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CAMEL MILK AS A POSSIBLE ALTERNATIVE IN PATIENTS ALLERGIC TO RUMINANT MILK

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ABSTRACT

Background: There are few reports on allergy to camels. Camel milk has been used to treat cow's milk allergy in Israelite and Saharawi children and might be an alternative to ruminant milk, since camels are not ruminants but tylopods, and the milk composition could differ. **Objective:** To assess the allergic response to camel milk in all patients with hypersensitivity to cow's milk treated in 2021 by the Rio Hortega Hospital allergy clinic. **Methods:** Samples of milk from Canary Islands dromedaries and hair from bactrians, dromedaries and llamas were obtained. In vivo (prick, provocation with cow and dromedary milk) and in vitro (ImmunoCAP, CRD, SDS_PAGE, immunodetection) tests were carried out in patients and controls after informed consent. **Results:** During 2021, 1479 patients presented proven food hypersensitivity. Of these, 68 (4.6%) had severe symptoms related to cow milk ingestion, principally young males and children. Patients with cow's milk allergy and eosinophilic esophagitis had significantly more positive in vitro and provocation tests and immunodetection showed a protein in cow's milk of about 18 kDa, compatible with beta-lactoglobulin, that was not recognized in dromedary milk by any patient. However, it was positive in three out of 135 patients who accepted provocation with dromedary milk. The remaining patients tolerated camel milk without serious reactions. **Conclusion:** Dromedary milk was better tolerated than cow's milk, especially in patients sensitized to beta-lactoglobulin. These results provide useful information for patients allergic to cow's milk and could have direct future clinical and industrial applications.

KEYWORDS: Milk allergy, Cow's milk, Dromedary, Camel milk, Beta-lactoglobulin.

INTRODUCTION

Milk allergy is very common in children. It may be mediated by IgE specific to milk proteins not and may progress to anaphylaxis. The most common non-IgE-mediated allergy is food protein-induced allergic proctocolitis (FPIAP), which is diagnosed in children with intestinal bleeding without other alarming symptoms, and in infants receiving both formula and breast milk.

This study assessed IgE-mediated milk allergy to determine whether camel milk would be useful and safe as a substitute for cow's milk in these patients and patients with eosinophilic esophagitis and celiac disease and atopic patients.

Camels are not ruminants, but tylopods, and the composition of their milk is very different.[1] The protein concentration of cow's milk (2.5-4.2%) is two times higher than that of human milk, and its main allergens include are beta-lactoglobulin, which is lacking in human milk, and alpha-s1-casein, which causes anaphylaxis.[2] However, camel milk allergy is extremely rare, even in countries where it is most consumed.[3] The most similar milk to human milk is donkey milk, which contains more protein in whey (35-50%) than cow's milk (20%). The beta-lactoglobulin of donkey milk is a monomer and the milk of ruminants a dimer, with a high lactose content, like human milk. Goat milk is better assimilated than cow's milk, and its main protein is beta-casein,[5] but the allergenicity is similar to that of cow's and sheep's milk,

so they are not an alternative in patients with cow's milk allergy.

Camel milk is more easily digested, as its beta-casein structure differs from that of other milks, containing more antibacterials (lysozyme, lactoferrin) than cow's milk and similar amounts of immunoglobulins to human milk[3-5]

Antibacterial and beneficial properties have been attributed to camel milk due to the intestinal microbiota,[4] immunomodulators, antioxidants and natural immunity enhancers[5,6] it contains. It also has anti-inflammatory and analgesic[7] and even antidiabetic properties.[8] Possible beneficial effects in autism, cancer, and poisonings require further study.[9]

Therefore, we aimed to determine whether camel milk, specifically that of Lanzarote dromedaries, is a safe, useful nutritional alternative in child and adult patients with severe allergic symptoms due to hypersensitivity to cow's milk.

MATERIAL AND METHODS

We obtained frozen, freeze-dried samples free of bacteria and other pathogenic microorganisms from Lanzarote dromedary milk (*Camellus dromedarius* L., 1758, Tylopoda: Camelidae) to perform tests in allergic patients and healthy controls and to test tolerance to this milk in healthy and atopic controls (pollen). We also tested it in celiac patients (in whom low milk tolerance is common) and patients with eosinophilic esophagitis with positive allergic tests.

The study used a cross-sectional case-control design. Patients diagnosed with hypersensitivity to cow's milk came from a database of patients with this possible etiology collected in 2021 in the Allergy, Digestive and Pediatric Services of the Rio Hortega University Hospital. Celiac patients and those with eosinophilic esophagitis come from databases collected in previous years. Informed consent and the approval of the Rio Hortega Research Ethics Committee were obtained (Ref. CEIm: 21-PI219, Protocol version 1.0; HIP/CI version 1.0).

The objective was to determine whether dromedary milk might be a safe alternative in patients hypersensitized to cow's milk, using routine allergy techniques, oral challenge and molecular techniques using component resolved diagnosis (CRD) and immunodetection. We analyzed four groups of patients and controls:

1. Patients with severe clinical urticaria, dermatitis, asthma, rhinitis, digestive symptoms, or anaphylaxis related to cow's milk ingestion treated in 2021
2. Healthy blood donor controls
3. Patients allergic to grass pollens without digestive symptoms related to milk or food
4. Patients with eosinophilic esophagitis
5. Patients with celiac disease

Calculation of the sample size: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 48 subjects in each group were needed to detect a minimum difference of 8 between the two groups, assuming there were 4 groups and a standard deviation of 10. A follow-up loss rate of 20% was estimated.

In vivo tests

Skin tests were carried out using conventional techniques in the case of commercialized allergens: *Prick-test* against common pneumo-allergens (grass, tree and weed pollen), mites, animal epithelia, fungi and food, and with commercial extracts of cow, sheep and goat milk (ALK-Abelló, Madrid, Spain). Prick tests were performed with twice-boiled dromedary milk using the prick-by-prick technique.

Epicutaneous tests with milk and dromedary hair at 0.01% in petrolatum using a standard battery of True-Test contact allergens (ALK-Abelló, Madrid)) (Bial-Aristegui, Bilbao); readings were made at 48 and 96 hours.

Provocation tests. We followed the amended method of Dunlop et al.[10] and the considerations of the Adverse Reactions to Foods Committee Work Group Report [11] We used twice-boiled dromedary milk. The starting dose was 0.1 ml for the first lip application and a sublingual test at one hour. The progressive introduction pattern is shown in **Figure 1**. We considered that provocation could continue when the prescribed dose was consumed without symptoms or the need for medication. After tolerance of each dose, the patient or family (in children) were instructed to continue the dose for 3-5 days: the subsequent dose was given in the clinic with surveillance of possible reactions for seven hours.

In vitro testing

Ten percent extracts were prepared with PBS and, after dialyzing, paper discs previously activated with BrCN were sensitized, as described by Ceska et al.[12] The quantity of proteins (7.96 mg/mL) was determined according to Bradford's method.[13]

Determination of specific IgE against ruminant milk (cow, sheep, goat) and camel milk was made using UniCAP, Thermofisher Uppsala, Sweden. Levels ≥0.35 kU/L were considered positive.

Assessment of **specific IgE against camel milk** was made using ImmunoCAP, Thermofisher, Uppsala, Sweden. The antigen binds to PDA by biotinylation, using Sander's method.[14]

SDS PAGE/IgE-Western blot: Camel and cow milk proteins were analyzed by electrophoresis in polyacrylamide gel with sodium dodecylsulfate (SDS-PAGE), according to Laemmli's method.[15] in 15% polyacrylamide gels under reducing conditions. Proteins were visualized with Coomassie R-250 bright blue

staining and electrophoretically transferred to polyvinylidene difluoride (PVDF), Trans-Blot Turbo™ membranes, Bio-Rad, Hercules, CA, USA). Binding of the IgE antibody to allergens was analyzed by Western blot using sera from three groups of patients: A. typical allergic pathology, B. EoE patients, and C: celiac patients. Human anti-IgE peroxidase conjugate (Southern Biotech, Birmingham, USA) and chemiluminescence detection reagents (Western Lightning® Plus-ECL, Perkin Elmer. Waltham, MA, USA) were added according to the manufacturer's instructions. IgE binding bands were identified using the Bio-Rad Diversity database program.

Molecular analysis was made using CRD (ISAC Thermofisher, Uppsala, Sweden), including 112 molecules of recombinant and native allergens, according to the manufacturer's instructions.

Statistical analysis

We collected clinical and demographic data from the 385 patients recruited. Of these, only the 135 who underwent camel milk provocation were included in the analysis.

Between-group proportions of positives in the CRD tests and prick tests were compared using Fisher's exact test[16] followed by a post-hoc pairwise test to determine which groups differed from the rest.

To check whether the proportions of positives in the provocation tests with camel milk differed from those found with cow milk, an exact binomial test was used in each group.[17]

To compare IgE concentrations of different compounds (whole milk, α-lactalbumin, β-lactoglobulin, α-casein) between patient groups, Wilcoxon signed rank tests were carried out.[18] First, IgE concentrations of patients allergic to cow's milk and patients with esophagitis were compared with IgE levels in healthy controls. Secondly, IgE levels of both groups of patients were compared to check whether the immunological response differed between them.

All multiple comparisons were corrected using the Benjamini-Hochberg method.[19] Graphics were constructed using *ggplot2* version 3.3.5 and *reshape2* version 1.4.4 according to Wickham.[20]

RESULTS

In 2021, 3688 patients were diagnosed with hypersensitivity to allergens, of whom 1479 had proven food hypersensitivity. Of these, 68 (4.6%) had severe IgE-mediated symptoms after cow milk ingestion. We also included 67 patients diagnosed with eosinophilic esophagitis, 52 celiac patients, 50 patients with pollen allergy and 50 healthy controls.

Demographic characteristics

Milk sensitization mainly affected young people and males (81 males/54 females) aged < 30 years. Mean age ± sd were 11.38 ± 6.99 in patients with milk hypersensitivity, 26.09 ± 19.17 in patients suffered from esophagitis, 25.82 ± 10.26 in allergic to pollen, 5.17 ± 4.26 in celiac patients and 31.4 ±10.91 in healthy control. Thirteen patients were sensitive to other foods.

Skin tests and IgE.

The results of skin tests by patient group differed significantly ($p = 7.99 \cdot 10^{-11}$). The post-hoc test (**Table 1**) shows that patients with milk allergy and eosinophilic esophagitis showed, in general, significantly-higher proportions of positives than the other groups. The proportion of positives between patients allergic to cow's milk and those with eosinophilic esophagitis also showed significant differences.

Specific IgE concentrations in patients with eosinophilic esophagitis and those with cow's milk allergy were significantly positive in all cases (**Table 2**). Overall, patients allergic to cow's milk showed a higher concentration of specific IgE than patients with eosinophilic esophagitis, although no significant differences were found.

There was no positivity in the patch tests with camel milk or hair.

Provocation with Cow and Camel milk

In three patients who had anaphylaxis after cow milk provocation, positivity was reached at 0.2 ml of camel milk, with mild symptoms and/or urticaria). The remaining patients tolerated 100 ml of camel milk without immediate or late reactions.

Of the 67 patients with eosinophilic esophagitis tested with camel milk, 11 accepted the provocation test, which was completed in 10 patients with esophagitis, with no immediate symptoms. They were instructed to take 100 ml of camel milk daily until the scheduled check-up in the digestive service, where they underwent clinical and endoscopic studies with biopsy, with no symptoms of worsening. In five children with celiac disease and problems with cow's milk, but with negative prick and IgE to milk, an increasing dose was given (after consent), starting with 1 ml of camel milk daily, up to 50 ml, without no clinical signs of worsening of celiac disease.

According to the binomial tests (**Figure 2**), there was a significant difference in the response to camel milk provocation compared with the positive cow milk tests in patients allergic to milk and those with eosinophilic esophagitis ($p \lll 0.001$). In contrast, no differences in the response were found in celiac patients, patients allergic to pollen or healthy controls ($p=1$).

These results support the hypothesis that camel milk could be a safe substitute for cow's milk in sensitive patients.

CRD

The results of for the CRD molecular tests by patient group differed significantly ($p = 2.12 \cdot 10^{-18}$). The post-hoc test (**Table 3)** shows that patients with milk allergy and eosinophilic esophagitis had positive proportions to cow's milk molecules (Bos d 4 Alpha-lactalbumin, Bos d 5 Beta-lactoglobulin, Bos d 8 Casein and Bos d lactoferrin Transferrin) which were significantly greater than the other groups. However, the proportions of positives between patients allergic to cow's milk and those with eosinophilic esophagitis showed no significant differences.

Immunodetection using patient sera

Analysis by Western blot (**Figure 2)** of cow's milk extracts (bottom) and camel milk (top), compared with 18 patients with: A. typical allergic disease, B. EoE patients and C: celiac patients, revealed a series of specific allergen recognitions common for both sources, specifically proteins with a molecular weight around 25 kDa, compatible with the range of caseins (Alpha S1, Alpha S2 and beta casein), and with a series of proteins around 70-75 kDa in patients with typical allergic disease and EoE, but not in celiac patients. A protein of about 18 kDa compatible with beta-lactoglobulin, which is not recognized in camel milk, was recognized in the same groups of patients and in patients allergic to cow's milk.

DISCUSSION

Human and animal migration may intervene in allergies. Spain is receiving people, mostly from Africa and South America, with other sensitizing allergens, including camels. We have observed that people from areas without bovids, such as the Sahara, have greater hypersensitivity.

We assessed whether camel milk, specifically Lanzarote dromedary milk, is a useful and safe nutritional alternative in children and adults with severe allergic symptoms due to IgE-mediated hypersensitivity to cow's milk. The hypothesis was that, as camels are not ruminants, their milk might be tolerated in patients with allergy to cow, sheep, and goat milk and that of other ruminants.

The ancestors of camels were natives of North America. Some moved to Asia across the Bering Strait, giving rise to Bactrian camels, from which dromedaries evolved. Bactrian camels have two humps and are found in Asia. Dromedaries have only one hump and are native to north Africa. Camels from North America include a group that migrated south to South America. Over time, this group evolved into the animals known today as Auchenids or South American camelids, including vicunas, llamas, alpacas and guanacos. The camelids that remained in North America did not survive and only fossils remain. Fossil remains show that, about 20 million years ago, camelids dominated the flat areas of North America, so camelid milk might have been the first tolerated by Native Americans.

The greatest limitation anticipated in our study was to ensure that camel milk was not contaminated by pathogens (*Brucella*, *Salmonella*, etc.). This was done by veterinary analyzes, carried out at the University of La Laguna de Canarias.

Another limitation is whether our results would be superimposable if milk from camels of different origins were used. A preliminary study (data presented in communication at a congress) assessed the differences in milk from camelids from various areas of Morocco (Dakhla, Errachida and Fès-Meknes), which underwent physicochemical and biochemical analyses.[9] No major differences were observed, although camelids originating in North Africa have greater quantities of proteins, fats and sugars, and those originating from Asia more vitamin C.

Allergenically, we assessed sensitization to camelids in three patients of Spanish, Moroccan and Ecuadorian origin, who presented allergic signs and symptoms related to contact. Extracts were tested from milk samples of the Bactrian camel (*Camelus bactrianus*), dromedary (*Camelus dromedarius*) and llama (*Lama glama*) (kindly donated by Madrid Zoo) and extracts from garments of these patients made with camel hair (jacket and tapestry). In vivo (prick, conjunctival provocation) and in vitro (SDS PAGE, Immunodetection) tests were carried out. Positive tests were obtained for all three species of camelids. The prick and provocation tests against camel and llama milk were positive. Immunodetection showed two bands around 18 and 32 kDa were recognized by the IgE of sera from the three patients for camel and llama extracts. A 20 kDa band was recognized by all three patients for the dromedary extract. Therefore, we assumed that our results might be comparable with the milk of any camelid.

Milk allergy is very common in children, both IgE-mediated and non-IgE-mediated (including FPIAP, food protein-induced enterocolitis syndrome, food protein-induced enteropathy, and Heiner syndrome (pulmonary hemosiderosis)).[21] The most frequent manifestation is FPIAP but we only included IgE-mediated milk allergy.

The management of milk allergy has changed in recent years from an elimination diet to improve symptoms to active modulation of the immune system[22] with oral immunotherapy, which has been shown to be effective by many studies[23] However, there is still no consensus on the different protocols of this technique.[24]

Tolerance has been achieved with cow's milk baked in the form of cupcakes. However, adverse reactions are common, and positive provocation does not guarantee subsequent tolerance.[24] Specific IgE levels and casein testing have been found to be useful predictors of baked milk tolerance.

Different cow's milk substitutes,[25] plant drinks based on different formulas and plant derivatives have been tried, which do not necessarily address the nutritional requirements of infants and children.

In 2017, Navarrete et al. included 15 patients with milk allergy confirmed using DBPCFCs. After administration of camel milk, no patient presented adverse effects.[26]

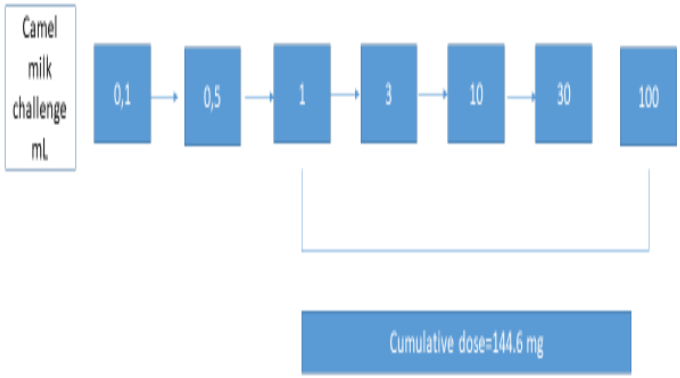

Figure 1: Open challenge tests with dromedary milk.

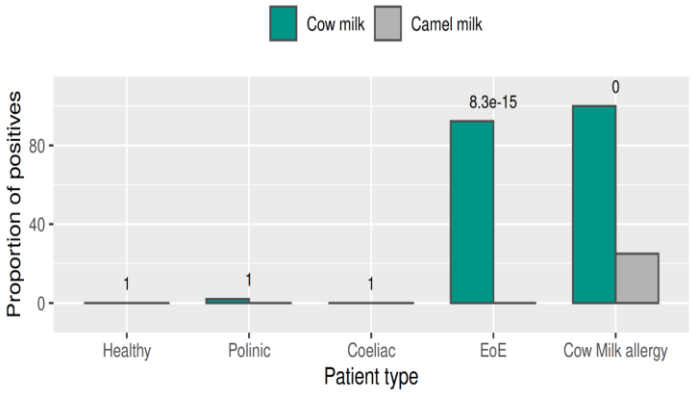

Figure 2: Positive proportions for provocation tests with cow's milk (Green) and camel milk (Gray) for each type of patient.

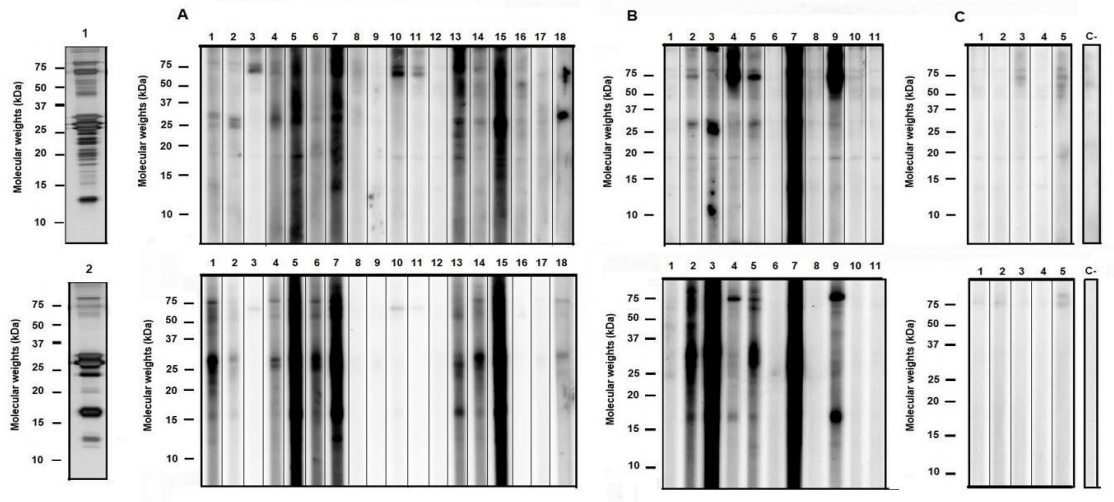

Figure 3: Analysis by Western blot of cow's milk extracts (Bottom) and Camel milk (top).

Table 1: Peer comparison of Fisher's test for the proportion of positives in prick tests.

	Celiac	Esophagitis	Pollen	Healthy	Cow
Celiac	-	***2.00E-02***	1.00E+00	1.00E+00	***9.00E-05***
Esophagitis	Inf	-	***3.00E-06***	***3.00E-06***	6.00E-02
Pollen	Inf	0.0147	-	1.00E+00	***9.00E-13***
Healthy	Inf	0.0147	1	-	***9.00E-13***
Cow	Inf	8.6636	445.0357	445.0357	-

Table 2: Adjusted *p*-values of Wilcox tests for specific IgE concentrations. The asterisks indicate the level of significance (*: p < 0.001; **: p < 0.01; *: p < 0.05).**

Comparison	Whole milk	Alpha	Beta	Casein
Cow	**7.22e-04 (***)**	**7.24e-04 (***)**	**1.08e-03 (**)**	**0.0007 (***)**
Esophagitis	**1.89e-03 (***)**	**1.25e-03 (**)**	**1.24e-03 (**)**	**0.0012 (**)**
Cow+esophagitis	**2.52e-02 (**)**	0.380	0.510	0.0686

Table 3: Peer comparison of Fisher's test for CRD molecular analysis. The molecules Bos d 4 Alpha-lactalbumin, Bos d 5 Beta-lactoglobulin, Bos d 8 Casein and Bos d lactoferrin Transferrin were assessed. The upper hemimatrix shows the adjusted p-values (significant values in bold); the lower hemimatrix shows the odds ratios.

	Celiac	Esophagitis	Pollen	Healthy	Cow
Celiac	-	5.00E-01	1.00E+00	1.00E+00	***1.00E-02***
Esophagitis	Inf	-	***3.00E-02***	***7.00E-03***	***3.00E-02***
Pollen	Inf	0.0725	-	1.00E+00	***4.00E-08***
Healthy	0	0	0	-	***4.00E-09***
Cow	Inf	6.7733	93.0914	Inf	-

CONCLUSION

We suggest that camel milk (dromedary milk in our study) is safe and tolerable in patients aged >1 year with IgE-mediated milk allergy and in patients with eosinophilic esophagitis and a clinical response to milk. It also appears to be well tolerated in atopic and celiac patients.

Camel milk might be considered as a good alternative, given the benefit of its taste and properties compared with other formulas.

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