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This chapter summarizes and discusses the results of the studies performed within the scope of this thesis and provides a direction for future studies.

PART I

Chapter 2

A patient's condition before surgery is of major importance for clinical outcome. In recent decades it has become clear that besides optimizing surgical techniques, the condition of the patient preoperatively is relevant to minimize postoperative complications, death, and improve the patient's well-being[1]. We found that supplementation of a carbohydrate-rich beverage before surgery is safe, does not affect gastric emptying time, and switches the fasted state to a fed state. Moreover, a preoperative carbohydrate-rich beverage supplementation results in a significant reduction in postoperative insulin resistance, a decrease in hunger, thirst, and anxiety, a lower decrease in arm muscle circumference, and prevents surgery-induced immunodepression. Administration of a preoperative oral nutritional supplement, which is an carbohydrate-rich beverage with added vitamins or other contents, has no disadvantages. The use leads to clinical benefits and is cost-effective in patients undergoing moderate to major surgery. Preoperative nutrition enriched with immune-modulatory nutrients normalizes the surgery-induced inflammatory response and counteracts the altered immune function and disturbed metabolism after surgery. The evidence in this review shows that fasting before surgery is outdated. We addressed several strategies of supplementation to improve preoperative nutritional status. Tailored advice that combines preoperative nutritional intervention with the specific needs of the patient is necessary for every patient undergoing surgery.

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Chapter 3

The use of immune-enhancing diets (IEDs) in critically ill patients is still debated, in particular in septic situations. However, considering all of the different IEDs as a whole is difficult because of their different compositions. Rats were exposed to a validated model combining head injury and infectious complications, mimicking the biphasic response to injury. We assessed the nutritional efficiency of a new nutrition with consecutive administration of antioxidants and glutamine compared with two classical high-arginine IEDs, with and without extra antioxidants. The new nutrition accelerated body weight recovery, improved the nitrogen balance, and increased protein utilization compared with the other diets. Improvement in nutritional status was not related to a decrease in septic occurrence. Although we were not able to define the specific role of each nutrient within the product, studies as seen this chapter may be useful as an example for nutritional care strategies. The data presented in this study show that every new immune-enhancing diet has to be evaluated to determine its clinical utility and potency in specific clinical situations.

Chapter 4 and the focus of this thesis

The metabolism of glutamine, arginine, and citrulline has not been investigated in several conditions such as when well-fed during critical illness or during and after major vascular surgery. This contributed to the relevance of investigating the role of glutamine as a possible precursor for the synthesis of arginine in these states of illness. This resulted in a number of stable isotope studies that clarified the complexity and the various conversion routes of these amino acids[2-8]. We focused on the metabolism of these amino acids perioperatively and during critical illness and questioned whether a glutamine supplement would enhance citrulline and arginine production.

The metabolic pathway of glutamine to citrulline and arginine was investigated extensively in the intensive care unit (ICU). However, the uptake and enteral metabolism of glutamine in critically ill patients who were well-fed has never been quantified. The effect of an enteral supplement of glutamine on the synthesis of citrulline and subsequently arginine in critically ill patients receiving enteral nutrition was assessed. We found that there was no extra citrulline or arginine synthesis and that splanchnic glutamine extraction was not increased.

Chapter 5

Less is known about the metabolism of glutamine, arginine, and citrulline during vascular surgery. In this chapter, we quantified arginine production from its precursor glutamine on whole-body level and established the contribution of the kidneys to de novo synthesis of arginine in patients receiving intravenous supplementation of glutamine dipeptide during major abdominal surgery. Results show that plasma glutamine, citrulline, and arginine concentrations increased significantly in patients receiving intravenous glutamine dipeptide. At the whole-body level, 91% of total citrulline turnover was derived from glutamine, whereas 49% of whole-body citrulline turnover was used for de novo synthesis of arginine. The kidneys were responsible for 75% of whole-body arginine production from citrulline. A comparison of our data with the results of previous similar studies suggests that an intravenous glutamine supplement doubles renal arginine production from citrulline.

Chapter 6

These results encouraged us to further elucidate the glutamine-citrulline-arginine metabolism in vascular surgery. We already know that postoperative renal failure is a common complication after open repair of an abdominal aortic aneurysm because the aorta is clamped, which results in ischemia-reperfusion injury of the kidneys. We therefore hypothesized that renal arginine production is diminished after ischemia-reperfusion injury caused by clamping of the aorta and that parenteral glutamine supplementation might compensate for this impaired arginine synthesis. A comparison

of these data with the results our previous similar studies suggests that production of citrulline and arginine is severely reduced after clamping during aortic surgery. In addition, this study shows that an intravenous supplement of glutamine increases the production of citrulline and arginine and can compensate for the inhibitory effect of ischemia-reperfusion injury.

General conclusion and discussion

The investigations of this part of the thesis comprise the following important results: In the well-fed non-septic critically ill patient, glutamine supplementation is safe but does not promote extra citrulline or arginine synthesis. In the surgical patient exposed to major abdominal vascular surgery, glutamine, citrulline, and arginine concentrations increased after receiving intravenous glutamine, and the kidney appeared to be the main production site for endogenous arginine. Postoperatively, after ischemia-reperfusion injury caused by clamping of the aorta, an intravenous supplement of glutamine increased the production of citrulline and arginine and compensated for the inhibitory effect of ischemia-reperfusion injury.

Other studies have observed a strong correlation between glutamine uptake by the small intestine and the release of citrulline[2-8]. Studies in animals and humans showed that plasma concentrations of citrulline and arginine increase after extra glutamine administration, supporting the possible precursor relationship between glutamine, citrulline, and arginine, as also demonstrated in this thesis [9, 10]. The increase in plasma levels of citrulline and arginine with provision of glutamine may also be the result of a common element of action: glutamine is the most important fuel for the enterocytes and citrulline is the indicator of gut mass and function. Therefore, glutamine administration has the potential to augment metabolic activity of the enterocytes and thereby increase citrulline synthesis and levels, without being a real precursor[11]. An increase in glutamine availability may also cause a reduction in citrulline clearance from the circulation because they share important cell membrane transporters, resulting in higher plasma citrulline concentrations.

By outlining this intestinal-renal axis with all of its complex intermediate and parallel steps in various organs, it becomes clear that the formation of the final arginine molecule could incorporate various parts of the primary glutamine molecule because of transamination, oxidation, and recycling of the molecules involved. Therefore, it has been a great challenge to assess the competence of stable isotope methodology in this pathway and develop study designs allowing us to investigate the interorgan metabolism in physiologic and pathophysiologic situations.

When quantifying the metabolic pathway of glutamine to citrulline and arginine with stable isotope methodology, studying whole-body and organ turnover is important to