Alcohol and gastric motility: pathophysiological and therapeutic implications

Zorisadday Gonzalez ,[1] Daniel Herlihy,[1] Cong Phan,[2] Jesus Diaz,[3] Kenneth Dominguez,[3] Richard McCallum[1]

[1]Gastroenterology, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA
[2]Paul L Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas, USA
[3]Nuclear Medicine, University Medical Center of El Paso, El Paso, Texas, USA

Correspondence to
Dr Zorisadday Gonzalez, Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79905-2709, USA; zgonzalez@phs.org

Accepted 29 April 2020
Published Online First 23 May 2020

ABSTRACT

Alcohol has been associated with alterations in gastric motility. The literature identifies that various factors play a role in alcohol's effect on gastric emptying including differences in alcohol concentration, osmolarity, caloric content, amino acids as well as different processing techniques (fermentation vs distillation). Additionally, chronic alcohol consumption has been shown to alter the myenteric nitrergic system resulting in impaired gastrointestinal motor function, and it also has an inhibitory effect on the release of several neurotransmitters that play a key role in gastrointestinal motility, including acetylcholine. Whether social or limited intake of alcohol could have a therapeutic role has not been apparent. Serendipitously, we have identified a therapeutic role for alcohol with a meal in the entity of dumping syndrome (DS) where there is postprandial rapid emptying of voluminous and hyperosmolar gastric contents into the small bowel. In the clinical setting of DS attributed to impaired vagal nerve function, there was normalization of gastric emptying and resolution of accompanying symptoms when drinking a glass of wine before and during meals. We propose that alcohol's anticholinergic effect was augmented in the setting of vagal nerve denervation resulting in slowing of gastric emptying and in alleviation of symptoms of early DS. This review article provides an in-depth analysis of the published literature on alcohol and gastric motility focusing on the accumulated knowledge that may have clinical application and relevance.

CASE PRESENTATION

A 65 year old female presented with abdominal pain, bloating, nausea, vomiting and diarrhea occurring immediately after meals. These symptoms suggestive of dumping syndrome (DS) started a few years following a Nissen fundoplication for severe gastroesophageal reflux disease. A 4-hour gastric emptying study using the standardized isotope-labeled Eggbeaters® meal (255 kcal) showed 71% emptying at 1 hour meeting criteria for DS of >65% emptying by 1 hour accompanied by early symptoms of DS (figure 1). Given her previous history of Nissen fundoplication, it was hypothesized that her symptoms of DS were most likely caused by vagal nerve injury during this surgery. Over multiple clinic visits she was treated with dietary modification, dicyclomine and glycopyrronium bromide without success and with side effects of dry mouth, dry eyes and blurred vision. The patient noticed that when she drank an 8-ounce glass of red or white wine, specifically before eating and continuing throughout the meal, her DS symptoms were eliminated. We subsequently repeated the gastric emptying study using the same nuclear medicine methodology with the patient drinking an 8-ounce glass of wine in her usual fashion. The patient drank a glass of Bogle Merlot, a wine she frequently drank at home, which is 14.5% alcohol with no tannins or other additives noted on the label. This resulted in complete normalization of gastric emptying, specifically 23% emptied at 1 hour without accompanying symptoms, compared with 71% emptying at baseline (see detailed results of gastric emptying studies in table 1 and figures 1 and 2). We theorize that, in the clinical setting of DS attributed to impaired vagal nerve function, our patient experienced normalization of gastric emptying, along with normalization of accompanying symptoms of DS when drinking a glass of wine. We propose that the alcohol's anticholinergic effect was augmented in the setting of vagal nerve denervation, resulting in slowing of gastric emptying with subsequent alleviation of symptoms of early DS. In this review, we attempt to provide an assessment of the published literature on the acute and chronic effects of alcohol on gastric motility, concentrating on existing accumulated knowledge felt to have the most practical clinical relevance and application, while attempting to emphasize a new therapeutic direction we have recently observed.

In view of this surprising outcome, we have endeavored to hypothesize several possible explanations for the normalization of gastric emptying after a glass of wine. First, the alcohol concentration, as well as the type and composition of alcoholic beverages are important factors that affect stomach motility. In general, alcoholic drinks can be categorized into three different types depending on the alcohol content and concentration: beer (~4%–7%), wine (~10%–13%) and spirits (~30%–50%).[1 2] Beverages with higher alcohol concentrations of >15% have been shown to delay gastric

Linked

► http://dx.doi.org/10.1136/jim-2020-001436

Check for updates

To cite: Gonzalez Z, Herlihy D, Phan C, *et al*. *J Investig Med* 2020;**68**:965–971.

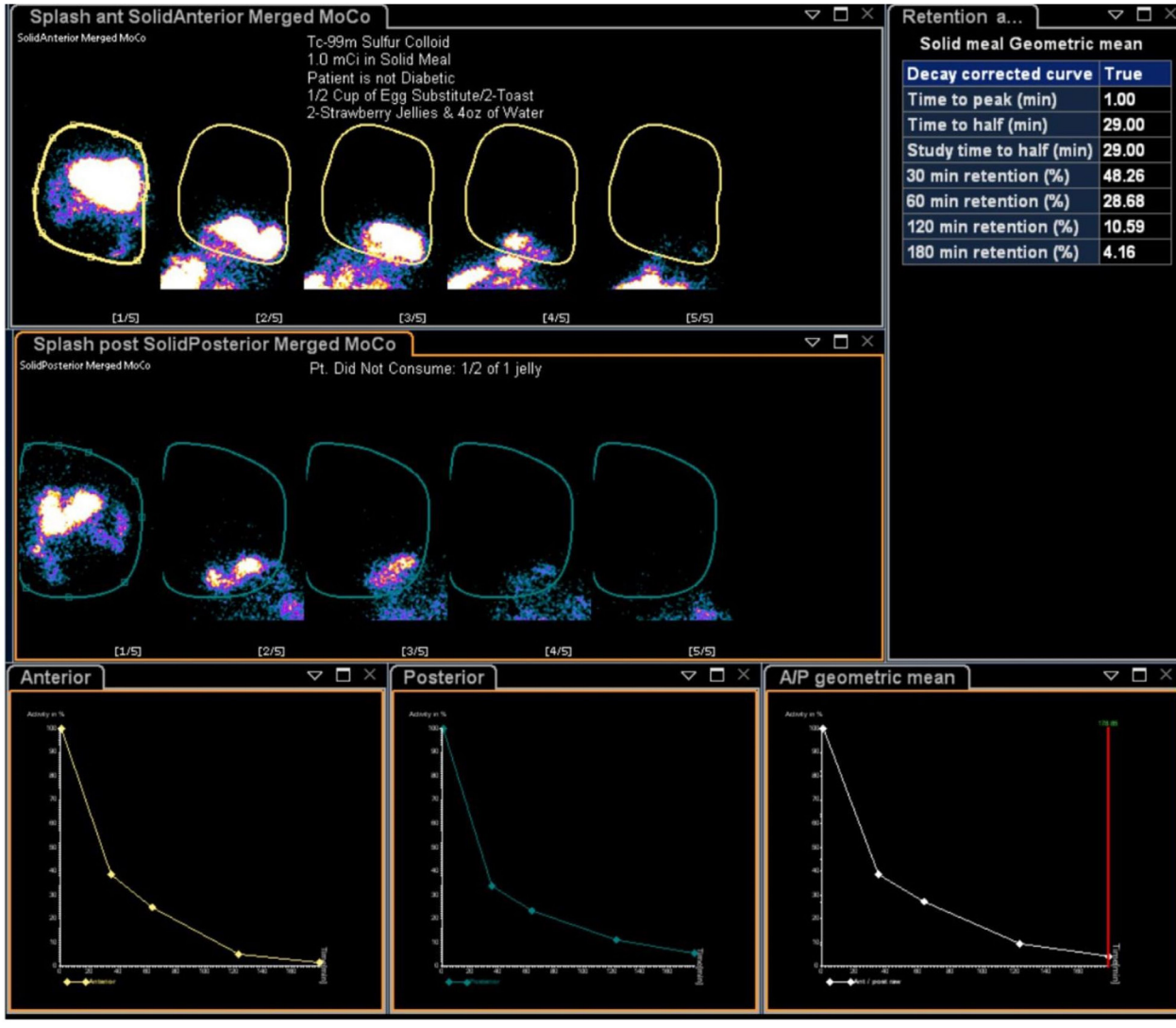

Figure 1 A 4-hour gastric emptying study using an isotope-labeled Eggbeater® meal (255 kcal) showed 71% emptying at 1 hour, meeting criteria for DS of >65% emptying at 1 hour. At 2 hours, the study showed 89% emptying, meeting criteria for DS of >80% emptying at 2 hours.

emptying and inhibit peristalsis more than those with a lower alcohol concentration.[3–5] In a study by Lenz *et al*, emptying times were noted to be similar with 5% ethanol, 5% control and water.[6] Additionally, a progressive slowing of gastric emptying times was noted for beverages with a higher alcohol content: 34 min for 5% ethanol, 42 min for 10% ethanol and 87 min for 20% ethanol. Our patient typically enjoyed wine of 14.5% alcohol content with meals.

Table 1 Gastric emptying studies

	30 min	60 min	120 min
Baseline study (% emptied)	52%	71%	89%
With wine (% emptied)	12%	23%	55%
Normal (% emptied)	<30%	<65%	<80%

This table summarizes the gastric emptying results expressed as % isotope emptied from the stomach using the same isotope-labeled egg beater meal on both occasions. There is a baseline study as well as a repeat study on a different day while drinking a glass of wine before and during the same meal ingested over a 10 min timeframe. Normal criteria for postprandial gastric emptying are included for 30, 60 and 120 min.

Second, another mechanism by which alcohol may affect gastrointestinal (GI) motility is that alcoholic beverages also contain different non-alcoholic elements that exert different physiological effects on gastric emptying. For example, hundreds of compounds, additives, impurities, flavor and aromatic ingredients have been identified in different alcoholic beverages, including in wine.[7 8] Some of these ingredients are calorically and osmotically active and may be responsible for some of the inhibitory effects imposed on gastric emptying such as added glucose, amines and L-amino acids.[9]

Third, alcoholic beverages differ by type and concentration and they vary by how they are produced—either by fermentation or distillation or both—and different processing techniques also result in distinctive effects on gut motility. For example, beer is produced by fermentation of high-carbohydrate foods, wine is produced by fermentation

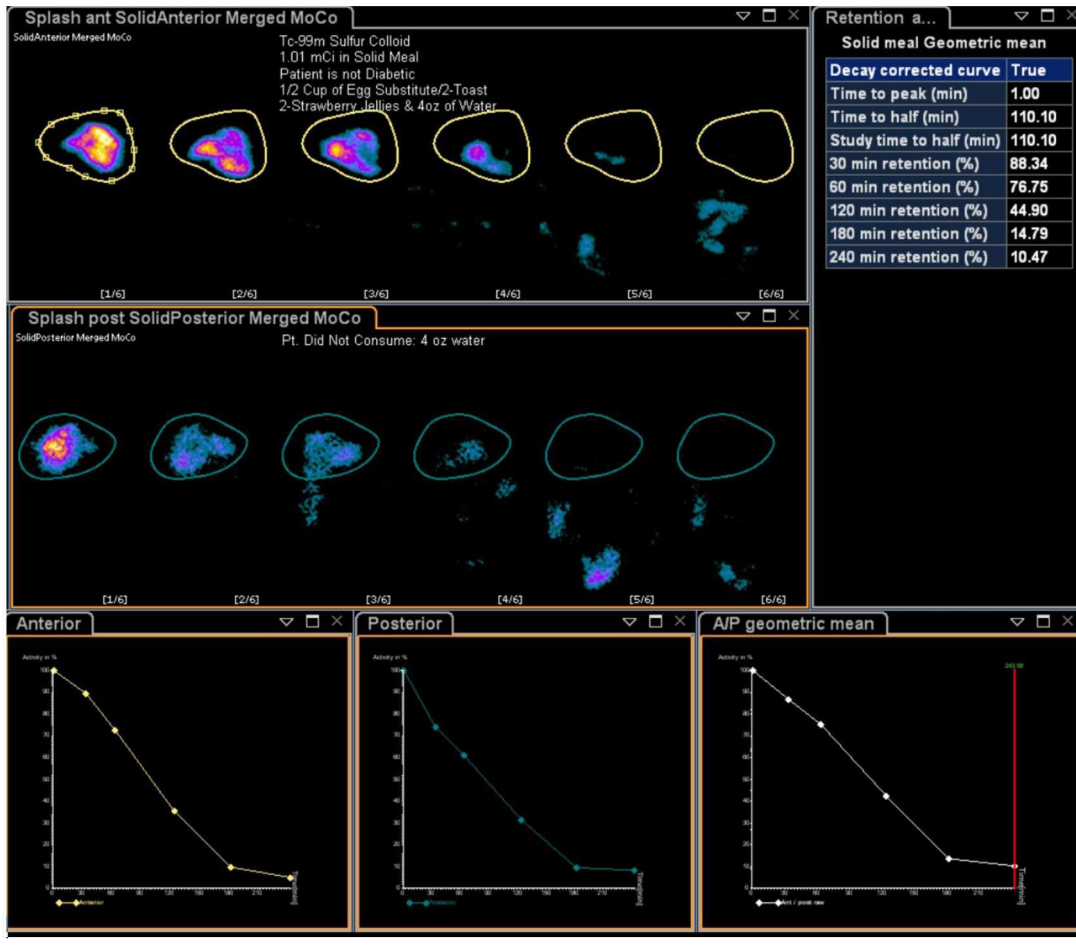

Figure 2 Repeat 4-hour gastric emptying study with the patient drinking a glass of red wine right before and during ingestion of the meal over approximately 10 minutes resulted in complete normalization of gastric emptying, specifically 23% emptying at 1 hour and 55% emptying at 2 hours—along with resolution of accompanying symptoms of dumping syndrome.

of grapes, and spirits are produced by distillation of ethanol after fermentation.[2] These different processing techniques have been proposed to play a role in the inhibitory effects that alcohol has on gut motility. Fermentation alone has been shown to stimulate the release of gastrin which promotes gastric motility thereby accelerating gastric emptying.[9] Fermentation followed by distillation results in loss of this stimulatory effect because the latter distillation process leads to the loss of this stimulatory gastrin effect.

A fourth possible mechanism that might explain the impaired effect that ethanol has on gastric motility is its inhibitory effect on the release of several neurotransmitters in the GI tract, including that of acetylcholine.[10–12] Acetylcholine is a neurotransmitter that plays a key role in promoting GI motility by acting on the GI smooth muscle. Less acetylcholine reduces smooth muscle contractions which results in decreased motility of gastric and small intestinal muscle.[13] Reduced smooth muscle contractions in the stomach consequently results in a less effective 'peristaltic pump' in the antrum of the stomach that helps drive chyme into the small intestine. This is relevant to the patient we described who had an accidental vagal nerve damage during a Nissen fundoplication for gastroesophageal reflux, and therefore had a decreased cholinergic drive. In this unique setting, the addition of a further anticholinergic effect by alcohol's mechanism related to a single glass of wine of 14.5% alcohol concentration could have profoundly slowed gastric emptying and alleviated early symptoms of dumping resulting from rapid emptying of food from the stomach into the small intestine.

REVIEW ON THE EFFECT OF ALCOHOL ON GASTRIC MOTILITY

The ramifications of chronic alcohol consumption on the digestive tract have been well studied, and its association with various GI pathologies well established, which include toxic consequences on the esophagus, liver and pancreas.[14 15] However, not as much attention has been paid to the different effects that alcohol has on gastric motility and gastric emptying (Box 1). A literature review on this subject revealed scant and inconsistent results with some studies noting accelerated gastric emptying,[16] others describing delayed emptying in both humans[17 18] and animals[19] and others showing no real difference (Box 2).[20 21] Contributing factors to the confounding interpretation of these studies could be attributed to differences in experimental techniques including different test meal variables

Box 1 Factors in alcohol that exert different effects on gastric emptying

Factors in alcohol that exert different effects on gastric emptying

Osmolarity

- Higher osmolarity in alcoholic beverages has been found to be more inhibitory of gastric emptying.[22]

Concentrations

- Higher alcohol concentrations over 15% have been shown to be more inhibitory of gastric motility, whereas beverages with a lower alcohol concentration accelerate gastric emptying.
- Higher alcohol concentrations (ie, pure ethanol) does not cause release of gastrin whereas alcoholic beverages with a lower ethanol content (beer and wine) are strong stimulants of gastrin release and gastric acid secretion.[55] Of note, gastric acid secretion is influenced by several factors including pH, osmotic activity, caloric value and volume of the infusate. Thus, the fact that beverages with a lower alcohol content stimulate the release of gastrin, whereas pure alcohol does not suggests that this response is mostly mediated by non-alcoholic components.[55]

Different processing techniques

- Fermentation alone (ie, wine, beer) has been shown to promote slower gastric emptying compared with distillation techniques.

Different non-alcoholic elements may exert different physiological effects on gastric emptying

- Additives, impurities, glucose, amines, L-amino acids, flavor and aromatic ingredients.

Inhibitory effect on the release of neurotransmitters involved in GI motility

- Acetylcholine(ethanol has an inhibitory effect on the release of acetylcholine; less acetylcholine reduces GI motility).

as well as differences in alcohol osmolarity[22] volume and energy content,[23] and hydrogen ion concentrations[24]—all of which have been shown to delay gastric emptying . Certain amino acids contained in various alcoholic beverages have also been shown to delay gastric emptying.[25–29] Moreover,

Box 2 Summary of controversies regarding gastric motility and alcohol consumption

Controversies on effects of alcohol on gastric motility:

Delayed gastric emptying.[16]

Accelerated gastric emptying.[17–19]

No significant difference.[20 21]

Contributing factors to the confounding interpretation of different studies could be related to differences in experimental techniques (ie, different test meal variables as well as differences in alcohol osmolarity, energy content, and hydrogen ion concentrations) — all of which have been shown to delay gastric emptying.

both solids and liquids with a greater weight and kilocalorie content are associated with longer emptying times,[30] and higher osmolarity solutions have been shown to be more inhibitory to gastric emptying.[22] Contrary to this, some studies have shown that the inhibitory effects of red wine, beer and ethanol on gastric emptying does not depend on the caloric content of meals and is not dose-dependent when given in concentrations of 10% or less.[2 4] . Furthermore, in the aforementioned studies showing that ethanol accelerates gastric emptying,[4 16] the control solution was adjusted to match that of the alcohol-containing beverages by adding hyperosmolar glucose and/or NaCl in order to delay gastric emptying. Another possible explanation as to why these studies concluded that ethanol accelerates gastric emptying is that alcohol has a low osmotic pressure and a high diffusion capacity allowing it to easily pass through the GI barrier. Also, the presence of alcohol dehydrogenase in the gastric mucosa aids in its initial metabolism.[2 3 31] These unique features of alcohol can be misleading as one cannot rely on blood levels of alcohol to indicate reliable gastric emptying.

). A literature review on this subject revealed scant and inconsistent results with some studies noting accelerated gastric emptying,[16] others describing delayed emptying in both humans[17 18] and animals[19] and others showing no real difference (Box 1).[20 21] Contributing factors to the confounding interpretation of these studies are differences in experimental techniques including different test meal variables as well as differences in alcohol osmolarity[22] volume and energy content,[23] and hydrogen ion concentrations[24]—all of which have been shown to delay gastric emptying . Certain amino acids contained in various alcoholic beverages have also been shown to delay gastric emptying.[25–29] Moreover, both solids and liquids with a greater weight and kilocalorie content are associated with longer emptying times,[30] and higher osmolarity solutions have been shown to be more inhibitory to gastric emptying.[22] Contrary to this, some studies have shown that the inhibitory effects of red wine, beer and ethanol on gastric emptying does not depend on the caloric content of meals and is not dose-dependent when given in concentrations of 10% or less.[2 4] . Furthermore, in the aforementioned studies showing that ethanol accelerates gastric emptying,[4 16] the control solution was adjusted to match that of the alcohol-containing beverages by adding hyperosmolar glucose and/or NaCl in order to delay gastric emptying. Another possible explanation as to why these studies concluded that ethanol accelerates gastric emptying is that alcohol has a low osmotic pressure and a high diffusion capacity allowing it to easily pass through the GI barrier. Also, the presence of alcohol dehydrogenase in the gastric mucosa aids in its initial metabolism.[2 3 31] These unique features of alcohol can be misleading as one cannot rely on blood levels of alcohol to indicate reliable gastric emptying.

Other studies have demonstrated that it is the concentration and type of alcoholic beverage that exerts different effects on gastric emptying. For example, alcoholic beverages produced by fermentation alone such as red wine and beer have been shown to have a slower gastric emptying compared with alcoholic beverages produced by distillation.[9] Indeed, beverages with a higher alcohol concentration over 15% have been shown to inhibit gastric motility

to a greater degree, whereas beverages with a lower alcohol concentration such as beer and wine, accelerate gastric emptying more.[5] Therefore, the effects of ethanol on gastric motility are complex, multifactorial and depend on several factors including the type of alcoholic beverage, the concentration of alcohol as well as different processing techniques.

Motility of the stomach is mediated by motor neurons embedded in the myenteric plexus, an intricate bundle of nervous tissue found between the circular and longitudinal muscle layers in the stomach wall. There is some evidence that alcohol-induced motility disturbances are caused by the effect that alcohol has on the nitric oxide (NO) system.[32–34] NO is a non-adrenergic, non-cholinergic inhibitory neurotransmitter that has been shown to play a critical role in GI smooth muscle motility, secretion, digestion and absorption.[35] NO is produced by the enzyme nitric oxide synthase (NOS), which is localized in gut nerve endings in the gut myenteric plexus. NO is mostly present in inhibitory motor neurons and causes relaxation of gut smooth muscle. Some studies in mutant mice lacking neuronal NOS have been shown to have severe intestinal dysfunction, and that NOS inhibitors delayed gastric emptying.[36] Other studies have suggested that NO may play a role in alcohol-related GI motility disorders.[32 34] In a study by Bagyánszki *et al*, chronic alcohol consumption in rats resulted in a significant increase in NO synthesis by jejunal myenteric neurons, and the authors postulated that this NO overproduction might play a role in delaying gastric emptying and intestinal transit.[32] These same authors previously showed that chronic alcohol use in mice resulted in a decreased number of nNOS-containing myenteric neurons which subsequently resulted in decreased gastric motility in mice.[31]

Ethanol, along with many of its non-alcoholic metabolites exerts both direct and indirect effects on gut motility, permeability and absorption.[37] Alcohol's high diffusion capacity and low effective osmotic pressure allows it to diffuse easily across the GI mucosa where first pass metabolism and oxidation of ethanol begins by the enzyme alcohol dehydrogenase found in the gastric mucosa.[38 39] The acute ingestion of alcohol has been shown to decrease stomach contractility by acting on both the local smooth muscle and the enteric nervous plexus.[31 40] Reduced synthesis of smooth muscle contractile proteins has been observed in rats after both acute and chronic alcohol intake.[41 42] On the other hand, chronic alcohol ingestion may accelerate gastric emptying[43] (figure 3). Izbéki *et al* investigated chronic alcohol ingestion in rats for two different lengths of time (10 days, 30 days), and demonstrated that alcohol administered over a longer period of time accelerated gastric emptying compared with rats who used alcohol for a shorter period of time.[43]

There is a widely held belief that having a glass of wine or a cocktail before and with dinner helps with digestion. While imbibing to levels of intoxication slows gastric emptying, there is evidence supporting the use of alcohol as an aperitif to aid in digestion. A study performed by Heinrich *et al* examined this widely held social norm by having 20 volunteers eat a standardized high fat meal of cheese fondue and randomized them to either a glass of white wine or a cup of black tea beforehand. They examined the effect on gastric emptying and abdominal symptoms and showed that gastric emptying was noticeably slower and appetite was suppressed with higher doses of alcohol and that this effect was not associated with any dyspeptic symptoms.[6] Other studies have shown mixed results regarding alcohol intake with some studies showing alcohol to increase appetite and others showing no effect. Certainly, this varies depending on the type of alcohol and the dose and more controlled studies would be needed to better understand this phenomenon.

As we now better understand the effects of alcohol on gastric motility, we can attempt to evaluate if there may be a clinical application for alcohol for specific patient settings. DS is a condition characterized by postprandial rapid emptying of voluminous and hyperosmolar gastric contents into the small bowel. DS is associated with vagal nerve injury related to diabetes mellitus or previous gastric surgeries such as a Nissen fundoplication for gastroesophageal reflux. In some idiopathic cases, vagal nerve damage secondary to a gastroenteritis illness has been hypothesized. Early DS symptoms occur within 30 min after meals and include nausea, abdominal pain, diarrhea and sometimes vomiting. Uncontrolled DS can result in fear of eating, weight loss and malnutrition.

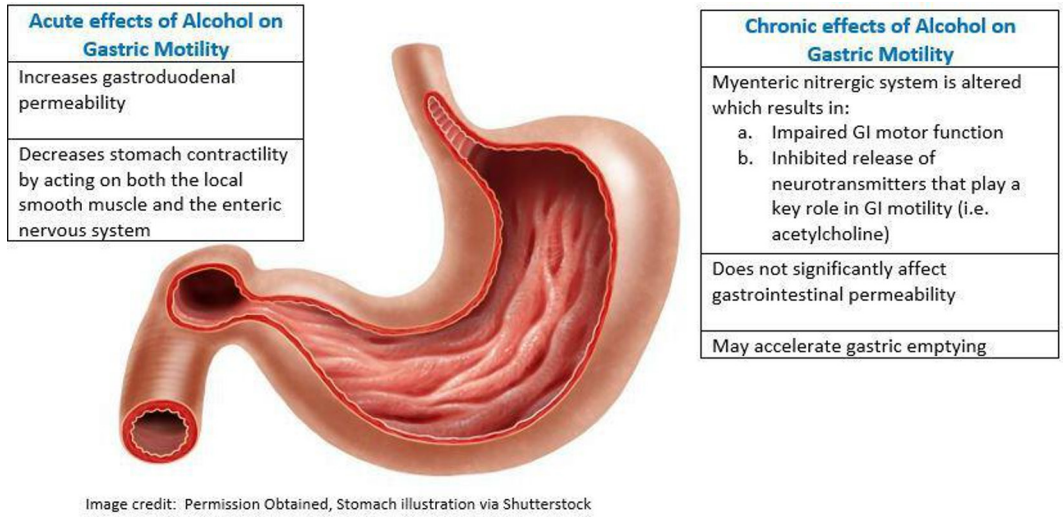

Figure 3 Proposed mechanisms of acute vs chronic alcohol intake on gastric motility.

Serendipitously, as previously described, we made an observation of a patient with DS experiencing normalization of gastric emptying along with complete resolution of accompanying symptoms of DS when drinking a glass of red or white wine before and during meals.

In retrospect in our patient, all of the possible mechanisms inhibiting gastric emptying may have been magnified by the fact that there was underlying vagal nerve damage resulting from injury to the vagus nerve from a previous Nissen fundoplication, which resulted in the development of DS through loss of accommodation of the gastric fundus. Therefore, the vagus nerve was already impaired and had diminished function. Hence, further inhibitory perturbations by one or more of factors induced by drinking a glass of wine resulted in an exaggerated inhibitory effect on her gastric emptying, thus resulting in restoration of normal gastric emptying and resolution of the accompanying symptoms, a unique outcome documented in this patient. The alcohol concentration of 14.5% in the glass of merlot the patient drank is essentially at the 15% threshold often quoted as inhibiting gastric motility. In the setting of vagal denervation, this alcohol concentration further augmented a net anticholinergic effect and markedly slowed gastric emptying restoring it to the normal rate.

With respect to wine, some studies show that red wine results in slower emptying of the stomach compared with other corresponding ethanol beverages in healthy adults.[20 44–46] A study by Kasicka-Jonderko *et al* showed that rates of gastric evacuation of a solid meal followed by intake of different alcoholic beverages was directly proportional to the potency of the alcoholic beverage, with slower gastric emptying more pronounced in alcoholic beverages with a higher concentration (43.5% whiskey >13.7% red wine >4.7% beer).[45] Franke *et al* showed that the inhibitory effect of red wine resulted in prolonged gastric emptying rates comparable to strong alcoholic drinks such as gin and whiskey.[44] On the other hand, a study by Moore *et al* comparing the effects of pure red wine (9.5 g/dL) on gastric emptying with modified, 'dealcoholized', isocaloric red wine (ethanol components were exchanged by isocaloric medium-chained triglycerides resulting in reduced mean ethanol concentration to 1.312 g/dL) showed no significant difference in the gastric emptying rate of normal wine compared with the 'dealcoholized' red wine.[20] The effect seen in this study has been postulated to be a result of additive effects of other ingredients found in alcohol (i.e. tannins and others).[44]

Endorsing social alcohol intake with meals has to be tempered with current research indicating that individuals who consume 50 g or more (3.5–4 drinks) daily have at least a two to three times greater risk of developing head and neck cancers than non-drinkers and women who drank >45 g of alcohol per day (approximately 3 drinks) had 1.5 times the risk of developing breast cancer as non-drinkers (a modestly increased risk).[47 48] However, the latest Centers for Disease Control and Prevention guidelines still deem that a drink or two a day is relatively safe and might even be beneficial through the actions of antioxidant compounds such as polyphenols such as resveratrol.[49–51]

FUTURE RESEARCH CONSIDERATIONS

The presented observations point toward potential therapeutic effects of alcohol in the relief of DS. In addition to dietary modifications (smaller, more frequent meals with separation of solid and liquid contents) and pharmacological interventions currently recommended for DS, future directions might entail studies investigating gastric motility effects of different alcoholic beverages to see if this treatment approach truly provides a safe and therapeutic effect in these patients - specifically in the group where DS is attributed to vagal nerve damage. It is also important to be aware of the many factors that control gastric emptying and consequently influence alcohol absorption. For example, there are significant intraindividual and interindividual variations when it comes to the magnitude and timing of intoxication after the ingestion of certain quantities of alcohol. These variations are extremely complex when you also take into account the development of tolerance as well as the different rates of absorption and metabolism of different alcoholic beverages in subjects who are alcohol-naïve compared with chronic alcoholics.[52] And because the rate of alcohol absorption depends on the rate of gastric emptying, gastric motility changes are also an important factor to consider in the degree of inebriation reached after ethanol consumption.[52] Additionally, consideration of psychological and behavioral factors are important components to consider in future research to better understand an individual's response to alcohol consumption. For example, studies have shown that individuals display less social anxiety[53] and more aggressive interpersonal behavior[54] despite the actual content of alcohol in a drink. All in all, alcohol effects on gastric motility are extremely complex with physiological, psychological, social and biological variables to consider, in addition to differences in alcohol concentration, content and processing techniques.

We believe that in undertaking this review of alcohol's effect on gastric motility and gastric emptying, we have unmasked a heretofore unrecognized and possible therapeutic role for a socially acceptable small intake of wine, specifically in individuals where DS resulted from a vagotomy or vagal nerve damage. In this specific setting where we serendipitously identified a therapeutic role for drinking a glass of wine before and during meals, we suggest patients go ahead and indulge their gustatory pleasures and enjoy a glass of wine with meals—and maybe 'voilà' that will do the trick.

Contributors ZG, DH and CP drafted and edited the article under the guidance of RM. JD helped performed the nuclear medicine studies and participated in acquisition of the data. KD helped performed the nuclear medicine studies and participated in acquisition and interpretation of the data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Zorisadday Gonzalez http://orcid.org/0000-0003-3917-7041

REFERENCES

1 Bhardwaj SB. Chapter 5 - Alcohol and gastrointestinal tract function. In: Watson RR, Preedy VR, eds. *Bioactive food as dietary interventions for liver and gastrointestinal disease*. San Diego: Academic Press, 2013: 81–118.
2 Bandera EV, Kushi LH. Chapter 11 - Alcohol and cancer. In: Heber D, ed. *Nutritional oncology*. 2nd edn. Burlington: Academic Press, 2006: 219–72.

3 Bode C, Bode JC. Alcohol's role in gastrointestinal tract disorders. *Alcohol Health Res World* 1997;21:76–83.
4 Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract. *Am J Gastroenterol* 2000;95:3374–82.
5 Grad S, Abenavoli L, Dumitrascu DL. The effect of alcohol on gastrointestinal motility. *Rev Recent Clin Trials* 2016;11:191–5.
6 Lenz HJ, Ferrari-Taylor J, Isenberg JI. Wine and five percent ethanol are potent stimulants of gastric acid secretion in humans. *Gastroenterology* 1983;85:1082–7.
7 Nykänen L, Suomalainen H. *Aroma of beer wine and distilled alcoholic beverages*. Springer Science & Business Media, 1983.
8 Chemical composition of alcoholic beverages, additives and contaminants. *IARC Monogr Eval Carcinog Risks Hum* 1988;44:71-99.
9 Franke A, Teyssen S, Singer MV. Alcohol-related diseases of the esophagus and stomach. *Dig Dis* 2005;23:204–13.
10 Willson CA, Bushnell D, Keshavarzian A. The effect of acute and chronic ethanol administration on gastric emptying in cats. *Dig Dis Sci* 1990;35:444–8.
11 Rivera-Calimlim L, Hartley D, Osterhout D. Effects of ethanol and pantothenic acid on brain acetylcholine synthesis. *Br J Pharmacol* 1988;95:77–82.
12 Strong R, Rehwaldt C, Wood WG, *et al*. Effects of ethanol on acetylcholine and GABA release: differences in the role of potassium. *Alcohol Alcohol Suppl* 1987;1:631–5.
13 Sanders KM, Berry RG. Effects of ethyl alcohol on phasic and tonic contractions of the proximal stomach. *J Pharmacol Exp Ther* 1985;235:858–63.
14 Bode JC, Bode C. [Alcohol, the gastrointestinal tract and pancreas]. *Ther Umsch* 2000;57:212–9.
15 Rocco A, Compare D, Angrisani D, *et al*. Alcoholic disease: liver and beyond. *World J Gastroenterol* 2014;20:14652–9.
16 Kaufman SE, Kaye MD. Effect of ethanol upon gastric emptying. *Gut* 1979;20:688–92.
17 Jian R, Cortot A, Ducrot F, *et al*. Effect of ethanol ingestion on postprandial gastric emptying and secretion, biliopancreatic secretions, and duodenal absorption in man. *Dig Dis Sci* 1986;31:604–14.
18 Barboriak JJ, Meade RC. Effect of alcohol on gastric emptying in man. *Am J Clin Nutr* 1970;23:1151–3.
19 Scroggs R, Abruzzo M, Advokat C. Effects of ethanol on gastrointestinal transit in mice. *Alcohol Clin Exp Res* 1986;10:452–6.
20 Moore JG, Christian PE, Datz FL, *et al*. Effect of wine on gastric emptying in humans. *Gastroenterology* 1981;81:1072–5.
21 Keshavarzian A, Iber FL, Greer P, *et al*. Gastric emptying of solid meal in male chronic alcoholics. *Alcohol Clin Exp Res* 1986;10:432–5.
22 Meeroff JC, Go VL, Phillips SF. Control of gastric emptying by osmolality of duodenal contents in man. *Gastroenterology* 1975;68:1144–51.
23 Hunt JN, Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. *J Physiol* 1975;245:209–25.
24 Hunt JN, Knox MT. The slowing of gastric emptying by nine acids. *J Physiol* 1969;201:161–79.
25 Ochia BA. Influence of amino acids on gastric emptying in young pigs. *Acta Physiol Acad Sci Hung* 1976;48:41–50.
26 Bell FR, Nouri M, Webber DE. The interplay between hydrogen ions, bicarbonate ions and osmolality in the anterior duodenum modulating gastric function in the conscious calf. *J Physiol* 1981;314:331–41.
27 Lin HC, Doty JE, Reedy TJ, *et al*. Inhibition of gastric emptying by acids depends on pH, titratable acidity, and length of intestine exposed to acid. *Am J Physiol* 1990;259:G1025–30.
28 Cooke AR. Ethanol and gastric function. *Gastroenterology* 1972;62:501–2.
29 Thomas JE, Crider JO. Inhibition of gastric motility associated with the presence of products of protein hydrolysis in the upper small intestine. *Am J Physiol-Legacy Cont* 1939;126:28–38.
30 Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man. Evaluation by dual liquid- and solid-phase isotopic method. *Dig Dis Sci* 1981;26:16–22.
31 Bagyánszki M, Krecsmarik M, De Winter BY, *et al*. Chronic alcohol consumption affects gastrointestinal motility and reduces the proportion of neuronal NOS-immunoreactive myenteric neurons in the murine jejunum. *Anat Rec* 2010;293:1536–42.
32 Bagyánszki M, Torfs P, Krecsmarik M, *et al*. Chronic alcohol consumption induces an overproduction of NO by nNOS- and iNOS-expressing myenteric neurons in the murine small intestine. *Neurogastroenterol Motil* 2011;23:e237–48.
33 Wang SL, Xie DP, Liu KJ, *et al*. Nitric oxide mediates the inhibitory effect of ethanol on the motility of isolated longitudinal muscle of proximal colon in rats. *Neurogastroenterol Motil* 2007;19:515–21.
34 Krecsmarik M, Izbéki F, Bagyánszki M, *et al*. Chronic ethanol exposure impairs neuronal nitric oxide synthase in the rat intestine. *Alcohol Clin Exp Res* 2006;30:967–73.
35 Kochar NI, Chandewal AV, Bakal RL, *et al*. Nitric oxide and the gastrointestinal tract. *Int J Pharmacol* 2011;7:31–9.
36 Mashimo H, Kjellin A, Goyal RK. Gastric stasis in neuronal nitric oxide synthase-deficient knockout mice. *Gastroenterology* 2000;119:766–73.
37 Reding KW, Cain KC, Jarrett ME, *et al*. Relationship between patterns of alcohol consumption and gastrointestinal symptoms among patients with irritable bowel syndrome. *Am J Gastroenterol* 2013;108:270–6.
38 Pfeiffer A, Högl B, Kaess H. Effect of ethanol and commonly ingested alcoholic beverages on gastric emptying and gastrointestinal transit. *Clin Investig* 1992;70:487–91.
39 Frezza M, di Padova C, Pozzato G, *et al*. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 1990;322:95–9.
40 Federico A, Cotticelli G, Festi D, *et al*. The effects of alcohol on gastrointestinal tract, liver and pancreas: evidence-based suggestions for clinical management. *Eur Rev Med Pharmacol Sci* 2015;19:1922–40.
41 Preedy VR, Peters TJ. Protein synthesis of muscle fractions from the small intestine in alcohol fed rats. *Gut* 1990;31:305–10.
42 Preedy VR, Duane P, Peters TJ. Acute ethanol dosage reduces the synthesis of smooth muscle contractile proteins in the small intestine of the rat. *Gut* 1988;29:1244–8.
43 Izbéki F, Wittmann T, Csáti S, *et al*. Opposite effects of acute and chronic administration of alcohol on gastric emptying and small bowel transit in rat. *Alcohol Alcohol* 2001;36:304–8.
44 Franke A, Nakchbandi IA, Schneider A, *et al*. The effect of ethanol and alcoholic beverages on gastric emptying of solid meals in humans. *Alcohol Alcohol* 2005;40:187–93.
45 Kasicka-Jonderko A, Jonderko K, Bożek M, *et al*. Potent inhibitory effect of alcoholic beverages upon gastrointestinal passage of food and gallbladder emptying. *J Gastroenterol* 2013;48:1311–23.
46 Teyssen S, Lenzing T, González-Calero G, *et al*. Alcoholic beverages produced by alcoholic fermentation but not by distillation are powerful stimulants of gastric acid secretion in humans. *Gut* 1997;40:49–56.
47 Baan R, Straif K, Grosse Y, *et al*. Carcinogenicity of alcoholic beverages. *Lancet Oncol* 2007;8:292–3.
48 Hamajima N, Hirose K, Tajima K, *et al*. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002;87:1234–45.
49 2015-2020 dietary guidelines, 2020. Available: health.gov
50 Su H-C, Hung L-M, Chen J-K. Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab* 2006;290:E1339–46.
51 Agouni A, Lagrue-Lak-Hal A-H, Mostefai HA, *et al*. Red wine polyphenols prevent metabolic and cardiovascular alterations associated with obesity in Zucker fatty rats (Fa/Fa). *PLoS One* 2009;4:e5557.
52 Holt S, Cervantes J, Wilkinson AA, *et al*. Measurement of gastric emptying rate in humans by real-time ultrasound. *Gastroenterology* 1986;90:918–23.
53 Wilson GT, Abrams D. Effects of alcohol on social anxiety and physiological arousal: cognitive versus pharmacological processes. *Cognit Ther Res* 1977;1:195–210.
54 Lang AR, Goeckner DJ, Adesso VJ, *et al*. Effects of alcohol on aggression in male social drinkers. *J Abnorm Psychol* 1975;84:508–18.
55 Chari S, Teyssen S, Singer MV. Alcohol and gastric acid secretion in humans. *Gut* 1993;34:843–7.