

Is a Citric Acid Meal Useful for Increasing Accuracy of the ¹³C-Urea Breath Test in Asian Populations?

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See "Effect of Citric Acid on Accuracy of ¹³C-Urea Breath Test after *Helicobacter pylori* Eradication Therapy in a Region with a High Prevalence of Atrophic Gastritis" by Yong Hwan Kwon, et al. on page 506, Vol. 13, No. 5, 2019

Tests for *Helicobacter pylori* infection are divided into invasive and noninvasive methods. Among them, ¹³C-urea breath test (¹³C-UBT) is one of the noninvasive tests used to diagnose *H. pylori* infection and verify eradication after treatment.¹ In 1987, ¹³C-UBT was reported as a method to detect *H. pylori* infection.¹ The method of UBT is as follows: The patient blows before and after administering a tablet of urea labeled with the nonradioactive stable isotope ¹³C.¹ Urea is hydrolyzed by *H. pylori* urease, thus if the patient is infected *H. pylori*, labeled carbon dioxide (¹³CO₂) is detected in breath samples. Additionally, it has been shown that sensitivity and specificity of ¹³C-UBT are higher than 90% for identifying *H. pylori* infection.² Thus, ¹³C-UBT is simple as well as highly accurate, and this test is regarded as an established test in detecting *H. pylori*.

However, there are considerable limitations to ¹³C-UBT, such as being cautious with interpretation of results. Recently used proton pump inhibitors, antibiotics, and bismuth salts may reduce the number of gastric bacteria which may affect the ¹³C-UBT results as false negative.³ Bleeding peptic ulcer and atrophic gastritis (AG) with or without intestinal metaplasia (IM) may also decrease sensitivity of ¹³C-UBT.³ On the contrary, other urease-producing bacteria (*Streptococcus*, *Staphylococcus*, *Gardnerella*, *Lactococcus*, and *Enterococcus*) reside in the stomach, and may represent false positive results of ¹³C-UBT.⁴ Additionally, interpretation of the gray zone, of which the exact range is not defined, remains a controversial issue.

Various attempts have been suggested to overcome these limitations and to improve diagnostic accuracy. These modifications have contained dosage of labeled urea used, the collection time of breath samples, testing with or without fasting, type of

test meal, cutoff value and equipment for measuring isotope enrichment.² Numerous studies associated with the UBT technique and its methodology have been revealed. However, no standardized method of UBT has been confirmed.

In terms of the test meal, it remains debatable if a test meal is required for ¹³C-UBT, or which test meal is superior. Theoretically, test meals were introduced to increase accuracy of UBT by delaying gastric emptying and maximizing distribution of the substrate within the stomach thereby enhancing the contact area and time between the bacteria and the substrate.¹ Various nutrient meals containing carbohydrates, protein, and fats have been applied,² and citric acid is a preferred test meal because it decreases antral motility and relaxes gastric fundus by reducing duodenal pH.⁵ Thus, protocols in the United States and Europe incorporate citric acid meal in ¹³C-UBT.⁶ However, the Asian protocol does not necessarily recommend use of citric acid meal. In this regard, this article investigated the effect of citric acid meal on diagnostic accuracy of ¹³C-UBT in Asian populations.

In this issue of *Gut and Liver*, Kwon *et al.*⁷ reported that the rate of false positivity of the citric acid group is higher than the control group in ¹³C-UBT in Korea where there exists high prevalence of AG or IM. This prospective study conducted ¹³C-UBT for patients who received *H. pylori* eradication therapy, with one group administering a citric acid solution (citric acid 4 g in 200 mL of water with 50 g glucose polymer, n=562) and the other group administering a glucose meal without citric acid (n=645). In terms of ¹³C-UBT value, mean ¹³C-UBT value of the citric acid group was significantly higher than the control group (p<0.001). However, when compared with the histology, accuracy (83.3% vs 87.7%), specificity (81.3% vs 88.2%), and positive predictive

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value (55.0% vs 62.5%) of ^{13}C -UBT for the citric acid group were lower than those of the control group, and sensitivity (91.7% vs 90.9%) and negative predictive value (97.5% vs 97.8%) of ^{13}C -UBT were similar between the two groups.

Several studies have investigated the efficacy of citric acid meal in UBT by a direct comparison with or without citric acid. Most of the studies have been published on the Western population. Graham *et al.*,⁸ one of the representative studies, revealed that citric acid at 1, 2, or 4 g developed significant increases in breath $^{13}\text{CO}_2$ activity in comparison with commercial pudding ($p < 0.05$). However, few studies have been conducted assessing citric acid in ^{13}C -UBT on Asian populations. Interestingly, in accordance with this study, Wong *et al.*⁹ also reported that ^{13}C -UBT protocol without citric acid demonstrated highly reliable data similar to ^{13}C -UBT protocol with citric acid in the Chinese population. Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 90% or more in both groups. Reasons for debatable results are unclear. However, it may be associated with difference in distribution, delivery and emptying of ^{13}C -urea,⁹ and ethnic differences in gastric emptying according to race.¹⁰ Additionally, although this study could not demonstrate it, it is considered that moderate and severe AG and IM also influenced the difference in results.

There are several limitations in this study. First, there was no validation study of ^{13}C -UBT using citric acid meal for the Korean population. Although the authors used the U.S. Standard Protocol, the standard may not be suitable for Koreans. Second, the gold standard method compared to ^{13}C -UBT was only histology, and it is well-known that histology is susceptible to sampling error due to inconsistent *H. pylori* colonization in the gastric mucosa. Thus, some studies have conducted more than one *H. pylori* test and have defined *H. pylori* positive if both tests are positive.⁹ Finally, the number of patients accepted histology is only 9.9% of all enrolled patients, which may have affected the relatively low accuracy of ^{13}C -UBT. Studies such as this study have not been conducted in recent years, and it is of academic value in that this is the first study to examine the efficacy of citric acid meal on ^{13}C -UBT in Korean populations. Further well-designed prospective studies are required to elevate diagnostic accuracy of ^{13}C -UBT in countries with high prevalence of AG or IM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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