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Liver Transplantation from Female Donors Provokes Higher Complement Component C5a Activity

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Background: Transplanted organs from female donors are associated with less favorable prognoses and outcomes. This study aimed to determine whether donor gender affects levels of serum terminal complement component C5a and oxidative stress in pediatric living related liver transplantation (LRLTx) recipients.

Material/Methods: The subjects were 43 patients (20 males and 23 females) who underwent LRLTx during childhood (age range 1.2 years to 14.4 years; mean age 5 years). Serum samples were taken during the patients' regular outpatient visits after LRLTx. Serum C5a was measured using the specific human C5a ELISA kit. Serum total hydroperoxide (TH) and biological antioxidative potential (BAP) were measured using the free radical analytic system, and the oxidative stress index (OSI) was calculated as the ratio of TH to BAP. Serum glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), gamma-glutamyl transpeptidase (γGTP), and lactate dehydrogenase (LDH) were also measured as part of a typical outpatient examination for such patients.

Results: C5a serum levels were higher in the 29 recipients who received their grafted livers from female donors than in the 14 recipients who received their grafted livers from male donors. Recipients who received their grafted livers from female donors had higher incidence of post-LTx (liver transplantation) complications. Female recipients from female donors showed the highest serum GPT and GOT levels, but this difference was only significant when compared to the female recipients from male donors (41.4±9.8 IU/L *vs.* 17.3±1.8 IU/L for GPT and 42.2±7.5 IU/L *vs.* 23.4±2.2 IU/L for GOT; $P<0.05$).

Conclusions: Pediatric LRLTx patients who receive their grafts from female donors exhibit higher levels of serum C5a that probably plays a role in the immunological response against grafted livers from female donors in LTx.

MeSH Keywords: Base Pair Mismatch • Liver Transplantation • Oxidative Stress

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Background

Gender mismatch between donor and recipient is associated with relatively worse outcomes after liver, renal, and heart transplantation [1–3]. It is well known that the immune responses of women are more vigorous than those of men, and that the incidence of immunologically-based illness is higher among women [4].

In this study, we set out to determine whether donor gender affects levels of serum terminal complement component C5a and oxidative stress in pediatric living related liver transplantation (LRLTx) recipients. Liver transplantation leads to activation of the complement cascade in association with reperfusion of the transplanted liver [5]. Complement anaphylatoxin C5a (C5a) activates leukocytes through the expression of adhesion molecules [6] and the release of arachidonic acid metabolites, interleukins, reactive oxygen species (ROS), and lysosomal and proteolytic enzymes [7].

Oxidative stress has been defined as a disturbance in the equilibrium status of pro-oxidant/antioxidant systems in intact cells. The overproduction of ROS that occurs during oxidative stress plays a crucial role in the induction and progression of various liver diseases ranging from acute hepatitis to hepatocellular carcinoma [8].

Oxidative stress can be quantified by total hydroperoxide (TH), which functions as a measure of overall oxidative injury because hydroperoxides are the intermediate oxidative product of peptides, amino acids, and lipids [9,10]. Therefore, measurement of TH provides information regarding some of the fundamental mechanisms of oxidative stress in liver diseases [8]. Conversely, biological antioxidative potential (BAP) is used to determine overall antioxidative activity. Serum BAP provides a reliable measure of the resistance of the antioxidant barrier to oxidation, and decreasing oxidant potential due to ROS exposure is a feature of many adverse physiological and biological conditions [11,12]. Oxidative stress occurs when the homeostatic balance between the formation of oxidants and their removal or buffer by endogenous antioxidant-scavenging compounds is disrupted by excessive oxidant production for any reason or by inadequate antioxidant defenses, both of which are indicated by low BAP. The status of this balance can be assessed by calculating the ratio of TH to BAP, which represents the oxidative stress index (OSI) [9].

We hypothesized that changes in C5a levels and OSI values could explain the effect of gender mismatch on graft survival and long-term outcome in LRLTx.

Material and Methods

Patients

Our study enrolled 43 patients (20 males and 23 females) with an age range of 1.6 to 25.1 years (mean age at time of study: 12.3 years) who had received LRLTx at ages ranging from 1.2 to 14.4 years (mean age at LRLTx: 5 years). The interval between LRLTx and study sampling ranged from 5 months to 17.5 years (mean: 7.3 years).

The patients' clinical data are presented in Table 1, classified according to recipient and donor gender.

Blood samples for regular post-LRLTx follow-up laboratory measurements were drawn from all patients during their regular follow-up visits at the Clinic for Pediatric Surgery and Liver Transplantation at Fujita Health University between November 2008 and March 2009. As per standard practice at every follow-up visit, each patient's serum glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), gamma-glutamyl transpeptidase (γGTP), and lactate dehydrogenase (LDH) levels were measured. Once informed consent was obtained, serum TH, BAP, and C5a levels were measured. The study protocol was approved by the Ethics Committee of Fujita Health University.

Patient classification

The subjects were classified by gender in 3 ways:

1. By recipient's gender [male (M), (n=23), and female (F), (n=20)].
2. By donor's gender [male (M-donor), (n=14), and female (F-donor) (n=29)].
3. By both recipient's and donor's gender [female-donor-female-recipient (F-F), (n=17); female-donor-male-recipient (F-M), (n=12); male-donor-female-recipient (M-F), (n=6); and male-donor-male-recipient (M-M), (n=8)].

The patients' original underlying diseases, ages at LRLTx, body weights, post-transplantation durations, liver enzyme levels, donors' ages, and status of ABO compatibility between the recipients and their donors are presented in Table 1, classified according to recipient and donor gender.

Measurements

Serum blood samples for GPT, GOT, GTP, and LDH were sent to the hospital's lab. Serum samples for TH, BAP, and C5a were collected and prepared as previously described [13].

Serum total hydroperoxide (TH) assay

A small volume (10 µl) of each serum sample was used. TH was measured using a Diacron-reactive oxygen metabolites

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Table 1. Clinical data of the enrolled patients classified according to both recipient's and donor's gender.

Donor–Recipient gender	Disease diagnosis (n)	Patients' Age (Y.M) (range)	Donors' age (Y.M) (range)	Post-LTx interval (Y.M) (range)	Patients' BW (Kg)	ABO compatible (%)	Laboratory data (U/L)	
							GPT	GOT
							γGTP	LDH
Female-Female (n=17)	BA (13), Metabolic (2), Byler's disease (1), Alagille syndrome (1)	10.1 (1.6–23)	34 (24.6–56)	6.4 (0.9–15.9)	25.1±4	14 (82.4)	41.35±10.4*	42.9±7.9*
							35.2±13	235±12.9
Female-Male (n=12)	BA (4), Metabolic (3), Byler's disease (2), Alagille syndrome (2), HF (1)	12.4 (2.9–25.1)	33.3 (25.7–43.7)	7.9 (0.9–17.9)	23.6±4.9	10 (83.3)	24.75±4.6	31±2.3
							43.3±10.6	232.1±16.6
Male-Female (n=6)	BA (4), HF (1), AFH (1)	17.9 (10.7–2)	41 (33.2–48.3)	8.8 (3.1–16)	41.2±5	5 (83.3)	18±2	23.8±2.5
							26.7±3.4	182.7±19.2
Male-Male (n=8)	BA (4), Metabolic (1), PSC (1), PVD (1), Hepatoma (1)	12.7 (2.4–24.5)	36.8 (30.9–48)	7.1 (0.9–15.9)	32.4±6.7	7 (87.5)	22.9±3.2	29.6±3.5
							78±51.3	215.7±14.1

BA – biliary atresia; HF – hepatic fibrosis; AFH – acute fulminate hepatitis; PSC – primary sclerosing cholangitis; PVD – portal vein deficiency; Metabolic – metabolic diseases, including propionic acidemia (n=1), methylmalonic acidemia (n=1), arginase deficiency (n=1), tyrosinemia (n=2) and glycogen storage disease type 1β (n=1). * P<0.05 compared to the Male-Female group.

(d-ROMs) kit (Diacron srl, Grosseto, Italy) in the free radical analytical system (FRAS) as previously described [9,10,13].

Serum biological antioxidative potentials (BAP) assay

BAPs were measured using a commercial assay kit (Diacron srl) in the FRAS using a small amount of serum (10 µl). The principle of the investigation depends on the serum samples' ability to reduce ferric ions to ferrous ions, giving a measurement of the reducing ability or antioxidant potential of the tested serum. The reduced ferric ions can be counted with sufficient accuracy through a photometric assessment [9]. The oxidative stress index (OSI) was calculated as a ratio of TH to BAP, as the shift in oxidative/antioxidative balance toward the oxidative side is considered to be oxidative stress [9,12].

Serum C5a assay

Serum C5a was measured using the BD OptEIA human C5a ELISA kit II (BD Biosciences, Franklin Lakes, NJ). The test is a solid-phase sandwich ELISA (enzyme-linked immunosorbent assay) that uses a monoclonal antibody specific for human C5a-desArg. Once it forms in the blood serum, nascent C5a anaphylatoxin is rapidly cleaved to the C5a-desArg form by the endogenous serum carboxypeptidase N enzyme. Thus, the quantitation of C5a-desArg in serum samples should yield a reliable measurement of the level of complement activation that has occurred therein.

Statistical analysis

The distributions of data were tested using the Shapiro-Wilk test. To compare between 2 groups, we used the *t* test; if the data were nonparametric, a Mann-Whitney test was used instead.

We compared the mean C5a levels and OSI values of the 4 groups using analysis of variance (one-way ANOVA) followed by Bonferroni multiple comparison correction. If the data were not normally distributed, the Kruskal-Wallis test was used instead. When significance was detected, the Mann-Whitney test was also used. Chi-squared Fisher's exact test analysis was conducted to determine if recipient's or donor's gender had any influence on the incidence of developing post-LTx (liver transplantation) complication and immunotolerance.

Data are reported as mean ±SEM unless indicated otherwise. Probability values less than 0.05 were considered to indicate significance. All data analyses were performed with the commercially available statistical analysis software package SPSS 20 (Statistical Package for Social Sciences, Chicago, IL).

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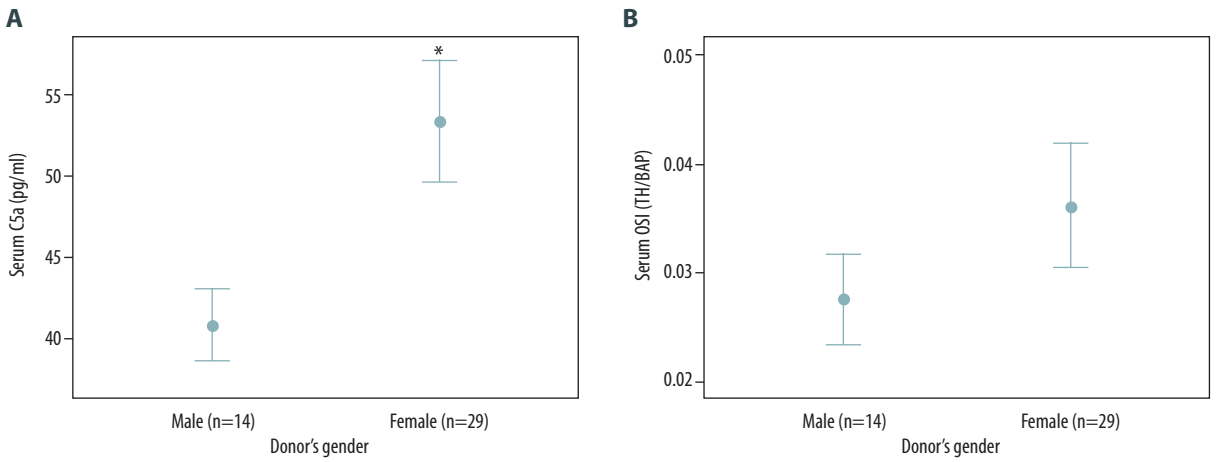

Figure 1. Serum levels of (**A**) C5a and (**B**) OSI in the serum samples of 43 patients who underwent living related liver transplantation during childhood classified according to donor's gender. * P<0.05.

Results

Comparisons among groups

According to recipient's gender

There were no significant differences between male (n=23) and female (n=20) recipients in terms of their original underlying diseases, ages, body weights, post-transplantation durations, liver enzyme levels, donors' ages, or ABO compatibility with donors; nor did serum OSI values or C5a levels differ between male and female recipients.

According to donor's gender

The donor's gender had a slight effect on the recipient's oxidative stress: mean OSI was higher in recipients of grafted livers from female donors, but this difference did not reach significance. Donor's gender had a significant effect on serum C5a levels: these were higher in recipients of livers from female donors than in recipients of livers from male donors (52.84±3.6 pg/ml *vs.* 43.22±2.8 pg/ml, P<0.05) (Figure 1A, 1B).

GPT and GOT were also higher in recipients who received their grafted livers from female donors than in those who received their livers from male donors (38.2±7 U/L *vs.* 20.3±1.8 U/L for GPT and 38.8±4.6 U/L *vs.* 27.7±2.6 U/L for GOT; P<0.05).

According to recipient's and donor's gender

In a 4-group comparison, the F-F group showed the highest serum GPT and GOT levels, but this difference was only significant when the F-F group was compared to the M-F group (41.4±9.8 IU/L *vs.* 17.3±1.8 IU/L for GPT and 42.2±7.5 IU/L *vs.* 23.4±2.2 IU/L for GOT; P<0.05) (Table 1). Mean serum levels of C5a were higher in the 2 groups with F donors than in the 2 groups with M donors, but significance was only found between the F-F and M-M groups (53.44±4.66 pg/ml *vs.* 41.54±2.8 pg/ml; P<0.05). Mean OSI values were higher in the F-F group than in the other 3 groups, but this difference did not reach significance (Figure 2A, 2B).

Follow-up and complications

Eight (27.59%) out the 29 recipients of livers from female donors had repeated periods of hospitalization due to complications during clinical follow-up. The complications were common cold-like symptoms with liver dysfunction (n=3), Epstein–Barr virus infection (n=1), chronic hepatitis B infection (n=1), humoral rejection (n=1), ileus (n=1), and cellular rejection (n=1). None of the 14 recipients of livers from male donors showed complications related to the transplantation *per se* (0%, P=0.039, Fisher's exact test), but 1 recipient in the latter group showed recurrence of his original disease, which was primary sclerosing cholangitis (PSC). The recipient's gender had no influence on the development of post-LTx complications.

All of the recipients were on immunosuppressive treatment except for 4 (13.7%) of the 29 recipients of livers from female donors and 1 (7%) of the 14 recipients of livers from male donors who were immunotolerant and thus required no immunosuppressive treatment. We detected no significant influence of recipient's and donor's gender on the development of immunotolerance.

Discussion

Animal studies have demonstrated not only that gender-dependent dimorphic immune responses occur after tissue damage,

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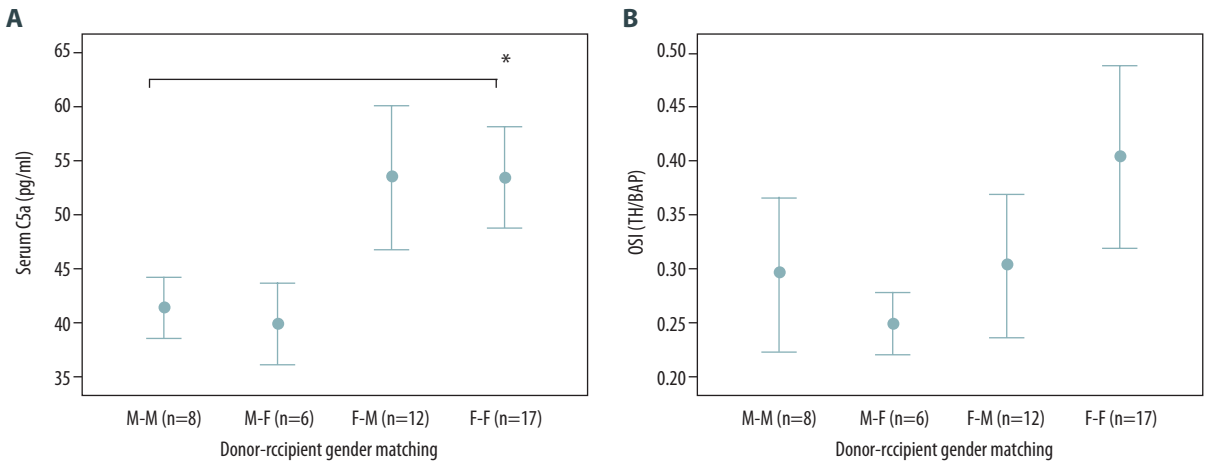

Figure 2. Serum levels of (**A**) C5a and (**B**) OSI in the serum samples of 43 patients who underwent living related liver transplantation during childhood classified according to both recipient's and donor's gender. * P<0.05.

but also that early immunological therapy with 1 type of cytokine may restore immune function and promote survival in 1 gender but not in the other [14]. In addition, human livers exhibit gender-based differences, such as the increased hepatic content of microsomal oxidative enzymes in men and the different numbers of estrogen and androgen receptors on hepatocytes in men and women [15]. Both of these factors may contribute to the effects of gender on the clinical outcome of LRLTx.

The effects of gender in organ transplantation are particularly complicated because both the recipient's gender and the donor's gender or (as it is sometimes described, the grafted organ's gender) can influence the outcome. Several clinical reports have concluded that a female organ donor is a risk factor for poor outcome. In heart transplantation, for example, it has been found that the transplantation of female hearts into male recipients is associated with worse outcomes and increased rejection rates [3]. In kidney transplantation, kidneys from female donors show a poor prognostic trend [16], and in liver transplantation less favorable outcomes have been reported for male recipients of female organs among both adults [17] and children [18].

In heart transplantation, graft survival rates are inferior when the donor is female and the recipient is male, but no statistical difference according to donor gender is demonstrable in female recipients. Using a large database compiled as part of a collaborative transplant study, Zeier et al. analyzed differences in graft survival according to donor gender for kidney, heart, and hepatic allografts [19], and found that, compared with male kidneys, survival rates of kidney allografts from female donors were relatively low in female recipients and even lower in male recipients.

Kahn et al. reported that, among 789 adult orthotopic liver transplantation patients, recipients of livers from female donors had higher rates of failure [20]. Furthermore, Wittnich et al. reported that the livers of female rats accumulated more tissue lactate and H+ more rapidly during ischemia than their male counterparts did. This results in a greater degree of acidosis during ischemia in female livers, which could adversely affect transplant outcome [21].

Using real-time PCR experiments, Farkas et al. revealed that E2 increases the expression of C5aR mRNA in GT1-7 neurons, suggesting that increased C5aR synthesis could be involved in the estrogenic modulation of calcium response [22]. C5a, a multifunctional proinflammatory mediator [23], has been observed to increase vascular permeability, to be spasmogenic and chemotactic, and to induce the release of pharmacologically active mediators from a number of cell types. C5a production *in vivo* may also initiate, contribute to, or exacerbate the inflammatory reactions seen in several autoimmune diseases, thereby inducing tissue injury [23]. Tokodai et al. found that C5a-inhibitory peptide combined with a clinically available anticoagulant (gabexate mesylate) inhibited inflammatory reaction in a rat model of pancreatic islet transplantation [24]. The higher serum C5a levels observed in our study in the recipients of grafted livers from female donors, with their greater tendency toward oxidative stress, could explain why several reports have suspected female grafted livers to be a risk factor for rejection and reduced graft survival time with worse recipient outcome [1]. In our study, recipients of grafted livers from female donors also showed a higher incidence of developing post-LTx complications. Among the recipients of grafted livers from male donors, in contrast, only 1 experienced recurrence of his original PSC, which is a frequent complication occurring in approximately 20% of liver-transplanted PSC recipients and is related to the original disease rather than to LTx *per se* [25]. Thus, selective C5a inhibitors warrant further

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study with an eye toward their potential application as medications for the prevention and treatment of graft rejection.

Gender-based differences in cytokines and oxidative markers have been studied during exposure to immunological stimulants caused by various diseases and conditions [12]. Syn et al. found that female gender of the donor was a risk factor for progressive liver fibrosis after liver transplantation [26] and suggested that this finding was related to donor minor histocompatibility antigen mismatches. Candinas et al. made a similar suggestion on discovering that, in their studied population of liver-transplanted recipients, female recipients were more likely to develop chronic rejection of liver grafts from male donors than from female donors (9.4% *vs.* 1.4%, respectively) [27].

Candinas et al. did not identify a causative factor for the worse outcomes seen in liver grafts from male donors to female recipients, as their study was a retrospective observational study following patients' outcomes and hence assumed that sensitization to antigens expressed by bile-duct epithelium, as in primary biliary cirrhosis, or exposure to donor bile-duct minor histocompatibility antigens, such as the male gender-related H-Y antigen, may provide an explanation [27]. Furthermore, their study included mainly adult patients with a median age of 49.2 years (range 16.4–69.1) and detected a gender mismatch influence in females with primary biliary cirrhosis and females less than 30 years of age [27]. Our population, on the other hand, included mainly children and young adults with a median age of 10.7 years (range: 1.6–24.9). None of our patients had primary biliary cirrhosis; rather, BA was the major underlying disease for LTx in the recipients (n=25, 58%). This could explain the differences between our results and those of Candinas et al.

Our measurement of the activated complement marker C5a in the serum of LRLTx recipients provided us with an index of the recipients' immunological status as well as their oxidative status due to the strong correlation between C5a and OSI ($r=0.72$, $P<0.05$). Thus, serum C5a levels in post-LTx recipients warrant further study as possible targets for follow-up on therapy efficacy or targets for future innovated immunosuppressive drugs.

Conclusions

Based on the present results, we speculate that C5a plays a role in the immunological response against grafted livers from female donors in LTx, as indicated by the higher incidence of post-LTx complications and higher levels of serum GPT and GOT in recipients of female livers. An immunosuppressive drug targeting C5a could be of clinical importance in minimizing graft rejection in LRLTx.

Conflict of interest

None.

Limitations

1. Patients' serum samples had to be collected and stored at –70°C until a sufficient number of patients' samples were collected prior to the measurement of C5a levels using the C5a ELISA kit II.
2. There were a limited number of patients enrolled in the study. A larger study would have yielded more evidence and clearer significance of differences in the measured oxidative marker levels.
3. The length of the interval between LRLTx and the study varied, ranging from 5 months to 17.5 years (mean interval: 7.3 years). Although this interval was not significantly different between the groups, it would be impossible to collect patients with a uniform post-LTx interval.
4. A longer follow-up period would probably have yielded additional information on longer-term outcomes.

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