Low pre-transplantation Mannose-binding lectin levels predict superior patient and graft survival after simultaneous pancreas-kidney transplantation

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Summary

Simultaneous pancreas-kidney transplantation (SPKT) is the treatment of choice for type 1 diabetics with renal failure. However, this procedure is characterized by a high rate of post-operative infections, acute rejection episodes and cardiovascular mortality. The lectin pathway of complement activation contributes to cardiovascular disease in diabetes and may play an important role in inflammatory damage after organ transplantation. We therefore studied how mannose-binding lectin (MBL), a major recognition molecule of the lectin pathway of complement activation, influences outcome after SPKT.

MBL serum levels were determined in 99 and MBL genotypes were determined in 97 consecutive patients who received a SPKT from 1990 through 2000, and related to patient and graft survival.

At 12 years, cumulative death-censored kidney graft survival was 87.5% in patients with an MBL level below 400 ng/ml and 74.8% in the group with MBL levels above 400 ng/ml (p = 0.021). Pancreas graft survival was significantly better in patients with low MBL-levels (p = 0.016). MBL levels above 400 ng/ml were associated with a hazard ratio of 6.28 for patient death (95% CI 1.8-20.3 p = 0.003). Accordingly, survival was significantly better in recipients with MBL gene polymorphisms associated with low MBL levels.

Our findings identify MBL as a potential risk factor for graft and patient survival in SPKT. We hypothesize that MBL contributes to the pathogenesis of inflammation-induced vascular damage both in the transplanted organs as well as in the recipient's native blood vessels.
**Introduction**

Simultaneous pancreas-kidney transplantation (SPKT) is the preferred treatment option for patients with long standing type 1 diabetes and end-stage renal failure. The major arguments favoring SPKT in these patients rather than renal transplantation alone include improved quality of life, prevention of recurrent diabetic nephropathy, and stabilization of diabetic neuropathy and retinopathy. Recent studies demonstrated that SPKT, compared to kidney transplantation alone, leads to improved allograft survival [1] and improved patient survival [2;3]. In spite of these benefits, mortality after SPKT transplantation remains high with 10 year patient survival rates of less than 70% [2;4].

The complement system contributes to tissue damage at various stages of the transplantation process. An important role in ischemia/reperfusion injury and acute rejection has been demonstrated in various animal models [5;6]. Recently, the F/F and F/S donor allotypes of the C3 complement molecule have been associated with better long term outcome after kidney transplantation [7].

Mannose-binding lectin (MBL) is the major recognition molecule of the lectin pathway of complement activation. In host defense wildtype MBL binds to carbohydrate moieties leading to complement deposition, opsonisation and elimination of pathogens. Single nucleotide polymorphisms (SNPs) in the structural as well as regulatory parts of the MBL gene lead to large interindividual variations in the concentration of functional MBL in serum [8].

Various studies showed an association of low serum MBL levels and MBL SNPs with decreased host defense against various infectious agents. This is especially apparent in situations of impaired adaptive immunity such as early childhood or prolonged immunosuppression [9-12].

However, wildtype MBL may also interact with tissue and lead to complement-mediated enhancement of damage in various non-infectious inflammatory settings. In ischemia/reperfusion damage MBL may contribute to tissue injury by binding to host cells exhibiting a modified surface [13;14]. Recently, high MBL levels have been related to an increased risk of vascular disease and diabetic nephropathy in both patients with type 1 and type 2 diabetes [15-17].

Our group has shown that low pre-transplantation MBL levels are associated with better graft survival after deceased donor kidney transplantation [18]. In view of the role of MBL in diabetes and transplantation, we hypothesize that MBL could be major determinant of outcome in SPKT which is characterized by a high rate of infectious complications, acute graft rejection and cardiovascular mortality.
Methods

Study Population
Between January 1990 and December 2000, 114 SPKTs were performed in the Leiden University Medical Center. All patients had diabetes mellitus type 1. Pre-transplantation serum was available from 99 and DNA was available from 97 of these consecutive recipients. Both pre-transplant serum and DNA was available from 87 of these patients. Pre-transplantation sera were routinely obtained at the time of admission for transplantation and stored in aliquots at -80°C. All measurements of MBL were performed in sera that had been frozen and thawed only once. All included patients were regularly followed at our center. None of the 99 patients were lost to follow up. The study was performed according to the guidelines of the ethics committee of the Leiden University Medical Center and patient anonymity was maintained.

The following clinical data were collected using the Leiden Transplant Database: donor variables including gender and age at time point of death, recipient variables (age at time of transplantation, gender, panel-reactive antibodies, CMV status, duration of diabetes and dialysis treatment, smoking status and cholesterol levels), transplantation-related factors (human leukocyte antigen-A [HLA-A], -B, and -DR mismatches; cold ischemia time), and post-transplantation features including immunosuppressive regimen, occurrence of delayed graft function, acute rejection history, rejection treatment, status of both the kidney and pancreas allograft, cause of allograft loss, vital status and cause of death. Rejection was defined as either biopsy proven rejection or clinical rejection of the kidney with a favorable response to anti-rejection treatment. Since pancreas rejection is difficult to diagnose and isolated rejection of the pancreas is a rare event this was not analyzed separately in this study. After transplantation, patients were followed until death or until January 1st 2006. Until May 1995 standard maintenance immunosuppression consisted of prednisone, cyclosporine and azathioprine. All recipients transplanted after May 1995 received prednisolone, cyclosporine and mycophenolate mofetil. Eighteen patients received induction treatment with OKT-3 between 1991 and 1994. From 1999 onwards, induction treatment was reinitiated and consisted of either polyclonal antithymocyte globulin (ATG-Fresenius) or Daclizumab (n = 19). Acute rejection episodes were treated according to a standard protocol consisting of methylprednisolone 1 g intravenously for three consecutive days; a 10 day course of antithymocyte globulin at a dose of 5 mg/kg guided by absolute lymphocyte counts; or again methylprednisolone for the first, second (or steroid-resistant), or third rejection episode, respectively.
ELISA
Serum MBL levels were assessed by sandwich ELISA as described previously (18). In brief, 96-well ELISA plates (Greiner, Frickenhausen, Germany) were coated with the monoclonal antibody 3E7 (mouse IgG1 anti-MBL at 2.5 μg/ml), kindly provided by Dr. T. Fujita (Fuhushima, Japan). Serum samples were diluted 1/50 and 1/500 and incubated in the coated wells. MBL was detected with Dig-conjugated 3E7. Detection of binding of Dig-conjugated antibodies was performed using HRP-conjugated sheep anti-Dig Abs (Fab fragments, Roche, Mannheim, Germany). Enzyme activity was detected using 2,2’-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (Sigma Chemical Co., St. Louis, MO)). The optical density was measured at 415 nm using a microplate biokinetics reader (EL312e; Biotek Instruments, Winooski, VT). A calibration line was produced using human serum from a healthy donor with a known concentration of MBL. Earlier studies indicated that this assay primarily detects wildtype MBL in serum and plasma and that there is a direct association with the MBL genotype and with MBL function [19].

Genotyping
DNA from 97 SPKT recipients was isolated routinely from blood. MBL single nucleotide polymorphisms (SNPs) at codons 52, 54 and 57 of the mbl2 gene were typed by high resolution DNA melting analysis [20]. The detailed methodology will be published separately (A. Roos and R.H. Vossen et al., manuscript in preparation). The MBL genotype of only wildtype allele carriers is designated as A/A and the presence of 1 or 2 variant allele(s) (B, C, or D) is designated as A/O or O/O. In the survival analysis carriers of A/O and O/O MBL genotype were considered as one group.

Statistical analysis
Categorical characteristics were compared using cross-tables with calculation of the exact p-values. Interval variables were analyzed using the Independent-Samples T-test when assumptions for parametric testing were met. Otherwise the Mann-Whitney U test was used. Patient and graft survival was estimated using the Kaplan-Meier product-limit method and the curves were compared with the Log-Rank test. For both pancreas and renal allograft survival the analysis was censored for patient death. Organs lost due to technical failure or thrombosis within one week after transplantation were excluded from survival analysis.

Cox Proportional Hazards Regression was used to identify possible confounders influencing baseline MBL levels. In the multivariate model, MBL was adjusted for...
recipient age, sex and baseline CRP level. MBL was tested both as a dichotomous (MBL below or above 400 ng/ml) and a continuous factor (after log transformation). P-values < 0.05 were considered to be significant. Data analysis was performed with SPSS Statistical Software Package (Version 11.0.1; SPSS, Inc., Chicago, Ill.).

Results

The mean MBL concentration in the 99 available sera obtained directly prior to transplantation was 1053 ng/l. The median concentration was 694 ng/ml. A cut-off of 400 ng/ml was used to discriminate between high and low MBL levels. This cut-off correlates with the presence of single nucleotide polymorphisms (SNPs) in the first exon of the MBL gene in both a control population [19] and the recipients studied here (Figure 1). The median MBL concentration in SPKT recipients with only wild-type MBL alleles (A/A) was 1493 ng/ml (n = 54). In recipients with the A/O (n = 29) or O/O (n = 4) genotypes the median MBL concentrations were 245 ng/ml and 166 ng/ml, respectively. Of the patients with an MBL level above 400 ng/ml, 89.3% had only wild-type MBL alleles (A/A) whereas 90% of the patients with an MBL level below 400 ng/ml had at least one of the exon 1 MBL polymorphisms (A/O or O/O). To assess whether pre-transplant MBL levels are representative for the levels after transplantation we determined the MBL concentrations one year after SPKT in 30 patients and compared them with the levels measured in the pre-transplant sample. We found a high intra-individual correlation of MBL levels over time (r = 0.87, P < 0.0001).

Thirty-four (34.3%) SPKT recipients had a low MBL level and 65 (65.6%) recipients had high MBL levels. Table 1 shows the characteristics of the high and low MBL recipients. No significant difference between both groups concerning demographic and clinical characteristics including donor and recipient age, CMV status and sex distribution was noted. Both groups had a comparable proportion of patients undergoing SPKT before initiation of dialysis treatment. Both the high and low MBL-groups had a comparable proportion of patients receiving triple immunosuppression including mycophenolate mofetil. The proportion of patients with at least one significant coronary stenosis was 27.3% in the low MBL-group and 22.3% in the high MBL-group (p = 0.58). Of note, there was no difference in the baseline CRP levels between the two MBL groups. The majority of patients required treatment for acute rejection, 88.2% and 86.2% in the low and high MBL groups, respectively (p = 0.99). Likewise the number of rejection treatments per patient was comparable in both groups (1.85 vs. 1.68, p = 0.49).
Figure 1. Pre-transplantation MBL levels stratified according to MBL genotype. The dashed line represents the cut-off level of 400 ng/ml. MBL levels are represented on a log scale.

Analysis for death-censored graft survival revealed a significant survival advantage for both the renal and pancreas allografts in favor of the low MBL recipients. At 12 years after transplantation, cumulative death-censored pancreas graft survival was 100% in the low MBL-group vs 82% in the high MBL-group (p = 0.016 by the log-rank test with grafts lost within 1 week excluded) (Figure 2A). Death-censored renal allograft survival at 12 years after transplantation was 87.5% in patients with an MBL level below 400 ng/ml and 74.8% in patients with an MBL level above 400 ng/ml (p = 0.021 by the log-rank test) (Figure 2B).
Subsequently, the MBL status was related to patient survival. Twelve years after transplantation cumulative patient survival was 86.9% in the low MBL group and 49.1% in the high MBL group \((p = 0.001\) by the log rank test) (Figure 3A). To examine whether
the inferior patient survival in high MBL recipients was a mere consequence of graft loss we repeated the survival analysis after excluding the patients who lost either the kidney or pancreas allograft. In the group with functioning allografts patient survival remained inferior in those with MBL levels above 400ng/ml (p = 0.02).

**Table 1. Characteristics of study population according to MBL levels**

<table>
<thead>
<tr>
<th>Acceptor MBL levela (ng/ml)</th>
<th>MBL ≤ 400</th>
<th>MBL &gt; 400</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Recipient age (yrs)</td>
<td>39.9 ± 7.8</td>
<td>40.8 ± 6.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Female recipient (%)</td>
<td>32.4</td>
<td>38.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Years diabetes</td>
<td>27.1 ± 6.2</td>
<td>26.2 ± 6.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Active smoking (%)</td>
<td>32.4</td>
<td>19.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Significant stenosis in Pre-tx CAG (%)</td>
<td>27.3</td>
<td>22.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Baseline CRP (mg/l)</td>
<td>4.3 ±6.4</td>
<td>4.45 ± 7.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Baseline cholesterol (mmol/l)</td>
<td>5.11 ±1.2</td>
<td>5.27 ± 1.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Pre-emptive SPKT (%)</td>
<td>44.1</td>
<td>35.4</td>
<td>0.40</td>
</tr>
<tr>
<td>CMV sero-positive (%)</td>
<td>41.2</td>
<td>35.9</td>
<td>0.61</td>
</tr>
<tr>
<td>Donor age (yrs)</td>
<td>33.0 ± 9.1</td>
<td>29.8 ± 11.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Cold ischemia time (hrs)</td>
<td>14.8 ± 2.9</td>
<td>15.2 ± 3.9</td>
<td>0.59</td>
</tr>
<tr>
<td>Rejection episodes</td>
<td>1.85 ± 0.9</td>
<td>1.69 ± 1.13</td>
<td>0.49</td>
</tr>
<tr>
<td>HLA DR mismatches</td>
<td>1.32 ± 0.64</td>
<td>1.29 ± 0.63</td>
<td>0.81</td>
</tr>
<tr>
<td>Mycophenolate (%)</td>
<td>47.1</td>
<td>47.6</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**a** MBL, mannose-binding lectin; CIT, cold ischemia time; CMV, cytomegalovirus; tx, transplantation; CAG, coronary angiogram, CRP, C-reactive protein, where appropriate values are given as mean ± s.d.

To confirm these findings we also analyzed recipient survival according to the MBL genotype. Superior survival was found in patients with a variant MBL genotype when compared with recipients with only wildtype MBL alleles (p = 0.026) (Figure 3B).
Figure 3. Unadjusted Kaplan-Meier survival curves of patient survival and cardiovascular survival according to MBL status. (A) Patient survival according to pre-transplantation MBL level, (B) Patient survival according to recipient MBL genotype, (A/A= wildtype MBL genotype; A/O or O/O= variant MBL genotype)

We analyzed various characteristics in relation to patient survival (Table 2). An MBL level above 400 ng/ml was associated with a strongly increased mortality (HR 6.28; 95% CI 1.89-20.87, p = 0.003). Accordingly, the presence of wild-type MBL alleles
was associated with an increased risk of patient death (HR 3.6; 95% CI 1.22-10.6, p = 0.02). MBL was also significantly associated with an increased risk of patient death when analyzed as a continuous parameter (p = 0.013). MBL remained significantly associated with patient death when entered into a multivariate model adjusted for recipient age, sex and baseline CRP using the Cox regression method (Table 2).

The reasons for patient death in the high and low MBL groups are shown in table 3. The excess mortality in patients with an MBL level above 400 ng/ml was explained to a large extent by a higher cardiovascular mortality in this group. No significant difference in infection-related deaths between the low and high MBL-groups was observed.

Table 2. Risk factors for patient death.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL &gt; 400 ng/ml</td>
<td>6.28</td>
<td>1.89-20.87</td>
<td>0.003</td>
<td>4.44</td>
<td>1.3-15.1</td>
<td>0.017</td>
</tr>
<tr>
<td>Log MBL ng/ml</td>
<td>2.75</td>
<td>1.24-6.11</td>
<td>0.013</td>
<td>2.56</td>
<td>1.04-6.3</td>
<td>0.04</td>
</tr>
<tr>
<td>MBL genotype A/A</td>
<td>3.6</td>
<td>1.22-10.06</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant coronary stenosis at baseline</td>
<td>2.00</td>
<td>0.92-4.30</td>
<td>0.077</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male recipient</td>
<td>0.61</td>
<td>0.29-1.26</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient age &gt; 40 yr</td>
<td>1.52</td>
<td>0.73-3.19</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.96</td>
<td>0.49-2.01</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline cholesterol &gt; 5 mmol/l</td>
<td>0.99</td>
<td>0.47-2.09</td>
<td>0.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years diabetes</td>
<td>0.99</td>
<td>0.93-1.06</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>1.03</td>
<td>0.98-1.07</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF vs. Aza</td>
<td>0.53</td>
<td>0.22-1.31</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-emptive transplantation</td>
<td>1.25</td>
<td>0.58-2.73</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a HR, hazard ratio; MBL, mannose-binding lectin; CI, confidence interval; CRP, C-reactive proteine, MMF, mycophenolate mofetil; Aza, Azathioprine bFor the multivariate analysis MBL was adjusted for recipient sex, age and CRP
Table 3. Reason for death according to MBL levels

<table>
<thead>
<tr>
<th>Recipient MBL-level</th>
<th>MBL ≤ 400 ng/ml</th>
<th>MBL &gt; 400 ng/ml</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>All causes</td>
<td>34</td>
<td>8.8</td>
<td>65</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>2.9</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2.9</td>
<td>4</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1</td>
<td>2.9</td>
<td>4</td>
</tr>
</tbody>
</table>

a MBL, mannose-binding lectin

Discussion

Our study demonstrates superior graft and patient survival after SPKT in recipients with low MBL levels. A high MBL level was associated with an increased incidence of death-censored loss of both the renal and the pancreatic allograft. Furthermore, a high-MBL status was associated with markedly increased mortality, and we demonstrate that this high MBL-status is genetically determined.

These findings corroborate our recent report demonstrating an association of MBL levels above 400 ng/ml with poorer graft survival after deceased donor kidney transplantation [18]. Our earlier study on the role of MBL in kidney transplantation showed a non-significant trend towards poorer patient survival in renal allograft recipients with a high MBL level. This difference between the two studies may be explained by the higher risk profile in the type 1 diabetic population receiving SPKT compared with the general population of kidney allograft recipients. In addition the harmful effect of MBL in cardiovascular mortality may be enhanced in the diabetic population.

Reports on the cardiovascular effects of MBL deficiency in the general population have been inconclusive. The predictive value of MBL levels for myocardial infarction was studied in the population-based Reykjavik study [21]. In this population MBL levels
above 1000 ng/ml were associated with a lower odds ratio for myocardial infarction. Interestingly no data on mortality were reported. In the Strong Heart Study cohort, native Americans with coronary heart disease had an increased frequency of variant MBL genotypes when compared with a matched cohort without coronary heart disease [22]. Contrary to these findings, but in agreement with our current data, a recent study in 964 apparently healthy men did show an association of elevated MBL levels with coronary heart disease [23].

So how can we explain the adverse effect of high MBL levels on graft and patient survival in our study? The finding of superior graft survival after SKPT confirms our earlier report demonstrating superior allograft survival in recipients with low MBL levels after deceased donor renal transplantation [18]. Like in the current SPKT cohort the incidence of acute rejection was similar in the high and low MBL groups, but graft loss due to rejection occurred much more frequently in recipients with high MBL levels. We hypothesize that MBL contributes to tissue damage in various inflammatory settings including graft rejection. Models of ischemia/reperfusion damage in heart, intestine and kidney have shown that MBL A & C-deficient mice are protected from ischemia/reperfusion injury as compared to wild type animals [13;24;25]. In line with these findings MBL deposition has been detected in human kidneys with ischemia/reperfusion damage [26], indicating that wildtype MBL may contribute to local complement activation and enhanced inflammation in tissue damage. Next to the interaction of MBL with apoptotic and necrotic cells [27], MBL-mediated damage may also be related to its antibody-binding capacities [28-30]. A recent study has failed to show an association between MBL levels and patient or graft survival after kidney transplantation [31]. In comparison with our studies it has to be noted that the analysis was performed using the median MBL level or the third quartile as cut-off values which may not be ideal for detecting MBL-mediated effects.

In addition to the effect of MBL on graft survival, we also observed a strong association of high MBL levels with inferior patient survival which was independent of graft survival. Earlier studies have pointed towards a detrimental role of MBL in patients with diabetes. High levels of MBL have been associated with an increased frequency of cardiovascular disease and proteinuria in patients with type 1 diabetes mellitus [15;16]. Similarly, high MBL levels have also been related to increased mortality in type 2 diabetics [17]. It may well be that MBL exerts a specific harmful effect in the diabetic milieu and the increased mortality in high-MBL subjects may be related to microvascular damage obtained prior to the pancreas transplantation. Additionally, the unfavorable effect of MBL observed in the context of ischemia/
reperfusion damage may also contribute to tissue damage and mortality following cardiovascular events.

Since intraindividual MBL-levels are highly stable over time [21] we are convinced that serum MBL levels measured prior to transplantation adequately represent the exposition to MBL. Moreover, our MBL assay strongly correlates with both the functional activity of the lectin pathway [19] and the presence of SNPs of the MBL gene. In fact, measurement of MBL levels in serum may be a more powerful and convenient method of detecting MBL-mediated effects than genotyping since not all intraindividual variations in MBL levels are explained by the known polymorphisms of exon 1 and other parts of the MBL gene.

Recently low MBL levels have been related to an increased incidence of clinically important infections after liver transplantation [12]. However, no association between MBL-deficiency and infection-related mortality was detected in our cohort. Low infection-related mortality after SPKT has been reported before [32]. Thus, although we cannot exclude that MBL deficiency is associated with an increased incidence of infections after SPKT this did not contribute to graft survival or patient mortality in our cohort.

We conclude that MBL levels are a powerful predictor of graft and patient survival after SPKT. If these findings can be confirmed in other study populations, determination of MBL levels and/or MBL genotyping may aid risk stratification prior to SPKT. Whether these findings eventually lead to new therapeutic approaches will depend on the elucidation of the underlying pathophysiological mechanisms.

Acknowledgements

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Reference List


