Dyspepsia

Does delayed gastric emptying really cause symptoms in functional dyspepsia?

M Camilleri

When the glove does fit, you should not acquit

In this month's issue of *Gut*, Talley and colleagues¹ report an interesting study on the opportunistic use of a database, acquired during the baseline period of four multicentre therapeutic trials, to explore the associations between gastric emptying and symptoms in functional dyspepsia (see page 933). This was not a prospective study designed to specifically address the question posed in the title of this commentary. Before analysing the information from this study, it is opportune to review three concepts that reflect recent papers from the literature.

Firstly, *combinations of symptoms are associated with abnormal gastric functions*. In a scholarly review, Tack *et al* surmised that 40–50% of patients with dyspepsia had impaired gastric accommodation after meal ingestion, 34–66% had gastric hypersensitivity, and 23–59% had delayed gastric emptying.² Moreover, delayed gastric emptying was associated with early satiety, nausea, vomiting and fullness; impaired gastric accommodation with early satiety and fullness, and with weight loss in two of four studies; and visceral hypersensitivity with pain, belching, and weight loss in one of four studies.²

Secondly, *symptoms of dyspepsia occur in combination, and they have already been shown to be associated with delayed gastric emptying*. A factor analysis of the clinical experience of more than 800 patients at one centre³ revealed four main factors in patients with dyspepsia: factor 1 of nausea, vomiting, early satiety, and weight loss, and associated with younger age, female sex, and sickness behaviour; factor 2 of postprandial fullness and bloating; factor 3 of pain symptoms and several psychosocial dimensions; and factor 4 of belching unrelated to psychosocial dimensions. Factors 1 and 2 were associated with delayed gastric emptying, and factors 3 and 4 were associated with gastric hypersensitivity to mechanical distension of the stomach. Similarly, in a large US epidemiological study,⁴ factor analysis identified four symptom groupings

among those with upper gastrointestinal symptoms: heartburn/regurgitation; nausea/vomiting; bloating/abdominal pain; and early satiety/loss of appetite.

Thirdly, while other factors (for example, hypersensitivity and somatisation⁵) also contribute to the development of symptoms, combinations of abnormal gastric motor functions with certain demographic factors (age and weight) accounted for a significant 50% of the variance in the post-meal symptoms^{6,7} in single centre studies using validated and optimised methods. Gastric emptying, accelerated at one hour or delayed at four hours, was among the factors that contributed to reported symptoms of dyspepsia⁶ or development of symptoms on meal challenge.⁷ The cause and effect relationship between physiology and symptoms is confirmed by pharmacological perturbations⁷ that showed gastric emptying and volume were significant factors in the final model to explain symptoms. Regression analysis showed that fasting gastric volume was a significant predictor of intra- and postprandial bloating, and there was significant (negative) association between gastric emptying and fullness score, and significant (positive) association with hunger score 30 minutes after a standardised meal under laboratory conditions.

The data in the paper by Talley and colleagues¹ in this issue of *Gut* actually show significant ($p < 0.002$ for each) associations for gastric emptying with individual symptoms of early satiety, postprandial fullness, bloating, nausea, and epigastric pain (see table 2). In a full multiple predictor model, postprandial fullness was a significant factor associated with delayed gastric emptying; other individual symptoms were not significant. The authors downplay the significance of the association with postprandial fullness on multivariate analysis and paradoxically question its clinical relevance.

Before accepting their conclusion, it is essential for the reader to be aware of the limitations and potential pitfalls of the study: a cohort of diverse patients

accumulated from four different trials performed in 67 centres in primary, secondary, or tertiary care; 25–33% patient dropout from the original cohort; heterogeneity of “functional dyspepsia” with fairly lax inclusion criteria (for example, a severity score of 2/4 abdominal pain and mild non-predominant heartburn would qualify as functional dyspepsia for this study); assessment of symptoms based on diaries in response to non-standard meals over two weeks; use of a low fat meal to measure gastric emptying; lack of consideration of accelerated gastric emptying at one hour as a potential factor in the relationship of gastric emptying and symptoms; and lack of any post-treatment data to determine whether change in gastric emptying was associated with change in symptoms. Given the limitations of a study that was not designed to prospectively assess the cause and effect relationship between gastric emptying and symptoms, one is amazed that any significant associations were identified on univariate or the more stringent multivariate analysis. Thus the significant associations of gastric emptying with early satiety, postprandial fullness (uni- and multivariate), bloating, nausea, and epigastric pain suggest that the cup is half full rather than half empty!

What is the important take home message from this study? Dyspepsia is not a single symptom. Therefore, associations should be sought with symptom combinations that factor together on clinical and epidemiological analyses.^{3,4} Moreover, the multivariate analysis results obtained for individual symptoms did not account for the fact that, when symptoms are intrinsically associated or related to fullness (such as early satiety or nausea), the model may not be able to demonstrate that they add significantly to the variance in gastric emptying or vice versa. Thus one should not interpret negatively the fact that the other *individual* symptoms do not contribute additionally to the variance of fullness (or “fall out”) in the multivariate analysis. Dismissing those significant associations would be analogous to disregarding the separate contributions of central obesity, serum cholesterol and triglycerides, and hypertension as independent risk factors for angina, as they “fall out” in a multivariate analysis that considers the closely associated hyperglycaemia in type II diabetes mellitus.

In summary, opportunistic studies of associations do not negate the overwhelming experimental evidence cited above, including studies that evaluate cause and effect through perturbations of gastric function. Accelerated emptying at one hour and delayed emptying at

four hours, as well as fasting gastric volume, are significant determinants of symptoms.^{6,7} To misquote a recent statement in a US Court of law: "When the glove *does* fit, you should *not* acquit."

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T cells

A ticket to the gut for thymic T cells

W Falk

The intestinal epithelium is colonised by, among other cells, normal T helper and cytotoxic T cells which obtain their antigen experience in the gut associated lymphatics after migration from the thymus. New evidence suggests a CD8 positive T cell that directly migrates to the intestinal epithelium increasing the role of the thymus in shaping intestinal immunity

A normal splenic T cell would be abhorred should it get close to the intestinal epithelium. Instead of its usual rather sterile environment, it would be bathed in an ocean of usually non-pathogenic microbial and food derived antigens never seen during its passage through the educating thymus. It would get ready to become very excited. However, although the number of T cells in the mouse small intestine is approximately 50% of those residing in all lymphoid organs,^{1,2} there is peace. This peace is the result of a balanced presence of activated protecting T cells and activated controlling T cells.

The gut represents a unique dilemma for the immune system. It has the largest surface of the body harbouring numerous species of microorganisms. It is thus challenged with the task to be a barrier to the outside world and also to be the organ for most effective absorptive and secretory functions. To be able to accomplish this task, mammals have evolved a special highly regulated protective immune system comprising T cells which are on constant alert, as is evident from their activated phenotype. Broadly, the gut harbours three categories of T cells. Those in the gut associated lymphoid tissues are very similar to T cells found in peripheral lymphoid organs. Another population of T cells is scattered between other

different cell types in the lamina propria. Their education follows the standard path of meeting their antigens presented by antigen presenting cells in the mesenteric lymph nodes and trafficking back to the lamina propria.³

The third category is a very peculiar one, intraepithelial lymphocytes (IEL). They sit on the luminal side of the basement membrane, singly scattered between and protected by intestinal epithelial cells, and are presumably the first T cells to encounter antigens. IEL comprise T cells carrying the $\alpha\beta$ T cell receptor (TCR) or the $\gamma\delta$ TCR, with their ratio depending on the species. Further subdivision may be made between conventional T cells characterised by a $\alpha\beta$ TCR and coexpression of CD4 or CD8 $\alpha\beta$ and non-conventional T cells which express either $\alpha\beta$ TCRs or $\gamma\delta$ TCRs but no CD4 or CD8 $\alpha\beta$ (double negative (DN)).⁴ Such cells are residents of the intestinal epithelium. A proportion of these cells express the CD8 $\alpha\alpha$ homodimer which, however, can also be detected on double positive conventional IEL together with CD4 or CD8 $\alpha\beta$. Non-conventional T cells are rarely found in tissues other than the intestinal epithelial layer and they are also characterised by a surprisingly high degree of autoreactivity. It was reported, using transgenic models, that CD8 $\alpha\alpha$ $\alpha\beta$ TCR IEL can be found in animals that

efficiently delete their CD8 $\alpha\beta$ cells in the thymus by negative selection.² This and other findings have led to the search for extrathymic sites allowing differentiation into gut specific T cells. In mice, small aggregations of haematopoietic cells were found in the lamina propria close to crypts which were named cryptopatches (CP).⁵ In elegant studies it was shown however that CP are most likely not the sites for extrathymic sources of IEL and that most, if not all, gut IEL originate from the thymus. Some recombinase activating gene activity was found in the absence of a functional thymus^{6,7} indicating that, under special conditions, extrathymic maturation of T cells can still occur in the mesenteric lymph nodes or Peyer's patches which is heavily skewed to generation of $\gamma\delta$ TCR T cells.

These $\gamma\delta$ TCR T cells do not recognise peptide antigens and leave the thymus at a DN stage to later colonise predominantly epithelial surfaces. They can be rapidly activated by some non-peptide antigens and self stress antigens, such as the human MICA and MICB molecules.^{8,9} Their capacity to secrete growth factors like KGF has also led to the assumption that they might be involved in repair of damaged tissue.¹⁰ Another fascinating feature was recently shown. Human V δ 2 expressing cells through activation were able to present peptide antigens to naïve $\alpha\beta$ TCR T cells, thus bridging innate and acquired immunity.¹¹ Whether a similar function is also true for IEL $\gamma\delta$ TCR T cells remains to be shown.

Non-conventional $\alpha\beta$ TCR CD8 $\alpha\alpha$ T cells are likely to be a consequence of "agonist" selection by self antigens in the thymus (reviewed and discussed by Cheroutre¹²). It is proposed that these T cells interact very strongly with self antigens at a DN stage and so acquire the activated phenotype. These cells can then express the mucosal integrin $\alpha_E\beta_7$ and in this way be guided to the intestinal epithelium where the binding partner E-cadherin is abundantly expressed. Such cells do not damage