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Alimentary Tract

Agreement between indirect calorimetry and traditional tests of lactose malabsorption

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ABSTRACT

Background: Lactose malabsorption occurs frequently and the variable consequent intolerance may seriously impair quality of life. No reliable and convenient test method is in routine clinical practice. A recent animal study showed that the respiratory quotient changed significantly after ingestion of sucrose and lactose in naturally lactase-deficient rats.
Aims: This exploratory study evaluated the relevance of monitoring the respiratory quotient after lactose ingestion to detect malabsorption.
Methods: Healthy volunteers were identified and classified lactose absorbers and malabsorbers by a lactose tolerance test (25 g). After an overnight fast, a second lactose challenge was performed to monitor hydrogen excretion and respiratory quotient kinetics over 4 h. Participants also completed questionnaires to score and localise their gastrointestinal symptoms.
Results: 20 subjects were enrolled (10 per group, 60% males, mean age 34 ± 4 years). Respiratory quotient kinetics were different between absorbers and malabsorbers during the first 100 min after lactose ingestion ($p < 0.01$) and during the initial 30–50 min period. Respiratory quotient was significantly, positively correlated to peak glycaemia ($R = 0.74$) and negatively correlated to hydrogen excretion ($R = -0.51$) and symptoms score ($R = -0.46$).
Conclusions: Indirect calorimetry could improve the reliability of lactose malabsorption diagnosis. Studies on larger populations are needed to confirm the validity of this test and propose a simplified measurement.

1. Introduction

Hypolactasia is a widespread intestinal problem that affects almost 75% of the population worldwide, with large variations depending on ethnic background. Despite the recent identification of the genetic locus, lactose intolerance remains poorly diagnosed by the medical community, mainly due to the heterogeneity of terminologies and the questionable reliability of the diagnostic tools.

Hypolactasia, which refers to the deficiency or absence of lactase secretion, may be detected by duodenal or jejunal biopsies and by genetic tests. A biopsy is the only direct method of detection, but is an invasive technique. The genetic test, identifying some mutations in the gene encoding lactase, has a reported sensitivity of 93–100% and a specificity of 95–100%, but remains poorly available.

Several other techniques are available to detect malabsorption, but they have some limitations. These tests require the ingestion of a lactose load and include the dynamic study of glycaemia, the analysis of stool pH, urine galactose, the hydrogen breath test (HBT) or the measurement of ^{13}C-glucose in serum or $^{13}CO_2$ in exhaled air. Glycaemia analysis presents sensitivity and specificity both reported to be between 70% and 95% [1], with no reliability in diabetics or in patients with bacterial overgrowth. The stool pH is easily analysed but its reliability may be disturbed by intestinal motility and water reabsorption. Urine galactose analysis presents variable sensitivity (77–96%) and specificity (88–100%) [2]. The HBT, quantifying the amount of hydrogen created from the colonic fermentation of undigested carbohydrates, has been considered a gold standard for over 30 years. Its sensitivity and specificity are approximately 80–100% and 70–100%, respectively [3]. However, around 20% of patients present an intestinal bacterial overgrowth,

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leading to false positive results, or a methanol excretion, leading to false negative results [4]. Since 2008 it has been suggested to detect both hydrogen and methane in the expired air to reduce the number of false negatives [5]. The monitoring of ^{13}C-glucose in serum or $^{13}CO_2$ in exhaled air following ingestion of labelled ^{13}C-lactose was developed in 2000. According to these studies, the proportion of lactose malabsorbers is almost 50% higher than described in the literature [6–8]. However, this technique remains rarely used.

Subjective techniques, related to the manifestation of symptoms, can highlight lactose intolerance. The available tests are usually self-completed questionnaires to score the main gastrointestinal symptoms, such as rumbling, bloating, cramping, nausea and diarrhoea. The sensitivity and specificity of these questionnaires are only 75% and 67%, respectively, due to the variability in evaluating one's own symptoms [9], and present an overestimation observed in 30% of the subjects [10].

Thus, none of the available techniques allows a precise and absolute diagnosis. In this context, it is useful to evaluate new tools or new combinations of tests to optimise the diagnosis of lactose malabsorption.

A recent animal study showed that the kinetics of respiratory quotient (RQ), carbohydrate oxidation (Cox) and lipid oxidation (Lox), after ingestion of sucrose and lactose, depended on the capacity of the host to absorb sugars [11]. Therefore the aim of our study was to monitor the RQ, Cox and Lox during and after a lactose load (25 g) in selected absorbers and malabsorbers, and to evaluate the efficacy of these tests in diagnosing lactose malabsorption. Concomitantly, blood sugar levels were measured using a portable glycaemia reader, hydrogen breath excretion was quantified using a portable hydrogen detector, and RQ, Cox and Lox kinetics were monitored using a ventilated-hood system. Symptoms were also evaluated before ingestion of lactose and after 4 h, by subjectively scoring the 5 main gastrointestinal symptoms (diarrhoea, pain, nausea, rumbling and bloating).

2. Materials and methods

2.1. Participants

The study was carried out in healthy volunteers (lactose absorbers and lactose malabsorbers) identified by the 1-h glycaemia after lactose ingestion test. No participant had gastrointestinal or pulmonary diseases, had taken antibiotics or other drugs affecting intestinal function for 8 days prior to the study, or had practiced intense physical activity for 2 days prior to the study. Additionally, participants had followed the nutritional recommendations for meals during the 2 days before the study [12,13].

2.2. Experimental protocol

The study took place at the Gastroenterology Department of the Avicenne Hospital (Bobigny, France). After being identified as lactose absorbers or malabsorbers, the participants ingested 25 g of lactose diluted in 250 mL of water after an overnight fast. Their respiratory parameters were measured using a ventilated-hood system (canopy) for 4 h and their hydrogen excretions were recorded over 3 h. At the end of the test the participants also completed a symptoms questionnaire to score and localise their gastrointestinal symptoms.

2.3. Lactose tolerance test

Samples of capillary blood to test glucose concentration were taken at 0, 15, 30, 45 and 60 min, using a *Precision XceedPro* glycaemia reader (Abbott, Rungis, France). For each time point, measurements were taken twice on the same sample and the mean value was recorded. A glycaemia rise equal to or greater than 1.5 mmol/L was classified as "lactose absorption"; a plasma glucose rise equal to or less than 1.0 mmol/L was classified as "lactose malabsorption" [1]. All the included participants presented glycaemia peaks greater than or equal to 1.5 mmol/L for lactose absorbers and less than or equal to 1.0 mmol/L for lactose malabsorbers, confirming their classifications [2,14].

2.4. Hydrogen breath test (HBT)

The exhaled hydrogen was measured in parts per million (ppm) using a *GastroLyzer* (Bedfont Scientific Ltd., Maidstone, Kent, England). A hydrogen excretion 20 ppm higher than baseline in at least 2 subsequent measurements was associated with lactose malabsorption [15,16].

2.5. RQ, Cox and Lox kinetics

RQ, Cox and Lox were computed from $VCO_{2\ exhaled}$ and $VO_{2\ consumed}$, recorded each minute, using a *Deltatrac II* canopy (Datex Ohmeda, Limonest, France). In this system, the subject inhales atmospheric air through a hole in the capsule and exhales via a non-return valve into a measurement unit [17–19]. During these measurements participants were placed in the supine position with the canopy overhead; they had at least 30 min to familiarise with the system. Once parameters were stable, a 10-min baseline was recorded. Then the participants ingested lactose and measurements were taken over the following 4 h.

2.6. Symptom evaluation

Each participant rated the intensity of the 5 main gastrointestinal symptoms (diarrhoea, pain, nausea, rumbling and bloating), before and after the lactose challenge, on a 10-cm visual analogue scale ranging from 0 (no symptoms) to 10 (maximum symptoms) [9]. Symptoms were associated with lactose malabsorption for a mean delta above or equal to 7.5/10 [9].

Pain topology was also evaluated. Participants reported on a diagram the pain intensity that they experienced after the lactose challenge, using a 10 point Likert scale ranging from 0 (none) to 9 (extreme): right hypochondrium (segment 1), epigastrium (segment 2), left hypochondrium (segment 3), right lumbar (segment 4), periumbilical (segment 5), left lumbar (segment 6), right iliac (segment 7), hypogastrium (segment 8) and left iliac (segment 9) (Fig. 4).

2.7. Ethics

The study was conducted according to the Declaration of Helsinki, and approved by the Ethical Committee of Saint-Germain-en-Laye (Paris XI). Written informed consent was given by all participants before inclusion.

2.8. Statistical analysis

Results are presented as means ± SEM. Analyses were performed with either an ANOVA for repeated measures or a Student's *t*-test for unpaired data. The areas under the curves for RQ, glycaemia, HBT and symptoms were correlated by computing the Pearson's coefficients. The software used was SAS (version 9.1). The significance level of all statistical analyses was set at $p < 0.05$.