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SHORT COMMUNICATION

Glutamine supplementation favors weight loss in nondieting obese female patients. A pilot study

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Glutamine supplementation improves insulin sensitivity in critically ill patients, and prevents obesity in animals fed a high-fat diet. We hypothesized that glutamine supplementation favors weight loss in humans. Obese and overweight female patients ($n = 6$) were enrolled in a pilot, cross-over study. After recording anthropometric (that is, body weight, waist circumference) and metabolic (that is, glycemia, insulinemia, homeostatic model of insulin resistance (HOMA-IR)) characteristics, patients were randomly assigned to 4-week supplementation with glutamine or isonitrogenous protein supplement (0.5 g/KgBW/day). During supplementation, patients did not change their dietary habits nor lifestyle. At the end, anthropometric and metabolic features were assessed, and after 2 weeks of washout, patients were switched to the other supplement for 4 weeks. Body weight and waist circumference significantly declined only after glutamine supplementation (85.0 ± 10.4 Kg vs 82.2 ± 10.1 Kg, and 102.7 ± 2.0 cm vs 98.9 ± 2.9 cm, respectively; $P = 0.01$). Insulinemia and HOMA-IR declined by 20% after glutamine, but not significantly so. This pilot study shows that glutamine is safe and effective in favoring weight loss and possibly enhancing glucose metabolism.

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INTRODUCTION

The prevalence of obesity has reached alarming figures in many countries, independently of industrialization rates and gross domestic products.[1] Therefore, new strategies favoring weight loss and improving metabolic homeostasis are needed. The pathogenesis of obesity is mainly related to increased energy intake.[2] Therefore, hypocaloric diets are almost invariably prescribed to obese patients, together with other lifestyle changes. Unfortunately, compliance to prescribed diets is poor in daily practice, leading to treatment failures. Consistent data demonstrate that also the quality of the nutrients has a role in favoring obesity. In fact, Bo *et al.*[3] showed that obesity incidence at 6-year follow-up is not associated with higher daily energy intake but rather to higher daily consumption of saturated fats, among other contributors. In this light, modulation of nutrient composition of the diet may provide additional benefit than limiting calories only.

Glutamine is the most abundant circulating amino acid, and it exerts many relevant biological functions.[4] In clinical practice, glutamine supplementation at a dose not exceeding 0.5 g/KgBW/day has been consistently demonstrated to improve glucose homeostasis and decrease the need for exogenous insulin in critically ill patients.[5] In addition, glutamine supplementation in rats fed a high-fat diet prevents the development of obesity[6] and diabetes. Therefore, we studied, in a pilot study designed as a cross-over trial, whether the supplementation of glutamine to overweight/obese patients may favor weight loss and improve glucose metabolism, independently of calorie restriction.

SUBJECTS AND METHODS

Obese patients referring to our outpatient clinic at the Policlinico Umberto I of Rome, Italy, were considered for the study. The protocol was designed in line with the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee at our institution. Inclusion criteria were as follows: BMI ranging between 28 and 35, the presence of visceral obesity as assessed by waist circumference >102 cm (male) or >88 cm (female), fasting glycemia <105 mg/dl, fasting insulinemia <20 mIU/l and normal peripheral lipid profile. Exclusion criteria were the presence of type 2 diabetes mellitus, use of drugs interfering with appetite or body weight and adherence to a hypocaloric diet in the previous 3 months.

Upon enrollment, patients' weight (kg), height (m), BMI, waist circumference (cm), glycemia (mg/dl), insulinemia (μU/l) and calculated homeostatic model of insulin resistance (HOMA-IR; fasting insulinemia × fasting glycemia/22.5) were recorded. Patients were randomly assigned to a 4-week supplementation with glutamine (Adamin G; Nutricia, Milan, Italy) at a daily dose of 0.5 g/KgBW, fractioned in four daily boluses, or an isonitrogenous daily dose of a standard protein supplement (Protifar; Nutricia). At baseline visit, patients received all the product needed during the 4-week study period, either glutamine or placebo. As per the manufacturer's preparation, the glutamine supplement used in this study is soluble in water. Patients' compliance was assessed by interviewing a next of kin. During the supplementation period, patients were invited to maintain their regular dietary habits and lifestyle. At the end of the 4-week period, anthropometric and metabolic features of the patients were assessed. Then, after a 2-week period of washout, patients' anthropometry was evaluated, and patients switched to the other supplement for 4 weeks. At the end, anthropometric and metabolic variables were assessed.

Data have been analyzed using Students' *t*-test for paired and unpaired data (SPSS version 18.0; SPSS Inc., Chicago, IL, USA).

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Table 1. Baseline patients' characteristics

Age (years)	*Body weight (kg)*	*BMI*	*Glycemia (mg/dl)*	*Insulin (μUI/l)*	*HOMA-IR*
42.6 ± 16.1	85.0 ± 10.4	32.4 ± 3.2	86.3 ± 8.8	10.5 ± 4.1	2.26 ± 0.9

Abbreviation: HOMA-IR, homeostatic model of insulin resistance.

Table 2. Results of the study

	Protein supplementation			*Glutamine supplementation*		
	Baseline	*Post*	P	*Baseline*	*Post*	P
Body weight (kg)	83.2 ± 9.1	82.4 ± 8.8	NS	85.0 ± 10.4	82.2 ± 10.1	< 0.01
Waist circumference (cm)	100.8 ± 1.0	100.0 ± 2.0	NS	102.7 ± 2.0	98.9 ± 2.9	0.01
Glycemia (mg/dl)	89.8 ± 8.7	90.0 ± 8.4	NS	89.0 ± 1.5	87.4 ± 9.3	NS
Insulin (mIU/l)	7.8 ± 3.7	7.8 ± 1.9	NS	9.8 ± 4.3	8.3 ± 3.5	NS
HOMA-IR	2.1 ± 0.7	2.3 ± 1.5	NS	2.27 ± 0.6	1.86 ± 0.7	NS

$P < 0.05$ has been considered to be of statistical significance. Data are presented as mean ± s.d.

RESULTS AND DISCUSSION

In the period September 2012 to December 2012, six female patients were enrolled in the study. The female gender dominance is consistent with the high prevalence of women referring to our outpatient clinic. Patients' baseline characteristics are reported in Table 1.

Both supplements resulted to be safe, as no changes in the circulating markers of liver and renal function were observed at the end of each 4-week period. Only one patient reported dizziness early during glutamine supplementation, which disappeared when the daily dose was reduced to 0.25 g/KgBW/day for 1 week. Then, the investigational dose was reinstated without further appearance of side effects.

At the end of both periods, patients did not report the development of aversion or attraction toward any specific food. In addition, no changes were observed in peripheral lipid profile. Protein supplementation did not result in any significant change of body weight and waist circumference, which in contrast significantly declined after glutamine supplementation (Table 2). Glycemia, insulinemia and HOMA-IR did not change after any of the supplementation periods, although circulating insulin and HOMA-IR declined by ~15–20% only after glutamine supplementation ($P > 0.05$).

Our pilot study suggests that glutamine is safe, well tolerated and effective in favoring weight loss in overweight and obese patients. The preventive effects of glutamine supplementation on weight gain have been demonstrated in animal models.[6,7] Our pilot study extends previous data by showing that glutamine supplementation reduces body weight in outpatients, by likely yielding a daily negative energy balance of approximately 500 Kcal. Glutamine stimulates the release of the glucagon-like peptide 1, whose centrally mediated effects include reduction of appetite and food intake.[8] Therefore, it is plausible that glucagon-like peptide 1 levels increased after glutamine administration leading to reduced interest for food.

Glutamine is involved in glucose metabolism. In critically ill patients, Grau *et al.*[5] demonstrated that glutamine supplementation results in a 50% decrease of exogenous insulin to reach the same glycemic levels of nonsupplemented patients. In type 2 diabetic patients, glutamine supplementation reduces postprandial glycemia.[9] In contrast, we could not observe any significant enhancement of glucose metabolism. However, glutamine supplementation appears to improve insulin sensitivity when glutamine stores are depleted.[10] In our pilot study, we excluded clinical conditions associated with glutamine depletion, including diabetes. Despite this, we observed a robust, yet not significant, reduction of insulin and HOMA-IR after glutamine supplementation. These results suggest that also in our patients glutamine might have improved insulin sensitivity.

We acknowledge the limitations of our pilot study, which include the small number of patients enrolled. However, we believe that the cross-over design of the trial strengthens the results obtained. In addition, only a single dose has been tested, which has been decided on the basis of the dose tested in critically ill patients.[5] In fact, considering that glutamine depletion was unlikely in our patients, we aimed at reaching acute supraphysiological levels of circulating glutamine rather than replenishing stores. We acknowledge that the protein supplement used also contains carbohydrates and lipids (0.5% and 3.9%, respectively). However, this translates in a caloric difference between the two supplements < 15 Kcal/day, which we believe cannot explain the results obtained. Finally, in order to enhance compliance to the study protocol, patients were not required to fill out a food record or dietary diary during the study periods. We acknowledge that this could have revealed specific changes of dietary habits and detect changes in glutamine intake from food items. However, this is unlikely to have occurred, as patients were asked not to change their dietary habits. Moreover, modifications of dietary habits would have yielded negligible changes of daily glutamine intake, when compared with the amount daily supplemented.

CONFLICT OF INTEREST

Dr Rossi Fanelli has received research funds and compensation for consultation from Fresenius Kabi. Dr Laviano has received compensation for consultation from Abbott, Baxter, Danone Research, Fresenius Kabi. The remaining authors declare no conflict of interest.

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REFERENCES

1 Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM *et al.* National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr* 2012; **10**: 22.

2 Berthoud HR. The neurobiology of food intake in an obesogenic environment. *Proc Nutr Soc* 2012; **71**: 478–487.

3 Bo S, Ciccone G, Durazzo M, Ghinamo L, Villois P, Canil S *et al.* Contributors to the obesity and hyperglycemia epidemics. A prospective study in a population-based cohort. *Int J Obes (Lond)* 2011; **35**: 1442–1449.

4 Curi R, Lagranha CJ, Doi SQ, Sellitti DF, Procopio J, Pithon-Curi TC *et al.* Molecular mechanisms of glutamine action. *J Cell Physiol* 2005; **204**: 392–401.

5 Grau T, Bonet A, Minambres E, Pineiro L, Irles JA, Robles A *et al.* The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. *Crit Care Med* 2011; **39**: 1263–1268.

6 Opara EC, Petro A, Tevrizian A, Feinglos MN, Surwit RS. L-glutamine supplementation of a high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice. *J Nutr* 1996; **126**: 273–279.

7 Prada PO, Hirabara SM, de Souza CT, Schenka AA, Zecchin HG, Vassallo J *et al.* L-glutamine supplementation induces insulin resistance in adipose tissue and improves insulin signalling in liver and muscle of rats with diet-induced obesity. *Diabetologia* 2007; **50**: 1949–1959.

8 Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A *et al.* Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. *Am J Clin Nutr* 2009; **89**: 106–113.

9 Samocha-Bonet D, Wong O, Synnott E-L, Piyaratna N, Douglas A, Gribble FM *et al.* Glutamine reduces postprandial glycemia and augments the glucagon-like peptide 1 response in type 2 diabetes patients. *J Nutr* 2011; **141**: 1233–1238.

10 Oudemans-van Stratten HM, Bosman RJ, Treskes M, van der Spoel HJ, Zandstra DF. Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* 2001; **27**: 84–90.