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## ISLET CELL DAMAGE ASSOCIATED WITH TACROLIMUS AND CYCLOSPORINE: MORPHOLOGICAL FEATURES IN PANCREAS ALLOGRAFT BIOPSIES AND CLINICAL CORRELATION<sup>1</sup>

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### Abstract [TOP](#)

**Background.** The introduction of the potent immunosuppressive drugs tacrolimus (FK) and cyclosporine (CSA) has markedly improved the outcome of solid organ transplantation. However, these drugs can cause posttransplantation diabetes mellitus. Abnormalities in the glucose metabolism are of particular significance in pancreas transplantation.

**Methods.** We studied 26 pancreas allograft biopsies, performed 1-8 months posttransplantation, from 20 simultaneous kidney-pancreas transplant recipients, randomized to receive either FK or CSA. The biopsies were studied by light microscopy, immunoperoxidase stains for insulin and glucagon, in situ DNA-end labeling for detection of apoptosis, and

electron microscopy. The islet morphology was correlated with the mean and peak levels of CSA and FK in serum, with corticosteroid administration and with glycemia.

Results. On light microscopy cytoplasmic swelling, vacuolization, apoptosis, and abnormal immunostaining for insulin were seen in biopsies from patients receiving either FK or CSA. The islet cell damage was more frequent and severe in the group receiving FK than in the group receiving CSA (10/13 and 5/13, respectively) but the differences were not statistically significant. Significant correlation was seen between the presence of islet cell damage and serum levels of CSA or FK during the 15 days previous to the biopsy, as well as with the peak level of FK.

Toxic levels of CSA or FK and administration of pulse steroids were associated with hyperglycemia when these occurred concurrently ( $P = 0.005$ ). Toxic levels of CSA or FK by themselves were associated with hyperglycemia in a minority of cases (8 and 26%, respectively). Electron microscopy showed cytoplasmic swelling and vacuolization, and marked decrease or absence of dense-core secretory granules in  $\beta$  cells; the changes were more pronounced in patients on FK. Serial biopsies from two hyperglycemic patients receiving FK and evidence of islet cell damage demonstrated reversibility of the damage when FK was discontinued.

Conclusions. The structural damage to  $\beta$  cells demonstrated in this study is similar to morphological and functional abnormalities previously described in experimental animal models and can at least partially account for the glucose metabolism abnormalities seen in patients receiving these drugs. Toxic levels of CSA or FK and higher steroid doses potentiate each others' diabetogenic effects.

The use of potent immunosuppressive drugs such as cyclosporine (CSA\*) and tacrolimus (FK) has markedly improved graft survival in solid organ transplantation (1-5). The beneficial effects of these agents over previously used immunosuppressive strategies, however, have not been accompanied by diminished side effects. Both drugs can cause dose-dependent, reversible, nephrotoxicity, neurological complications, and gastrointestinal symptoms. Other side effects include gingival hyperplasia, hirsutism, or alopecia, and metabolic abnormalities including abnormal glucose metabolism. The latter is more frequently seen in patients receiving FK (6). Increased age and body weight (7), as well as family history of abnormal glucose metabolism, and racial factors (African-American and Hispanic descent) are associated with higher incidence of posttransplant diabetes mellitus (PTDM) (8). Hyperglycemia and hyperinsulinemia are known to promote atherosclerosis therefore increasing the risk of cardiovascular complications (9). PTDM also increases the risk of infectious complications and appears to be associated with more rapid deterioration of graft function in renal allografts (10, 11).

In the precyclosporine era, when large doses of corticosteroids were the primary agent used for immunosuppression, PTDM was reported in up to 46% of renal transplant recipients (11). PTDM secondary to steroid use is believed to occur due to insulin resistance with a relative deficiency of insulin. The mechanisms leading to insulin resistance are likely to be multifactorial and related to decreased insulin receptor number and affinity, impaired glucose uptake by muscle, and activation of the glucose free fatty acid cycle (12-14). It has been suggested that steroids may also have an inhibitory effect on insulin secretion in humans (14). In addition to islet hyperplasia,  $\beta$  cell degranulation, vacuolization, and necrosis have been reported with administration of hydrocortisone in animal models (15-17).

With the introduction of FK and CSA and the current use of lower doses of steroids the incidence of PTDM has decreased (3-14% of patients). Nevertheless, PTDM remains an important complication of organ transplantation (8, 18-20).

CSA and even more FK have markedly reduced the incidence of acute rejection in pancreas transplants, making possible good long-term results for this type of transplants (4, 21). However, both CSA and FK have been shown experimentally to be toxic to islet cells. The apparently reversible morphological abnormalities described in animal models for both CSA and FK506 are similar, and include cytoplasmic vacuolization, degranulation, and dilatation of the rough endoplasmic reticulum in  $\beta$  cells (22-26). The morphological features of islet cell toxicity of these drugs in humans have not yet been described.

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The occurrence of hyperglycemia in pancreas transplant recipients poses an especially frustrating dilemma, because the specific objective for this type of organ transplantation is the normalization of glucose metabolism and liberation from insulin in diabetes (27).

In this study, we evaluated the effects of both CSA and FK on the transplanted pancreas by analyzing the morphological changes in the islets of Langerhans in pancreatic allograft biopsies. We attempted to identify differential toxic effects of the two agents by comparing the biopsy material from patients who had been randomized to receive either FK or CSA as part of a triple immunosuppression regimen. Serial drug levels were correlated with the morphological findings and the occurrence of hyperglycemia.

## MATERIALS AND METHODS TOP

Twenty patients with simultaneous kidney-pancreas transplants performed at the University of Maryland Hospital between April and October 1995 were randomized to receive as maintenance immunosuppression either FK, azathioprine and corticosteroids (10 patients), or CSA, azathioprine, and corticosteroids (10 patients). The patients were 12 males and 8 females with a mean age of 40 years (range 24-64). Seventeen patients were Caucasian and 3 were African-American. The 12-hr target levels of CSA and FK were 200-400 and 12-20 ng/ml, respectively. During the span of this study the patients in both groups were maintained on prednisone doses of 10-25 mg/day (mean 17 mg). Twenty-six adequate pancreas allograft biopsies (13 from each group, including at least 1 from each patient) were available for evaluation. The biopsies were performed at 1 to 8 months posttransplantation, according to the previously described procedure (28). Ten of the 26 biopsies were protocol biopsies, performed at 3 months in 4 and 6 patients receiving FK or CSA, respectively. The remaining biopsies were performed as part of the evaluation for acute allograft dysfunction (increased serum amylase and lipase in eight patients, and hyperglycemia in two patients).

Tissue from a partial native pancreatectomy secondary to trauma, and a sample from a SPK recipient that developed posttransplant lymphoproliferative disorder and received only corticosteroids as immunosuppressive treatment during the 3 weeks before the biopsy were used as controls. Each biopsy was routinely processed and embedded in paraffin; 5- $\mu$ m sections were evaluated with light microscopy and with immunoperoxidase stains for insulin, glucagon (Dako, Carpinteria, CA) and in situ DNA end labeling for apoptosis (INSEL, ApopTag, Oncor, Gaithersburg, MD).

On light microscopy, the number, and size of the islets of Langerhans [defined arbitrarily for the purpose of this study as small (<10 cells), medium (10-20 cells), and large (>20 cells)] were recorded for each biopsy. The islet cells were evaluated for (1) cytoplasmic vacuolization and swelling and these changes were graded as mild, moderate, or severe (<25%, 26-50%, and >50% of cells affected, respectively), (2) cell drop-out leaving an empty space, (3) nuclear and cytoplasmic features of apoptosis (nuclear chromatin condensation with surrounding clear "halo," cellular, and/or nuclear fragments) and, (4) nuclear atypia (karyomegaly, hyperchromasia, anisocytosis).

Immunoperoxidase stains for insulin and glucagon were evaluated for intensity (graded as 1+-3+) and distribution of staining cells within the islets. The INSEL stains were performed according to the protocol previously described (29); apoptosis was indicated by positive nuclear staining and associated morphological features of apoptosis.

For electron microscopy all corresponding tissue samples were first deparaffinized and then processed as previously described (30). Islets were available for ultrastructural evaluation in samples from six and five patients receiving FK and CSA, respectively, as well as in both controls. All measurements of CSA and FK in serum performed during the first 12 months posttransplantation as well as the administration of pulse steroids were recorded and correlated with the glycemia, and with the biopsy dates and corresponding biopsy findings.

Statistical analysis was performed using Pearson's  $\chi^2$ , Spearman correlation coefficients, and Fisher's exact test.

## RESULTS TOP

*Light microscopic morphology.* The average number of islets per needle core section was 4, with a range of 1-10. The islets were predominantly (>60%) medium in size. There was no evidence of islet hyperplasia in any case; also no

difference was noted in the distribution, number, or size of islets between the two study groups and the controls.

The controls showed islet cells with granular or minimally vacuolated cytoplasm; coarse vacuolization or any significant cytoplasmic swelling with diffuse clearing was not seen (Fig. 1A). In contrast, cytoplasmic swelling and clumping of cytoplasm in threads alternating with clear, "empty" appearing areas (vacuoles) were present in 10 of 13 biopsies from the FK group (Fig. 1B) and in 5 of 13 biopsies from the CSA group (Fig. 1C). The degree of islet cell damage was mild or moderate in the CSA group, whereas biopsies with severe damage were only seen in the FK group.

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Figure 1. A, Light microscopic appearance of islet from patient receiving only steroids. The cytoplasm of islet cells is finely granular. Cytoplasmic swelling or "empty" looking vacuoles are not seen. Asterisks mark vascular spaces. B, Marked swelling and vacuolization of islet cells (arrows) in a patient receiving FK. C, Moderate swelling and vacuolization of islet cells (arrows) in a patient receiving CSA.

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Nuclear pyknosis and eosinophilic condensation of the cytoplasm (features consistent with apoptosis) were seen in occasional islet cells in six biopsies and two biopsies from the FK and CSA groups, respectively. Islets from five and one biopsies from the FK and CSA groups, respectively, showed irregular, open spaces not lined by endothelium, consistent with cell drop-out (Fig. 2A).

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Figure 2. A, Islet showing marked cytoplasmic vacuolization in occasional cells and empty spaces (arrowheads) consistent with cell drop-out. Asterisks mark vascular spaces. B, In situ DNA end labeling showing positive staining condensed pyknotic nucleus and surrounding halo typical of apoptosis (arrow).

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Apoptosis of rare cells was demonstrated with the INSEL stains in six biopsies from the group receiving FK506 and in one biopsy from the CSA group (Fig. 2B). All of the apoptosis-related features were absent from the controls.

Despite the more frequent occurrence of vacuolization and the overall higher degree of islet cell damage, including cell drop-out and apoptosis in the FK group rather than the CSA group, these differences were not statistically significant.

Nuclear atypia in islet cells was identified with similar frequency in both groups (7/13 FK and 8/13 CSA). One of the two controls also showed focal nuclear atypia in islet cells.

Immunoperoxidase stains for insulin in the controls showed strong and uniform stains in a large proportion of the islet cells (Fig. 3A). In contrast, a diminished intensity of the staining was seen in 8/13 biopsies from the FK group and in 2/13 of the CSA group; these findings were observed in the biopsies that on hematoxylin and eosin stain showed islet cell vacuolization (Fig. 3, B and C). These abnormalities were observed significantly more frequently in the FK than the CSA group ( $P=0.03$ ). Immunoperoxidase stains for glucagon did not show any difference in the pattern of staining among the different groups and in the biopsies with and without vacuolization.

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Figure 3. Immunoperoxidase stain for insulin. A, Control. Uniform intense staining of insulin. The central, nonstaining areas correspond to vascular spaces. B, Mild vacuolization and associated weaker and irregular distribution of staining in  $\beta$  cells (CSA). C, Marked swelling and vacuolization with weak, "washed-out" positive staining in  $\beta$  cells (FK).

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*Electron microscopic morphology.* The control samples showed islet cells with the expected array of organelles, including abundant endocrine secretory granules, ribosomes, mitochondria, a few stacks of rough endoplasmic reticulum, and Golgi

complexes. Cytoplasmic swelling and vacuolization were absent. Rare lipid intracytoplasmic inclusions were seen (Fig. 4A).

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Figure 4. A, Electron microscopy from patient treated with corticosteroids only. Islet cells show no significant cytoplasmic vacuolization and abundant endocrine secretory granules. B, CSA toxicity: moderate swelling and vacuolization of islet cells with decrease and irregular distribution of secretory granules (arrows). Some cells (presumably non- $\beta$  cells) have abundant secretory granules and minimal vacuolization (asterisk).

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The samples from patients receiving FK506 showed the most pronounced degrees of cytoplasmic swelling as well as vacuolization and marked decrease or complete absence of the endocrine secretory granules. The periphery of the islets (an area composed predominantly of non- $\beta$  cells) was less affected than the central portions. Therefore, minimally affected or unaffected cells resting on the surrounding basement membrane were commonly seen (Fig. 5A). Samples from patients receiving CSA showed variable vacuolization, again predominantly in the center of the islets; however, the cytoplasmic vacuolization was mild or minimal with the majority of the cells containing either normal or mildly decreased amounts of secretory granules (Fig. 4B). Cytoplasmic lipid inclusions in islets cells were prominent in two patients receiving CSA.

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Figure 5. A, FK toxicity: islet showing marked swelling and vacuolization of  $\beta$  cells with markedly decreased or absent secretory granules. Some peripheral (non- $\beta$ ) cells have abundant secretory granules and minimal vacuolization (asterisk). Insert, Light microscopic morphology of islets showing marked swelling and vacuolization. B, Follow-up biopsy from same patient in A after normalization of glycemia. There is minimal cytoplasmic vacuolization of islet cells and relatively abundant secretory granules. Insert, Light microscopic morphology showing minimal vacuolization of islet cells.

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When a semiquantitative ultrastructural comparison of the two groups was made, the islets from patients receiving FK and CSA both had an average of 40-50% of cells showing degenerative changes, but the vacuolization was consistently mild with CSA and more severe with FK.

*Correlation between drug levels, vacuolization, and hyperglycemia.* The mean 12-hr values of CSA and FK for the first 12 months posttransplantation were 291 and 13 ng/ml, respectively.

The degree of islet cell vacuolization (none, mild, moderate, and severe) in the biopsies correlated significantly with the FK and CSA mean levels in the previous 15 days ( $P=0.045$  and  $0.049$ , respectively). Significant correlation was also seen with the peak values of FK in the 2 weeks before the biopsy ( $P=0.04$ ).

The highest degrees of vacuolization (moderate and marked) were observed only in patients with high mean values of FK (>35 ng/ml, two patients) and CSA (>580 ng/ml, three patients). All other biopsies with no or mild vacuolization were from patients that had mean levels of CSA and FK506 within therapeutic ranges in the 2 weeks before the biopsy.

Only two biopsies were obtained after the administration of corticosteroids in two patients with normoglycemia and receiving therapeutic levels of FK; these two biopsies showed mild vacuolization.

Six patients receiving FK and five patients receiving CSA were treated with pulse steroids for 3 days followed by a tapering schedule one to three times each. Administration of corticosteroids in the presence of therapeutic levels of CSA and FK was associated with hyperglycemia (>200 mg/dl) only one of nine occasions (11%). Administration of corticosteroids in the presence of high levels of CSA or FK (>500 or >28) was associated with hyperglycemia (>200 mg/dl) four of five times (80%). The association between pulse steroids/high CSA or FK levels and hyperglycemia was statistically significant ( $P=0.005$ ).

High levels of CSA (>500 ng/ml) and FK (>28 ng/ml) by themselves were rarely associated with hyperglycemia (>200

mg/dl). During the first 12 months posttransplantation hyperglycemia (>200 mg/dl) occurred 4/47 (8.5%) and 5/19 (26.3%) times in patients receiving CSA and FK, respectively. There was no statistical difference between the occurrence of hyperglycemia in patients with high levels of CSA or with FK.

*Reversibility of tacrolimus toxicity.* The biopsy of one patient presenting with hyperglycemia (up to 400 mg/dl) and high levels of FK (41 ng/ml) showed diffuse swelling, vacuolization and cytoplasmic clearing involving all the islets (Fig. 5A). The patient was switched to CSA and glycemia normalized. A follow-up biopsy 2 weeks later showed resolution of most of the islet changes and only minimal vacuolization (Fig. 5B).

The other patient with persistent hyperglycemia was a markedly obese, African-American woman that had therapeutic levels of FK at all times. Glycemia normalized after FK was discontinued and CSA was started. The initial biopsy (FK) showed mild vacuolization and follow biopsy had unremarkable islets (CSA).

*Long term follow-up.* After 38-41 months of follow-up (mean 37.8 months), 18 patients (90%) have satisfactory graft function. The other 2 patients lost their grafts secondary to late graft thrombosis and graft involvement by posttransplant lymphoproliferative disorder, respectively.

Needle allograft biopsies performed at 24-39 months in three patients receiving CSA and one patient receiving FK were available for evaluation. All four patients were normoglycemic at the time of biopsy but showed increases in amylase and lipase. The islets were unremarkable in two patients receiving CSA and showed minimal vacuolization in the other two patients receiving CSA and FK, respectively. Three of the four patients showed mild fibrosis and exocrine acinar atrophy consistent with mild chronic rejection.

## DISCUSSION TOP

With the use of decreasing steroid doses after the introduction of CSA, the incidence of PTDM has markedly diminished from up to 46% to 3-20% (11, 31-33). PTDM, however, continues to be an important side effect of the current immunosuppression regimens, potentially associated with increased cardiovascular and infectious complications and decreased graft survival.

Although CSA has been associated to PTDM in 11-19% of transplant recipients (6, 34, 35) its diabetogenic effects have been questioned by investigators reporting the lack of detectable abnormalities in glucose metabolism in patients not receiving steroids (36, 37). The mechanism by which CSA interacts with steroids results from the inhibition of the P-450 system causing increased blood levels of steroids (38). However, other studies have demonstrated functional and morphological abnormalities in the islets of animals receiving only CSA (22, 34-45). Specifically, a reduction in insulin secretion (39, 42), diminished  $\beta$  cell density (39), decreased insulin synthesis (40), and defective insulin secretion (44, 45) have been reported.

Similar morphological findings have been reported in animals receiving FK (23). The incidence of PTDM in renal transplant recipients receiving FK has been reported to be in the 15-29% range (33, 46, 47). Functional abnormalities associated with FK include decrease in insulin secretion (23, 26) and more specifically inhibition of synthesis of insulin due to a mRNA transcriptional defect (48). The latter defect was reversible after discontinuation of the drug.

In concordance to the animal studies we report morphological evidence of islet cell toxicity in pancreas biopsies from patients receiving CSA or FK. These changes consist of cytoplasmic swelling and vacuolization, and immunohistochemical and ultrastructural loss of secretory granules. The latter finding is in agreement with the experimental studies showing decreased synthesis of insulin with the use of CSA and FK.

From animal models (23, 26, 49) as well as from clinical studies (32, 50) it appears that the occurrence of hyperglycemia with FK is dose related and reversible. With our clinical and morphological follow-up we were able to confirm the reversibility of the toxicity.

Comparison studies between the effects of CSA and FK on glucose metabolism in liver transplant patients have demonstrated that both agents independently of steroid use cause impaired glucose tolerance (35), with more abnormalities seen in FK-treated patients. In our study we observed more frequent and more severe islet cell damage in patients receiving FK, but we could not demonstrate a statistically significant difference in the incidence or degree of toxicity between the patients receiving FK or CSA. The degree of islet damage in needle biopsies correlated with the 12-hr levels of CSA or FK during the previous 2 weeks and with the peak level of FK.

We were able to demonstrate in this study that the diabetogenic effects of toxic levels of CSA or FK are potentiated when they occur concurrently with the administration of pulse steroids; this combination of factors is associated with hyperglycemia (>200 mg/dl) in most instances. On the other hand toxic levels of CSA or FK by themselves are associated with hyperglycemia only in rare cases.

Whereas the toxic damage with FK is thought to be reversible, one study has suggested, that the abnormalities of glucose metabolism may be slower to normalize after prolonged treatment with this drug (42). Independently of high dose of steroids, two hyperglycemic patients in our study achieved normalization of glycemia within 1 week after being switched from FK to CSA. Serial biopsies in these patients showed reversibility of the morphological islet cell damage as well.

Although clinical trials have demonstrated that calcineurin inhibitors increase the risk of PTDM, we have no definite evidence that the long-term graft function is affected, in view of the fact that 18 of the 20 patients have adequate graft function at 3 years. Biopsies performed 2 to 3 years posttransplantation, in four normoglycemic patients, showed minimally vacuolated or unremarkable islets; there was no evidence of chronic damage to the islets (e.g., fibrosis) but atrophy of the exocrine parenchyma indicating mild chronic rejection was identified in three of four patients. Theoretically these findings correlate with the lower doses of CSA and FK used after the first year posttransplantation, however, the number of patients with late biopsies is too small to reach definite conclusions.

In summary, persistent impairment of the glucose metabolism after pancreas transplantation has been attributed to various causes including impaired insulin secretion and systemic drainage of the pancreas (51). We demonstrated in this study that with the current immunosuppressive regimens used for pancreas transplants there are morphological abnormalities of islet cells that correlate with drug levels and impairment of glucose metabolism. CSA and FK which have significantly increased the success rate of this type of transplant (3, 4, 21, 52), undoubtedly contribute to the abnormalities in glucose metabolism observed in these patients. The use of pulse steroids with higher than targeted levels of CSA and FK are likely to be associated with hyperglycemia. The cell damage appears to be reversible and dose dependent.

Until the ideal immunosuppression regimen is developed, individualization of the immunosuppression for each patient including the conversion from calcineurin inhibitors to another regimen or reduction in steroids may be attempted to reduce the incidence of PTDM (4, 51, 52). New immunosuppressive drugs such as mycophenolate mofetil, anti-CD25, and other monoclonal antibodies appear not to cause abnormalities in the glucose metabolism (53, 54) and may be helpful by allowing safe reduction of calcineurin inhibitors and steroids.

Our findings are additional evidence of the usefulness of pancreas biopsies in the evaluation of pancreas allograft dysfunction. As much as the accurate diagnosis of acute allograft rejection rests on histopathological findings (55), the recognition of features of drug toxicity should be useful for the adjustment of the immunosuppression regimen in patients with suboptimal graft function.

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\* Abbreviations: CSA, cyclosporine; FK, tacrolimus; PTDM, posttransplant diabetes mellitus. [\[Context Link\]](#)

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