both of these immunosuppressive drugs in liver transplant patients. Greater diabetogenicity of tacrolimus has been reported in multicentre trials. Wyzgal et al (2003) found that changing medication from tacrolimus to ciclosporin resulted in better glucose metabolism and demonstrated a positive effect on the diabetic state of patients with post-transplant diabetes mellitus. This study was carried out on renal transplant recipients, however, and so may not be representative of liver transplant recipients. In contrast, in relation to liver transplant recipients, Fernadez et al (1999) found no evidence to suggest a significantly higher diabetogenic effect of tacrolimus compared to ciclosporin, but they do highlight that both drugs can be associated with diabetes after transplantation. Navasa et al (1996) also found a similar diabetogenic effect with both drugs.

Konrad et al (2000) state that previous studies have indicated that pancreatic beta-cells are the primary targets for the diabetogenic effects of tacrolimus and ciclosporin. Animal and clinical studies have also shown that tacrolimus can cause beta-cell dysfunction and beta cell toxicity (Tabasco-Minguillan et al, 1993; Strumph et al, 1995).

Is PTDM drug-induced diabetes?

From the research examined so far, the main cause of PTDM seems to be related to the combination of immunosuppressive drug therapy used to prevent graft rejection. It can be argued then that PTDM can also be classified as drug-induced diabetes, since the evidence suggests it is the immunosuppressive drugs that are causing the diabetes.

However, Tueche (2003) also found in his study that immunosuppression and steroid dosage was not predictive of diabetes but that there was a higher incidence of diabetes in those patients who had had a liver transplant for alcoholic liver disease. This suggests that the incidence of diabetes in liver transplant recipients cannot be solely associated with immunosuppressive drug therapy.

Knobler et al (1998) support this view. They subsequently found that patients receiving transplants for hepatitis C had a higher incidence of post-transplantation diabetes. Bigam et al (2000) have also found that there was a high prevalence of diabetes among liver transplant recipients with hepatitis C.

PAGE POINTS

1 Most patients receive a triple therapy of immunosuppressive medication after undergoing liver transplantation.

2 Early corticosteroid withdrawl has been observed to reduce the incidence of post-transplant diabetes, however steroid dosage is not predictive of PTDM.

3 The immuno-suppressant drugs tacrolimus and ciclosporin have been associated with an incidence of diabetes.

4 Evidence, however, suggests the incidence of diabetes in liver transplant recipients cannot be solely associated with immunosuppressive drug therapy.

5 Incidence of PTDM varies depending on the type of liver transplant.

PAGE POINTS

1 PTDM cannot be classified as drug-induced diabetes because it is not solely related to medication.

2 John and Thuluvath (2002) state that complications of diabetes are likely to be worse in liver transplant patients with PTDM.

3 Immunosuppressive drugs are known to accelerate atherosclerosis, can affect renal function, and are associated with hypertension, high cholesterol, weight gain and cardiovascular disease.

4 It is vitally important that people with PTDM are monitored very closely to improve long-term outcome.

5 PTDM is common among liver transplant recipients.

They compared patients with hepatitis B virus (HBV), hepatitis C virus (HCV) and cholestatic liver disease (CLD). Patients with HCV had higher incidence of PTDM (37%) compared to HBV (15%) and CLD (5%) on one year after transplantation. However, Bigam et al (2000) acknowledge that other forms of liver disease requiring transplantation, such as haemochromatosis, alcoholic liver disease and autoimmune hepatitis are also associated with diabetes. Other authors have also found supporting evidence that links HCV with diabetes after transplantation (Grimbert et al, 1996; Caronia et al, 1999; Baid et al, 2001; Aldosary et al, 2002).

Considering this evidence, PTDM cannot be classified as drug-induced diabetes because it is not solely related to medication and can be attributed to a number of factors, one of which is the type of liver disease.

Complications of diabetes in liver transplant patients

Diabetes is the commonest cause of blindness in adults, a quarter of patients require end-stage renal failure management, and it is responsible for a five-fold increase in risk of heart attacks, which are more severe and more life threatening (Shaw, 2003). John and Thuluvath (2002) state that such complications of diabetes are likely to be worse in liver transplant recipients with PTDM. The immunosuppressive drugs are known to accelerate atherosclerosis and can affect renal function in the longer term. These drugs are also associated with hypertension, high cholesterol levels, weight gain and cardiovascular disease (Stegall et al, 1997). The combined effects of diabetes mellitus and immunosuppression can, therefore, result in more advanced complications.

John and Thuluvath (2002) found that there was a higher incidence of complications in those patients with PTDM. It is therefore vitally important that people with PTDM are monitored very closely to improve long-term outcome.

Conclusion

In conclusion, PTDM is common among liver transplant recipients. It appears that PTDM can be precipitated by immunosuppressive drug therapy, namely prednisolone, tacrolimus and ciclosporin. There is evidence to suggest that all three medications have a diabetogenic effect.

However, it also appears that the incidence of PTDM can be attributed to different types of liver disease. There seems to be a higher incidence of PTDM associated with HCV, although other forms of liver disease, such as alcoholic liver disease and autoimmune hepatitis, have also been found to be associated with PTDM. It seems, then, that the pathogenesis of post-transplant diabetes is multifactorial and factors other than immunosuppressive therapy may contribute; therefore, PTDM cannot be classified as drug-induced diabetes.

Much of the research examined in this discussion has been carried out abroad with very little in the UK. These research findings can be applied generally, but more work into the longer-term effects of immunosuppression and diabetes could be undertaken in the UK and would provide a truer representation of people treated here.

Complications of diabetes are likely to be worse in liver transplant recipients because commonly used immunosuppressive drugs are known to precipitate diabetes and accelerate the atherosclerosis. Renal dysfunction also may be more common because of the combined effects of diabetes and immunosuppressive drugs. These patients should therefore be monitored very closely. ■

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