



An Association of Lower Serum Citrulline Levels Within 30 Days of Acute Rejection in Patients Following Small Intestine Transplantation

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ABSTRACT

Introduction. In a prospective protocol we studied whether serum citrulline level within 30 days of an acute rejection was predictive of the episode.

Methods. An acute rejection episode was defined as the date of occurrence of any biopsy-proven rejection in which treatment was initiated until two successive biopsies showed no further rejection. We compared the mean citrulline level based on values determined within 30 days of the start of an acute rejection episode with the mean citrulline level measured on the same patient during a rejection-free period. Serum citrulline measurements were available immediately prior to the occurrence of rejection for 22 patients who experienced 37 episodes.

Results. For the 12 episodes of mild rejection, the mean serum citrulline level \pm SE (standard error) was 15.0 ± 2.3 $\mu\text{mol/L}$ prior to rejection and 18.8 ± 2.4 $\mu\text{mol/L}$ during the rejection-free periods. A paired *t* test of the mean differences was not significant ($P = .17$). For the 25 episodes of moderate or severe rejection, the mean serum citrulline level was 12.4 ± 1.1 $\mu\text{mol/L}$ before rejection and 18.8 ± 2.0 $\mu\text{mol/L}$ during the rejection-free periods. A paired *t* test of the mean difference was statistically significant ($P = .002$).

Conclusions. Although further study of citrulline as a marker for the early detection of acute rejection episodes is needed, our hope is that its use will help to prevent some of these early episodes from evolving into full-blown moderate or severe grades of rejection.

SERUM CITRULLINE is a nonessential, nonprotein amino acid synthesized almost exclusively by enterocytes of the small intestine. Citrulline is produced from glutamine, which is then metabolized into arginine by the kidney. It has been found in recent years to be a candidate marker for small bowel enterocyte mass.^{1,2} Blood concentrations of citrulline directly reflect the cell mass of the small intestine, since (1) the small intestine is the principal source of its production, and (2) serum citrulline is not metabolized by the liver.³ In patients who receive small intestinal transplantation acute cellular rejection remains as a major cause of enterocyte damage.⁴ In our initial studies^{5,6} the mean serum citrulline concentration was observed to be significantly higher in healthy controls than pretransplant samples ($P < .0001$). The expected increase in serum citrulline levels over time following transplantation was significantly less among patients who experienced a moderate or severe rejection episode ($P < .0001$). In the current

ongoing prospective study, we compared the mean serum citrulline level from measurements within 30 days of a rejection episode versus the mean serum citrulline level of the same patient during a comparable (as close as possible in time) rejection-free period. It was hoped that this investigation would provide evidence for further study of

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serum citrulline as a potential marker of acute rejection in patients who receive small intestinal transplantations.

METHODS

Acute rejection of the small intestine was defined as the date of occurrence of any biopsy-proven rejection in which treatment was initiated. An episode of rejection was determined to have resolved once two successive biopsies showed no more evidence of the process. We compared the mean citrulline level based on values determined within 30 days of the start of an acute rejection episode with the mean citrulline level measured on the same patient during a free-rejection period linked as close as possible in time to the corresponding rejection episode. Serum citrulline measurements were available immediately prior to the occurrence of rejection among 22 patients who experienced 37 acute rejection episodes: 12 rejection episodes were mild, and 25 were moderate or severe. Eight of the 22 patients contributed citrulline data on more than one rejection episode. Among the 22 patients, 14 were children and eight were adults (≥ 18 years of age). Rejection episodes were studied following a primary transplant in all but one patient. The type of transplant was distributed as follows: five were isolated intestine; two were liver-intestine; four were modified multivisceral (without liver); and 11 were multivisceral.

RESULTS

For the 12 episodes of mild rejection, the mean serum citrulline level \pm SE (standard error) was 15.0 ± 2.3 $\mu\text{mol/L}$ during the 30 days prior to rejection and 18.8 ± 2.4 $\mu\text{mol/L}$ during the rejection-free periods. The paired *t* test of the mean difference was not significant ($P = .17$). For the 25 episodes of moderate or severe rejection, the mean serum citrulline level \pm SE was 12.4 ± 1.1 $\mu\text{mol/L}$ during the 30 days prior to rejection and was 18.8 ± 2.0 $\mu\text{mol/L}$ during the rejection-free periods. The paired *t* test of the mean difference was significant ($P = .002$). The rejection-free mean serum citrulline levels were nearly the same for the two comparisons, while the mean serum citrulline level within 30 days prior to the moderate and severe rejection

episodes was lower than the mean citrulline level in the mild rejection episodes.

DISCUSSION

Our findings suggest that a significant reduction in patient serum citrulline level occurred within 30 days prior to a moderate or severe rejection episode. While the mean serum citrulline level within 30 days prior to the occurrence of a mild rejection episode was also lower, the reduction was not significantly different from the mean citrulline level determined at comparable rejection-free periods. We next plan to investigate how the serum citrulline level is affected by episodes of intestinal infection or dehydration. While our data are still preliminary, the results support continued studies to determine the exact role that patient serum citrulline levels may play to predict an acute rejection episode.

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