



Trabajo Original

Epidemiología y dietética

Efficacy of a *Lupinus mutabilis* Sweet snack as complement to conventional type 2 diabetes mellitus treatment

Eficacia de un tentempié de Lupinus mutabilis Sweet como complemento al tratamiento convencional de la diabetes mellitus tipo 2

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Abstract

Introduction: therapeutic lifestyles changes including frequent consumption of legumes have resulted in improved metabolic control and decreased blood pressure in type 2 diabetes-mellitus (T2DM) patients.

Objective: this was a quasi-experimental-28-week crossover-study that assessed the effect of daily consumption of the legume *Lupinus mutabilis* (LM) on metabolic control of T2DM patients under hypoglycemic oral treatment.

Material and methods: we recruited 79 adult male and female patients that were followed for 14-weeks without LM consumption and then received increasing doses of a LM-based-snack for other 14-weeks.

Results: there was a significant decrease in blood pressure and a significant increase in HDL-cholesterol by the end of the study period. While patients with A1C concentrations > 8 and ≤ 10 did not significantly improve their metabolic control, patients with serum A1C concentrations ≤ 8.0% reduced significantly their A1C after the intervention and 71% achieved a target concentration of 6.5%.

Conclusion: patients with T2DM could benefit with the addition of LM-snack to their conventional treatment.

Key words:

Type 2 diabetes mellitus. Glycated hemoglobin. *Lupinus*. Humans.

Resumen

Introducción: los cambios recomendados sobre los estilos de vida, incluido el consumo frecuente de leguminosas, han resultado en un mejor control metabólico y disminución de la presión arterial en pacientes con diabetes mellitus tipo 2 (DMT2).

Objetivo: este fue un estudio casi experimental cruzado de 28 semanas que evaluó el efecto del consumo diario de la leguminosa *Lupinus mutabilis* Sweet (LM) en el control metabólico de pacientes con DMT2 con tratamiento oral hipoglucemiante.

Material y métodos: inicialmente se reclutaron 79 pacientes adultos, hombres y mujeres, que fueron seguidos durante 14 semanas sin consumo de LM y luego recibieron dosis crecientes de un tentempié de LM durante otras 14 semanas.

Resultados: se observó una disminución significativa en la presión arterial y un aumento significativo en el colesterol-HDL después del consumo de LM. Mientras que los pacientes con concentraciones de A1C sérica > 8 y ≤ 10 no mejoraron significativamente su control metabólico, los pacientes con concentraciones séricas de A1C ≤ 8,0% redujeron significativamente su A1C después de la intervención y el 71% de estos pacientes llegó a la meta de tratamiento ≤ 6,5%.

Conclusión: los pacientes con DMT2 podrían beneficiarse con la adición de un tentempié de LM a su tratamiento convencional.

Palabras clave:

Diabetes mellitus tipo 2. Hemoglobina glucosilada. *Lupinus*. Humanos.

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INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a major public health problem worldwide. Current pharmacological treatments aim to control serum glucose levels in order to prevent systemic-vascular and neural damage (1). Control of serum glucose levels in T2DM has been associated with improved quality of life and decreased metabolic complications (2). Intensive control of T2DM may require the addition or the increase of doses of oral hypoglycemic drugs or the use of insulin (3). However, these pharmacological strategies pose potential negative consequences for patients, including drug-side effects, increased costs, reduced compliance or even increased risk of mortality due to hypoglycemic events (4,5); these consequences could be even more severe in elderly patients that usually have other comorbidities. In addition, T2DM treatments can be difficult to obtain and are costly. The estimated cost for the treatment of diabetes considering direct and indirect expenses in the United States is 1.31 trillion dollars per year (6). The increasing frequency of chronic diseases in low- and middle-income countries anticipates a very high economic burden for those nations in the coming years (7). Although pharmacologic treatment for T2DM has an important role to control the disease, additional non-pharmacologic complementary treatments are needed to prevent and control this public health problem.

A healthy life style including physical activity, smoking cessation, and therapeutic lifestyle change (TLC) dietary options including consumption of complex carbohydrates, mono- and polyunsaturated fat, and animal or plant derived proteins are associated with better T2DM prevention and control (8). Regarding animal protein consumption, greater dairy products intake results in better glucose regulation and T2DM prevention (9). In addition to protein content, beneficial effects of dairy products can be associated with their micronutrient, fatty acids, low-glycemic carbohydrates, free amino acids, and active peptides content (10). Also, higher plant protein intake has been associated with decreased risk of T2DM (11). Consumption of legumes, grains characteristically rich in proteins, is associated with lower risk of non-cardiovascular and total mortality (12).

Lupin is a legume rich in proteins and widely consumed around the world whose consumption has been associated with decreased blood pressure, improvement of serum lipid profile, positive alterations of gut microbiota and glucose homeostasis (13). Together, these studies indicate that consumption of high-quality proteins as part of TLC could optimize current treatments of non-communicable chronic diseases, including T2DM.

We have demonstrated that Andean *Lupinus mutabilis* intake decreases blood glucose and improves insulin sensitivity in individuals with dysglycemia or T2DM. Those studies indicate that consumption of either raw as well as cooked *L. mutabilis* significantly lowered serum glucose and insulin levels in the short term (14,15). In addition, Bertoglio JC et al. have documented the hypoglycemic effect of lupin derived γ -conglutin protein in experimental animals and healthy human subjects (16). We recently demonstrated the potential molecular and cellular mechanisms for the hypoglycemic effects of Andean *L. mutabilis*

Sweet. Hydrolyzed γ -conglutin fraction from Andean *L. mutabilis* at 5 mg/ml inhibited dipeptidyl peptidase IV activity (100% inhibition), stimulated glucose uptake (6.5 fold) due to GLUT-4 cell surface translocation, and inhibited hepatic gluconeogenesis (50%) in a dual-layered enterocyte/adipocyte/hepatocyte culture system (17). These studies show that lupin proteins and peptides have several properties and their intake has positive effects in glucose metabolism.

There are limited human clinical studies on lupin consumption as complement for the pharmacologic treatment of T2DM. This quasi-experimental 28-week crossover-study aimed to compare the efficacy of the daily consumption of a snack of *L. mutabilis* on metabolic control of T2DM patients under conventional oral pharmacologic treatment.

METHODS

SUBJECTS AND STUDY DESIGN

This was a quasi-experimental clinical trial with a crossover design in which patients received their usual prescribed oral anti-diabetes treatment for 14-weeks and subsequently, in addition to their oral anti-diabetes treatment they consumed a snack based on *L. mutabilis* for other 14-weeks.

We recruited patients with T2DM who regularly attended the Paute Hospital near the city of Cuenca or the General Teaching Hospital in the city of Riobamba, in Ecuador.

Ninety-two T2DM patients under conventional oral-hypoglycemic-treatment of both sexes, older than 18 years of age were originally screened for the study. Patients were excluded if they were under insulin treatment, had a value of A1C > 10% either at the baseline-test or during the study, presented severe acute febrile diseases or chronic diseases (such as cancer, human immunodeficiency viral infection, autoimmune diseases or psychiatric diseases), or were not willing to sign an informed consent (Fig. 1).

Initially, patients received a complete nutritional assessment that consisted in a medical evaluation, anthropometric measurements, blood biochemistry analysis, and dietary intake. Patients also provided basal sociodemographic data and they answered the physical activity IPAC questionnaire (18). Patients under their usual treatment were followed for 14 weeks at which point the same measurements done at baseline were performed again. After this second visit, the nutritional intervention with lupin was initiated. During the initial seven-weeks of the intervention-phase, patients continued with their usual drug treatment plus one-daily-dose of 10 g of a *L. mutabilis*-based snack that was consumed 30 minutes before lunch. During the following seven weeks patients continued with their usual drug treatment plus two daily doses of 10 g of a *L. mutabilis*-based snack 30 minutes before lunch and 30 minutes before dinner. At the end of the intervention period a final measurement of the study variables was done.

Evaluators of outcomes and data analyst were blinded to the treatments that patients received during the study.

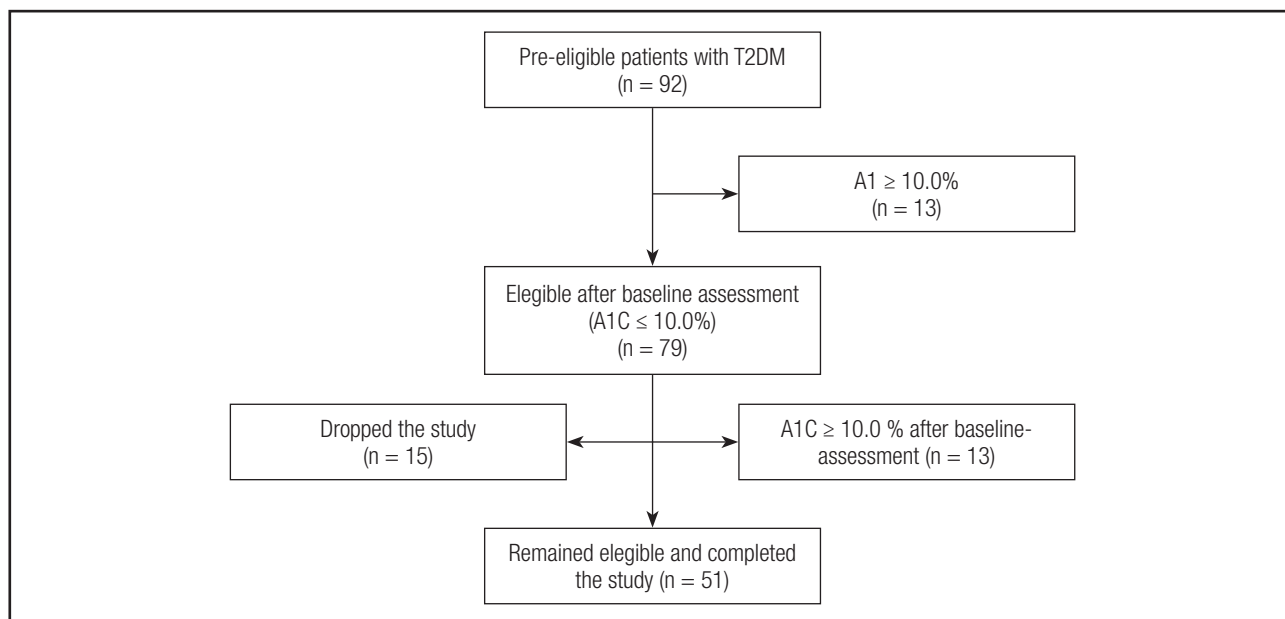


Figure 1.

Flowchart of data analyzed to evaluate the effect of consumption of a *Lupinus mutabilis*-based snack on T2DM metabolic control.

CHARACTERISTICS OF THE SNACK

Lupinus mutabilis grains cultivar 450 were used to prepare a dry crunchy snack by the Instituto Nacional de Investigaciones Agropecuarias (INIAP), Quito-Ecuador. The snack consisted in 10 g of dehydrated *L. mutabilis* lightly salted and packed in a small bag of aluminum paper which was completely sealed. The macro and micronutrient composition of the snack is presented in table I (19).

ANTHROPOMETRIC AND BLOOD PRESSURE MEASUREMENTS

Standardized clinic weight and height scales were used to determine both height and weight of each participant. A digital weight scale (Seca®, Quito-Ecuador) calibrated to the nearest 0.1 kg was used to weight patients. For height measurement, a portable stadiometer (Seca®) with a precision of 1 mm was used. Weight and height were taken with light clothing and no shoes (20). Blood pressure measurements were taken by a trained member of the research team using an automatic digital monitor (Omron HEM-757; Omron Corp., Tokyo, Japan); two consecutive recordings of blood pressure were taken after five minutes of rest in a sitting position. Two readings were obtained and the mean value was used for analysis.

BLOOD SAMPLES

Qualified personnel took blood samples in the morning between 8 a.m. and 10 a.m. after approximately 12 hours of fasting. Samples were centrifuged within two hours and

Table I. Macronutrient and micronutrient content of the snack of *Lupinus mutabilis*

Macronutrient	(%)
Protein	51.7
Fat	21.6
Total fiber	8.3
Ashes	2.4
Humidity	6
Carbohydrates	15.9
Dry matter	25.8
Micronutrient	(%) or ppm
Na (%)	0.04 ± 0.001
K (%)	0.02 ± 0.002
Mg (%)	0.16 ± 0.010
Ca (%)	0.50 ± 0.025
P (%)	0.43 ± 0.006
Fe (ppm)	99.33 ± 6.658
Zn (ppm)	54.33 ± 4.163
Mn (ppm)	24.00 ± 2.000
Cu (ppm)	9.23 ± 0.929

processed immediately. Samples were collected at baseline, 14 weeks and 28 weeks.

Serum glucose was measured using a glucose oxidase method (Roche-Diagnostics, Quito, Ecuador) using a Hitachi Roche 917 full-automated analyzer system. Serum insulin was determined

using an electro-chemiluminescence immunoassay (ECLIA) following the manufacturer's instructions (Roche Diagnostics/Hitachi, Quito, Ecuador) and chemiluminescent emission was measured using a fully automated analyzer system ELECSYS 2010 (Roche Diagnostics, Quito, Ecuador). Both glucose and insulin determinations were carried out in NetLab Laboratory. NetLab maintains an internal and external quality control system (College of American Pathologists, Brazilian Society of Clinical Pathologists, SBOC).

The primary end points of the study were the changes in A1C during the study periods (14 weeks vs 28 weeks and baseline vs 28 weeks). Secondary end-points included: changes in body mass index (BMI), blood pressure, insulin and lipid profile.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Human Subjects Protection Committee at the Universidad San Francisco de Quito approved this study. Each participant signed an informed consent form after receiving an explanation of the study and its possible consequences.

SAMPLE SIZE AND STATISTICAL ANALYSIS

A sample size of 63 patients was determined to have 80% power to detect a statistically significant decrease in the final A1C value from 8.1% at baseline to 7.7% at 28 weeks, assuming a standard deviation of 0.8. Since this was a quasi-experimental study, patients served as their own control during the two-phases of the study.

Descriptive statistics such as percentages and means with their standard deviation were calculated. To assess changes from baseline a paired t-test analysis was conducted. A p-value ≤ 0.05 was considered as statistically significant after the Benjamini-Hochberg correction (21).

RESULTS

A total of 79/92 (85.9%) patients who met the eligibility criteria were enrolled in the study. Twenty-eight patients were excluded during the development of the study because they either dropped the study ($n = 15$) or presented A1C levels $> 10\%$ ($n = 13$). Out of these 13 patients, eight had serum A1C levels greater than 10%, after the first phase of the study (without lupin consumption) and five patients at the end of the study period (after lupin consumption); these five last patients maintained serum A1C levels greater than 8% throughout the study period.

Lupinus mutabilis snack was well accepted and tolerated by all participants. Approximately 83% of patients reported a perfect adherence to snack consumption during the study. The remaining 17% also had a good reported adherence (more than 75% of snack was consumed), however, they did not take all the scheduled snacks due to forgiveness or denture poor conditions that made it difficult to chew the snack.

SOCIODEMOGRAPHIC CHARACTERISTICS

Table II shows sociodemographic characteristics of participating patients. There were more women than men and participants age ranged between 35 and 88 years. Most participating patients were married, with elementary school level of education. An important percentage of patients smoked and presented hypertension.

ANTHROPOMETRIC AND BLOOD PRESSURE CHANGES

There was a statistically significant decrease in weight and in BMI from baseline to the end of the study at 28 weeks, $p = 0.015$ and 0.009 , respectively (Table III). However, these two parameters did not changed significantly from the 14 to the 28 weeks. In addition, both systolic and diastolic blood pressure were significantly lower at 28 weeks after the supplementation with *L. mutabilis* compared with 14-weeks and baseline measurements.

Table II. Socio-demographic characteristics of participants

Variable	n (%)
<i>Gender</i>	
Male	19 (37.3)
Female	32 (62.7)
Age in years (mean \pm standard deviation)	64.1 \pm 11.1
<i>Marital status</i>	
Single	4 (7.8)
Divorced/widowed	13 (25.5)
Married	34 (66.7)
<i>Level of education</i>	
No formal education	2 (3.9)
Elementary school	34 (66.7)
High school	13 (25.5)
University	2 (3.9)
Smocking	15(29.4)
Diagnosis of hypertension	29 (56.9)

Table III. Changes in anthropometric and blood pressure parameters during the study period

Variable	Time-point during the study		
	Baseline	14 weeks	28 weeks
Weight (kg)	70.5 \pm 13.6	69.5 \pm 4.0 ¹	69.7 \pm 13.5 ¹
Height (m)	1.52 \pm 0.09		
BMI (kg/m ²)	30.3 \pm 4.5	29.9 \pm 4.4 ¹	29.9 \pm 4.4 ¹
SBP (mmHg)	134.8 \pm 16.1	134.0 \pm 18.7	127.5 \pm 19.5 ^{1,2}
DBP (mmHg)	80.9 \pm 9.2	79.1 \pm 8.7	76.3 \pm 8.5 ^{1,2}

¹Different from baseline. ²Different from 14 weeks.

CHANGES IN BLOOD BIOCHEMICAL PARAMETERS

As shown in table IV, there was a significant increase of glucose and insulin from baseline until the end of the study but there were not important changes between 14 and 28 weeks. Serum A1C levels did not change significantly during the study. In addition, serum HDL concentrations increased significantly at 28 weeks compared with baseline. No other serum markers of lipid metabolism, uric acid or CRP showed statistically significant modifications during the study.

A closer analysis in patients with levels of A1C ≥ 8.0 and ≤ 10 showed that there were no statistically significant changes in A1C levels throughout the study period (Table V).

However, it is noticeable that patients who maintained their A1C levels $\leq 8.0\%$ reduced significantly their levels of A1C after the consumption of the snack achieving a reduction of 0.2-0.4% by the end of the study. Although not statistically significant, only those patients who maintained their A1C serum levels $\leq 8.0\%$ more frequently reached the treatment target value of A1C of 6.5% (Table V). In addition, in this subgroup of patients, glucose increase by 14 weeks was attenuated after lupin consumption. This increase in glucose was accompanied

by an increase in serum insulin that was greater with lupin intake (Table VI).

DISCUSSION

The present study demonstrated that consumption of a snack based on the legume *L. mutabilis* by T2DM patients under regular hypoglycemic treatment improved glucose metabolic control. Thus, patients with serum A1C concentrations $\leq 8.0\%$ that consumed the snack more frequently achieved the ideal target of 6.5% A1C (1). The lower the level of A1C patients maintained, the greater the benefit of the addition of the snack of *L. mutabilis*. This study also showed a significant decrease in BMI and blood pressure and a significant increase in HDL cholesterol by the end of the study period.

A limited number of studies with humans have documented the hypoglycemic effect of *L. mutabilis* consumption in T2DM patients, although those reports are restricted to short-term interventions (14-16). The present report expands those results and demonstrated that consumption of *L. mutabilis* for 14 weeks improved glucose metabolism reflected in lower concentrations of A1C in patients with serum A1C levels $\leq 8.0\%$. In these patients, the typical decrease in A1C after 14 weeks of *L. mutabilis* consumption was 0.2-0.4%, which represents a diminution of about 10 mg/dl of serum glucose. Most oral hypoglycemic drugs lower A1C within a range of 0.5 and 1.5% (1). Patients with T2DM that maintained abnormal serum levels of A1C $\leq 8.0\%$ could benefit with the addition of a snack of *L. mutabilis* to their conventional oral glucose lowering treatment. It looks like the greatest benefit of *L. mutabilis* consumption by T2DM patients depends

Table IV. Changes in blood biochemical parameters during the study

Variable	Time-point during the study		
	Baseline	14 weeks	28 weeks
Glucose (mg/dl)	116.3 \pm 27.8	133.7 \pm 35.4 ¹	134.1 \pm 38.7 ¹
A1C (%)	6.9 \pm 0.9	6.9 \pm 1.0	6.8 \pm 1.2
Insulin (ng/dl)	15.3 \pm 11.8	19.7 \pm 27.2	20.2 \pm 18.2 ¹
TC (mg/dl)	187.2 \pm 39.4	189.5 \pm 32.7	183.4 \pm 37
LDL (mg/dl)	117.4 \pm 28.6	121.5 \pm 32.0	118.3 \pm 33.6
HDL (mg/dl)	43.9 \pm 11.3	48.4 \pm 11.7 ¹	46.3 \pm 11.3 ^{1,2}
TG (mg/dl)	180.4 \pm 129.7	175.0 \pm 100.2	179.9 \pm 114.6
Uric acid	5.1 \pm 1.2	5.1 \pm 1.4	5.0 \pm 1.3
CRPs	3.0 \pm 3.6	2.9 \pm 2.7	3.3 \pm 4.4

¹Different from baseline. ²Different from 14 weeks.

Table VI. Changes in glucose and insulin in patients with A1C serum levels $\leq 8.0\%$

Variable	Time-point during the study		
	Baseline	14 weeks	28 weeks
Glucose (mg/dl)	110.6 \pm 27.6	123.9 \pm 28.6 ¹	123.5 \pm 36 ¹
Insulin (ng/dl)	13.3 \pm 9.5	14.1 \pm 10.7	18.3 \pm 17.6 ¹

¹Different from baseline. ²Different from 14 weeks.

Table V. Changes in A1C and percentage of patients that achieved treatment target value according to the severity of metabolic alterations

Value of A1C maintained through the study	Baseline		14 weeks		28 weeks	
	Mean value (%) \pm standard deviation	% of patients that achieve a target value of A1C ≤ 6.5	Mean value (%) \pm standard deviation	% of patients that achieve a target value of A1C ≤ 6.5	Mean value (%) \pm standard deviation	% of patients that achieve a target value of A1C ≤ 6.5
> 8.0 - \leq 10.0 n = 13	8.1 \pm 0.7	7.7	8.2 \pm 0.9	7.7	8.4 \pm 0.7	0
\leq 8.0 n = 38	6.5 \pm 0.6	50	6.5 \pm 0.6	55.3	6.3 \pm 0.7 ^{1,2}	71.1

¹Different from baseline. ²Different from 14 weeks.

on the severity of their metabolic alteration manifested by A1C serum concentrations. On the other hand, patients with serum A1C levels > 8.0% did not show significant improvements of glucose metabolism. It is important to note that during the first 14 weeks of the study, when patients did not receive *L. mutabilis* there was an increment in blood glucose that was attenuated after *L. mutabilis* consumption in patients with A1C serum levels ≤ 8.0%. As expected, the observed increments in glucose were paralleled with greater concentrations of serum insulin; insulin increases were greater after *L. mutabilis* consumption. In this regard, oral administration of γ -conglutin from lupin (120 mg/kg) during one week increased the expression of *Ins-1* gene and pancreatic insulin content in an animal model for diabetes (22). It is possible that hydrolysates from *L. mutabilis* (including those derived from γ -conglutin) could have increased insulin production directly stimulating pancreatic β -cells or through the increase of GLP-1 produced by inhibition of dipeptidyl peptidase IV (DPP-IV) activity (17). These studies indicate that the consumption of *L. mutabilis* could increase serum insulin concentrations as observed in the present study.

It is important to consider that *L. mutabilis* is a high-quality food which provides other important health benefits; it is well accepted and affordable, it is feasible to increase its daily dosage and does not cause side-effects nor has negative interactions with other drugs unlike most hypoglycemic medications. The mechanisms of action related to the consumption of lupin and other legumes are under intensive study (16-19). We have shown that hydrolysates of *L. mutabilis* inhibit gluconeogenesis, DPP-IV, and enhance the sensitivity of the insulin receptor mediated by translocation of the transporter of GLUT-4 (17). These molecular and cellular mechanisms resemble the biochemical effects of sitagliptin (gliptins) and metformin drugs (biguanides).

Previous studies have reported a decrease of 2.4 to 8.4 mmHg in systolic blood pressure (23,24) after consumption of 15 to 25 g/day of *L. angustifolius* protein isolate for 12 month and eight weeks, respectively (23,24). In agreement with those observations, here we demonstrated that upon consumption of *L. mutabilis* there was a decrease of 7 and 3 mmHg in systolic and diastolic blood pressures, respectively. A possible mechanism of action of lupin consumption on blood pressure could be related to its important content of protein and fiber and the dietary substitution of carbohydrate with them (25-27). Also, amino acid sequences of hydrolysates generated after *L. mutabilis* protein digestion could have potential inhibition of the angiotensin converting enzyme (17). A reduction of 7 mmHg would reduce cardiovascular risk by about 14% (25). In addition, the observed increase in HDL-cholesterol in this study could further contribute to decrease the cardiovascular risk with *L. mutabilis* consumption. The present results agree with other observations that demonstrate increases in serum HDL of subjects with hypercholesterolemia after consumption of lupin protein isolates from *L. angustifolius* (23). It is difficult to estimate the magnitude of reduction in cardiovascular risk because there is controversy regarding the benefit of increasing HDL levels (28). Interestingly, recent epidemiological studies demonstrate that consumption of legumes is inversely

associated with total mortality and non-cardiovascular death (29). In addition, these studies indicate that lupin species intake can positively affect cardiovascular risk factors in at risk populations.

Limitations of the present study included the low number of eligible patients: 51 instead of the initially calculated sample of sixty-three. This could have precluded to achieve statistical significance of the effect of the consumption of *L. mutabilis* in subjects that regularly have A1C levels > 8%. Future studies should assess higher doses of *L. mutabilis* intake, the effects in glucose metabolism in subjects with A1C levels > 8% and, most important, the potential of this legume to prevent T2DM.

CONCLUSIONS

Therapeutic dietary changes including frequent consumption of legumes are promising complementary strategies for the management of patients with T2DM. In this quasi-experimental crossover study, an intervention with 15 g of LM resulted in a significant decrease in blood pressure and a significant increase in HDL-cholesterol. Patients with serum A1C concentrations < 8.0% reduced significantly their A1C after the intervention and 71.1% achieved a target concentration ≤ 6.5%. Patients with T2DM could benefit with the addition of LM-snack to their conventional treatment.

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