Salivary pepsin to diagnose GORD?

Nimish Vakil

GORD has been defined by international consensus based on symptoms of heartburn and regurgitation.[1] While this definition is useful for patients with the typical reflux syndrome, these symptoms may not be present in patients with extra-oesophageal GORD. The limitations of pH testing and endoscopy were highlighted in a recent study that demonstrated that each failed to identify approximately 30% of patients with proven GORD.[2] A test that establishes a diagnosis of GORD at low cost with minimal intervention would have great utility. The presence of pepsin in saliva or sputum has been proposed as a surrogate marker for reflux disease, albeit one that tells us nothing about a causal relationship between reflux and symptoms.

Pepsin may be detected in sputum or saliva by enzymatic or immunological tests.[3] Enzymatic tests have several limitations and are difficult to obtain and standardise in practice settings. Attention has therefore focused on immunologic assays with polyclonal and monoclonal antibodies that have been patented and commercialised.[3]

The question for the clinician is whether salivary pepsin determination is a diagnostic tool that is helpful in clinical practice. For a diagnostic test to be useful in clinical practice, we should be able to demonstrate that the test not only improves our accuracy but that it results in a treatment decision that changes patient outcomes.[4] Tests that improve accuracy modestly but don't change management or outcomes have little use in the clinic.

Hayat *et al*[5] are to be congratulated on their recent study, which addresses many unanswered questions about salivary pepsin measurements. This was a case control study using pH impedance as the reference standard. From the standpoint of a diagnostic test evaluation, a few limitations of the study design should be recognised. The reference standard itself is in need of further validation with outcome studies. The test population (patients with a primary symptom of heartburn) is not the population in which the test is likely to be used (extra-oesophageal GERD or children).

The results of this study offer several insights into the use of salivary pepsin assays in clinical practice and suggest avenues for further research. The first finding is that pepsin measurement in saliva is not a traditional near-patient test, performed and read within minutes in a doctor's office using a single sample. Three samples are recommended, and the test is generally mailed to a laboratory. The second finding is that apparently normal subjects may have detectable pepsin in saliva and, therefore, measurement of pepsin concentration is essential for a diagnosis.

Reflux disease is often postulated as the cause for hoarseness, cough, throat irritation, recurrent sinusitis and globus. Gastroenterologists around the world are confronted with the challenge of patients who have been told that their symptoms are caused by reflux disease, but show little or no response to acid inhibition, and have no abnormalities at endoscopy. Clinicians who treat children face similar difficulties and also deal with recurrent ear infections, feeding difficulties and other symptoms that are attributed to reflux disease.

Case control studies are known to overestimate sensitivity, specificity and predictive values because the prevalence of the disease is likely to be much higher than in a cross-sectional study.[6] To determine if salivary testing can help us in the clinical setting, we need to calculate post-test probabilities from the data presented by Hayat *et al*, which will help us determine if the test results are likely to change our management decisions and under what conditions.[5 7 8] Take the example of a patient who has chronic cough but no symptoms of traditional reflux disease (heartburn or regurgitation) and reports some improvement in cough after a trial of acid inhibition. The patient has been referred to gastroenterology for evaluation of 'refractoriness' to acid inhibitory therapy. Given some response to acid inhibition, our pretest estimate that the patient has GORD might be quite high at 50%, given a reported prevalence of silent GERD of 8–41% in this population.[9] We would like to improve our diagnostic uncertainty using the salivary pepsin assay, and we would like to be able to tell the patient and the referring physician with 90% probability whether reflux disease is present or not. Table 1 is a calculation of post-test probabilities from the data of Hayat *et* al,[5] and shows us if we can achieve this goal. We can see that only one cut-off value (a pepsin concentration greater than 210 ng/mL) increases the probability of having GORD from 50% to more than 90%, but only 44% of patients with GORD will have pepsin values that are this high. What if the test was negative? A negative test using this threshold decreases the pretest probability of having GORD from 50% to 36%, but this means that a patient with a negative test still has a 1 in 3 of having GORD based on our pretest probability.

Consider a low pretest probability situation such as a patient with ill-defined upper abdominal symptoms, without heartburn or regurgitation, referred for evaluation for possible GORD. Based on data from one recent study, we estimate that the pretest probability of GORD is low, approximately 5%.[10] Table 2 shows the post-test probabilities if we were to use the salivary pepsin assay as our diagnostic test to determine if the patient has GORD. A single positive test value that is greater than 210 ng/mL increases our post-test probability from 5% to 56%, but 56% of patients with established GORD will not have a positive test using this cut-off. A negative test with this cut-off reduces our already low pretest probability of 5% by 2%. In a low prevalence situation, regardless of the

Table 1 Post-test probabilities in patients with GORD and hypersensitive oesophagus based on a high pretest probability of 50% (data from table 2 in reference 5)

Test result	% of GORD subjects who have this test characteristic	Post-test probability of disease given a positive test (%)	Post-test probability of disease given a negative test (%)
1 sample >16 ng/mL	66/84 (78.6)	69	24
1 sample >50 ng/mL	59/84 (70.2)	72	28
1 sample >100 ng/mL	47/84 (56)	79	34
1 sample >150 ng/mL	40/84 (47.6)	84	36
1 sample >210 ng/mL	37/84 (44)	96	36

Correspondence to Professor Nimish Vakil, University of Wisconsin School of Medicine, Aurora Summit Hospital, 36500 Aurora Drive, Summit, Madison, WI 53066, USA; nvakil@wisc.edu

Table 2 Post-test probabilities in patients with GORD and hypersensitive oesophagus based on a low pretest probability of 5% (data from table 2 in reference 5)

Test result	% of GORD subjects who have this test characteristic	Post-test probability of disease given a positive test	Post-test probability of disease given a negative test
1 sample >16 ng/mL	66/84 (78.6)	10	2
1 sample >50 ng/mL	59/84 (70.2)	12	2
1 sample >100 ng/mL	47/84 (56)	17	3
1 sample >150 ng/mL	40/84 (47.6)	22	3
1 sample >210 ng/mL	37/84 (44)	57	3

threshold value of pepsin used for the assay or the result (positive or negative), the result would probably not increase our confidence in the diagnosis enough for us to alter or prescribe treatment. The need for diagnostic certainty changes with the proposed treatment. For example, we may require a much higher diagnostic threshold to refer the patient for antireflux surgery than we might need to prescribe acid inhibitory therapy.

The pepsin test has significant limitations, as do endoscopy and pH testing for a diagnosis of reflux disease. Whether it has a role in the diagnostic hierarchy for reflux disease depends on studies that are yet to be performed. The pepsin assay will need to be tested in a cross-sectional study in the target population in which it is to be eventually used (children and adults with extra-oesophageal GERD), and we will need to show that the results change therapy and improve outcomes before we can recommend the routine use of this test in clinical practice.

Competing interests Consultant: Astra Zeneca, Takeda, Ironwood, Otsuka, Respiratory Technologies.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Vakil N. *Gut* 2015;**64**:361–362.

Received 3 June 2014
Revised 25 June 2014
Accepted 3 July 2014
Published Online First 23 July 2014

► http://dx.doi.org/10.1136/gutjnl-2014-307049

Gut 2015;**64**:361–362.
doi:10.1136/gutjnl-2014-307485

REFERENCES

1 Vakil N, van Zanten SV, Kahrilas P, *et al*. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–20.
2 Dent J, Vakil N, Jones R, *et al*. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. *Gut* 2010;59:714–21.
3 Samuels T, Johnston N. Pepsin as a marker of extraesophageal reflux. *Ann Otol Rhinol Laryngol* 2010;119:203–8.
4 Center for Evidence based Medicine Toronto. Diagnosis Critical Appraisal Worksheet. http://ktclearinghouse.ca/cebm/teaching/worksheets/diagnosis (accessed 1 Jun 2014).
5 Hayat JO, Gabieta-Somnez S, Yazaki E, *et al*. Pepsin in saliva for the diagnosis of gastro-oesophageal reflux disease. *Gut* 2015;64:373–80.
6 Naeger D, Kohi M, Webb E, *et al*. Correctly using sensitivity, specificity and predictive values in clinical practice: How to avoid common pitfalls. *AJR* 2013;200:W566–70.
7 Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ* 2004;329:168–9.
8 Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1994;271:389–91.
9 Irwin R. Chronic cough due to gastro-esophageal reflux disease. *Chest* 2006;129:80S–94S.
10 Vakil N, Wernersson B, Ohlsson L, *et al*. Prevalence of gastro-oesophageal reflux disease with upper gastrointestinal symptoms without heartburn and regurgitation. *United European Gastroenterol J* 2014;2:173–8.