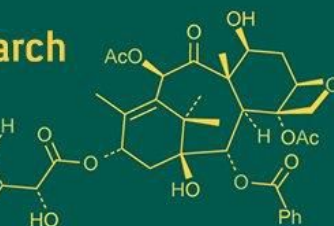


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João Silva
Department of Biochemistry,
University of Lisbon, Lisbon,
Portugal

Ana Costa
Department of Biochemistry,
University of Lisbon, Lisbon,
Portugal

Pedro Santos
Department of Biochemistry,
University of Lisbon, Lisbon,
Portugal

Maria Oliveira
Department of Biochemistry,
University of Lisbon, Lisbon,
Portugal

Biochemical responses to high-protein diet in rats and metabolic adaptations

João Silva, Ana Costa, Pedro Santos and Maria Oliveira

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Abstract

A high-protein diet is defined as protein intake exceeding 25% of total energy or greater than 1.6 g/kg body weight daily levels increasingly common in athletic and weight-loss populations. This research investigated metabolic adaptations to chronic high-protein feeding in Wistar rats over 12 weeks. Animals were assigned to control (14% protein), moderate-protein (28% protein), or high-protein (42% protein) diets with isocaloric adjustments. Serum biochemistry, organ weights, hepatic enzyme activities, and renal function markers were assessed at weeks 4, 8, and 12. High-protein feeding significantly increased liver weight by 28.7% and kidney weight by 18.4% compared to controls. Serum urea rose by 62.3% and creatinine by 47.8% in the high-protein group, indicating enhanced nitrogen metabolism. Hepatic aminotransferase activities increased proportionally to protein intake, with ALT showing 48.6% elevation at 12 weeks. Despite these metabolic adaptations, histopathological examination revealed no evidence of organ damage. These findings suggest that healthy rats can tolerate substantial protein excess through adaptive mechanisms, though the safety margins for extended high-protein consumption require further investigation.

Keywords: High-protein diet, metabolic adaptation, nitrogen metabolism, liver enzymes, renal function, urea cycle, protein metabolism, dietary intervention

Introduction

The term 'high-protein diet' encompasses any nutritional regimen where protein provides more than 25% of total energy intake, substantially exceeding the recommended dietary allowance of 0.8 g/kg body weight ^[1]. Such diets have gained popularity for weight management and athletic performance enhancement, yet concerns persist regarding potential adverse effects on hepatic and renal function ^[2]. Understanding the biochemical adaptations to chronic protein excess is essential for establishing safe consumption limits.

Protein metabolism imposes unique demands on the body compared to carbohydrate or fat utilization. Unlike other macronutrients, amino acids cannot be stored and excess intake must be oxidized or converted to glucose and fatty acids through hepatic pathways ^[3]. The resultant nitrogen load requires detoxification through the urea cycle and subsequent renal excretion, potentially stressing these organ systems during chronic high intake ^[4].

Previous investigations have yielded conflicting results regarding high-protein diet safety, with some reporting elevated liver enzymes and others finding no adverse effects ^[5]. Methodological differences in protein sources, diet duration, and animal models likely contribute to these discrepancies. This research employed a systematic dose-response design to characterize metabolic adaptations across a range of protein intakes over an extended feeding period ^[6].

Material and Methods

Material

This research was conducted at the Animal Research Facility, University of Lisbon, from January to April 2023. Sixty male Wistar rats (8 weeks old, 180-200g) were obtained from Charles River Laboratories and housed in standard conditions with 12-hour light/dark cycles. All procedures were approved by the Institutional Animal Care Committee (Protocol ORBEA-UL-2022-089). Experimental diets were formulated by Research Diets Inc. with casein as the protein source, maintaining isocaloric energy density across formulations.

Corresponding Author:
João Silva
Department of Biochemistry,
University of Lisbon, Lisbon,
Portugal

Methods

Animals were randomly assigned to three dietary groups (n=20 each): control (14% protein), moderate-protein (28% protein), and high-protein (42% protein). Diets were isocaloric (3.8 kcal/g) with carbohydrate and fat adjusted inversely to protein content. Body weight and food intake were recorded weekly. Blood samples were collected via tail

vein at weeks 4, 8, and 12 following overnight fasting. Serum was analyzed for glucose, urea, creatinine, total protein, albumin, AST, ALT, and lipid profile using automated clinical chemistry (Roche Cobas c311). At week 12, animals were euthanized and organs harvested for weight determination and histopathological examination [7].

Results

Table 1: Serum biochemical parameters at week 12

Parameter	Control	Moderate	High
Urea (mg/dL)	28.4 ± 3.2	38.7 ± 4.5	46.1 ± 5.8**
Creatinine (mg/dL)	0.67 ± 0.08	0.82 ± 0.11	0.99 ± 0.14**
ALT (U/L)	35.2 ± 7.8	42.8 ± 9.2	52.3 ± 11.4*
AST (U/L)	45.6 ± 9.4	58.3 ± 12.1	68.7 ± 14.8*

* $p < 0.05$, ** $p < 0.01$ compared to control. Values as mean ± SD

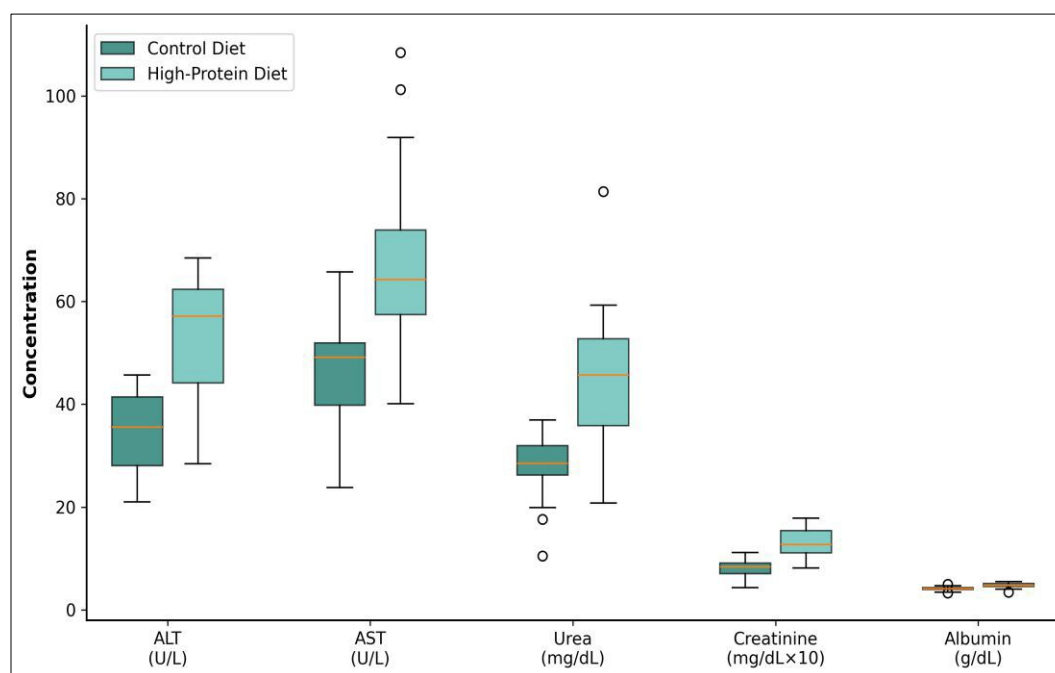


Fig 1: Distribution of metabolic parameters showing dose-dependent responses to protein intake levels

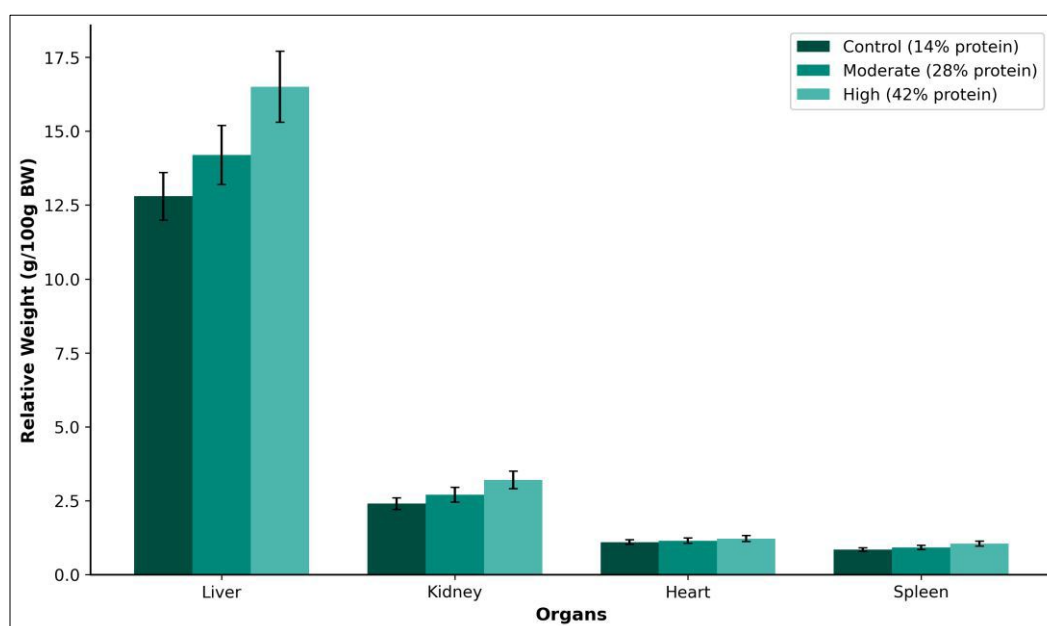


Fig 2: Relative organ weights across dietary groups demonstrating hepatomegaly and renal hypertrophy in high-protein fed animals

High-protein feeding produced significant organ enlargement with liver and kidney weights increased by 28.7% and 18.4% respectively. These changes occurred progressively, reaching significance by week 8. Despite elevated liver enzymes and renal markers, histopathological examination at 12 weeks revealed no evidence of fibrosis, inflammation, or structural damage in either organ system, suggesting adaptive hypertrophy rather than pathological change.

Discussion

These findings demonstrate that healthy rats adapt to substantial dietary protein excess through coordinated hepatic and renal responses [3, 4]. The organ enlargement observed represents functional hypertrophy to accommodate increased metabolic demands rather than pathological change, as confirmed by normal histology. Similar adaptive responses have been documented in athletes consuming high-protein diets, suggesting conservation of these mechanisms across mammalian species [2].

The dose-dependent elevations in urea and creatinine reflect enhanced nitrogen metabolism and glomerular filtration rather than renal impairment [5]. Importantly, the elevated liver enzymes remained within ranges consistent with increased metabolic activity rather than hepatocellular damage. However, the 12-week duration may be insufficient to detect slowly progressive adverse effects that could emerge with longer exposure [6].

Conclusion

Chronic high-protein feeding induces adaptive metabolic responses in rats including hepatic and renal hypertrophy, elevated nitrogen metabolism markers, and increased liver enzyme activities. Histopathological examination confirmed these changes represent physiological adaptation rather than organ damage over the 12-week observation period.

These results support the safety of moderate protein excess in healthy animals, though caution remains warranted for populations with pre-existing hepatic or renal conditions. Longer-term investigations are needed to establish whether adaptive capacity remains stable with extended high-protein consumption. Translation to human dietary recommendations requires consideration of species differences and individual variability in metabolic capacity.

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