Review Article

MANAGEMENT OF DYSPEPSIA

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SUMMARY

Upper gastro-intestinal motility disorders are not uncommon. While the exact prevalence in Pakistan is not known there are substantial number of patients who suffer from upper abdominal pain, fullness, nausea, vomiting, anorexia or heartburn and are found to be normal on endoscopy and liver function test. In such patients it appears that the disorder is a functional one with sluggish emptying of the stomach resulting in the symptoms as described above. Though this condition is not serious but can be extremely disturbing to these individuals. Symptoms may vary from mild to quite severe. Questions about the evaluation and management of dyspepsia remain unanswered. Symptoms of possible causes often overlap, which can make initial diagnosis difficult. In many patients, a definite cause is never established. The initial evaluation of patients with dyspepsia includes a thorough history and physical examination, with special attention given to elements that suggest the presence of serious disease. Endoscopy should be performed promptly in patients who have "alarm symptoms" such as melena, weight loss or anorexia. Although management should be individualized, a cost-effective initial approach is to test for *Helicobacter pylori* and treat the infection if the test is positive. If the *H. pylori* test is negative, empiric therapy with a gastric acid suppressant or prokinetic agent is recommended. If symptoms persist or recur after six to eight weeks of empiric therapy, endoscopy should be performed.

This review is based on clinical experience and extensive search and study through MEDLINE on research papers, review articles and conference reports on Functional Gastointestinal disorders.

KEY WORDS: Dyspepsia, Diagnosis, Medical Management, Endoscopy

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INTRODUCTION / BACKGROUND

Dyspepsia is defined as an upper abdominal pain or discomfort that is episodic or persistent and often associated with belching, bloating, heartburn, nausea or vomiting.[1] The term dyspepsia is derived from the Greek word (dys) and (peptein). The literal translation is "bad digestion". "Dyspepsia" is therefore a generic term which covers a variety of more or less well defined symptoms.

Symptoms may be of short duration or only mild in severity among many people, hence self-management is an option for the majority. Less than half of dyspepsia sufferers seek medical care for their complaints. Dyspepsia is responsible for substantial health care costs (medications and diagnostic evaluations) and considerable time lost from work.

Epidemiology:

The condition is reported to occur in approximately 25 percent (range: 13 to 40 percent) of the population each year, but most affected persons do not seek medical care.[2,3] In patients with dyspepsia who are investigated, four major causes can be identified for their complaints: chronic peptic ulcer disease, gastroesophageal reflux (with or without esophagitis), malignancy and functional (or non-ulcer) dyspepsia. Only a minority of patients with

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dyspepsia have peptic ulcers (15-25% of cases) or reflux esophagitis (5-15% of cases) and even fewer (<2%) have cancer.[4]

If the symptoms are chronic or recurrent for at least three months, and there is no clinical, biochemical, endoscopic or ultrasonographic evidence of known organic disease that is likely to explain the symptoms, pain or discomfort that is centred in the upper abdomen has been defined as "functional dyspepsia".[5] This diagnostic category accounts for up to 60% of patients with dyspepsia.[4]

DIAGNOSIS

Patients presenting with dyspepsia, peptic ulcer disease, reflux esophagitis, and gastric cancer need to be excluded. Other possible causes like cholelithiasis, acute or chronic relapsing pancreatitis, carbohydrate malabsorption, intestinal parasites, NSAID-induced gastropathy, or diseases like diabetes and thyroid or parathyroid disorders should also be considered in the differential diagnosis of dyspepsia.

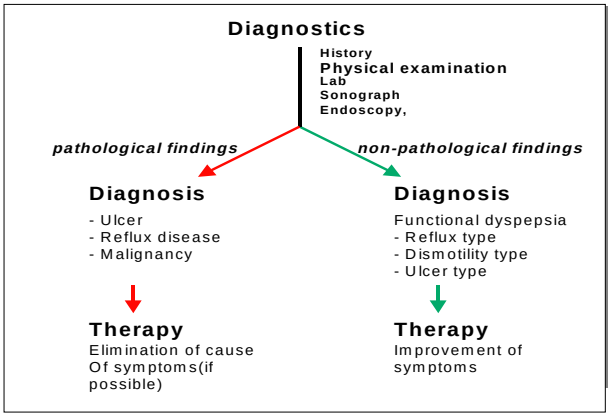
History:

A thorough history is important in evaluating the patient with dyspepsia, although symptoms alone may not be very useful in establishing a specific diagnosis. One group of investigators found extensive symptom overlap when they attempted to categorize patients into diagnostic groups, which included ulcer-like, dysmotility-like, reflux-like and unspecified dyspepsia.[6] Reflux-like symptoms may be of greater diagnostic value in that symptoms alone can reasonably identify the presence of GERD.[7,8]

Physical Examination:

With the exception of epigastric tenderness, the physical examination in patients with uncomplicated dyspepsia is usually unremarkable. In addition to evaluating the epigastric pain, it is important to assess the patient's hemodynamic status because hypotension or tachycardia may indicate significant blood loss from gastrointestinal bleeding.

Weight loss, a positive fecal occult blood test, a palpable mass, signal nodes (Virchow's nodes) and acanthosis nigricans are signs of possible malignancy. Patients with dyspepsia and any of these signs should undergo endoscopy as soon as possible. Clinical signs of anemia, such as brittle nails, cheilosis and pallor of the palpebral mucosa or nail beds, may also suggest malignancy.



Evaluation:

Historically, upper gastrointestinal radiographs were obtained in patients with dyspepsia. Today, radiographs are considered inferior to upper endoscopic examination for confirming or excluding ulcers, reflux disease and malignancies.[9,10] Although endoscopy with biopsy is considered the gold standard for diagnosing *H. pylori* infection,[11,12] the procedure is not always practical and may not be cost-effective.[12]

H. pylori can also be detected in the serum with antibody titers, in the breath with the urea breath test (UBT) and in the stool with a polymerase chain reaction (PCR) test or an antigen enzyme immunoassay (EIA). With the UBT, if *H. pylori* is present, the urease produced by the organism breaks down ingested carbon 14labeled urea into ammonia and labeled carbon dioxide, which can be detected in the patient's breath. The UBT is more sensitive and specific than serologic testing, but it tends to be more expensive.[13] Since serology is considered to have acceptable sensitivity and specificity for *H. pylori* infection, its cost and availability makes it more practical than the UBT.[12]

A positive serology test only indicates previous exposure to *H. pylori* and not active infection. Thus, the test is not useful for confirming eradication of the organism. The UBT is the best test for this purpose, because once *H. pylori* is eradicated, urease is no longer produced.

Noninvasive detection of *H. pylori* in the feces is of particular importance in young patients. The reported sensitivities of PCR and EIA for *H. pylori* are 93.7 percent and 88.9 percent, respectively; the respective specificities are 100 percent and 94.6 percent.[14]

MANAGEMENT STRATEGY

There are different views on the optimal management strategy for dyspepsia patients. The major options available today are:

* immediate diagnostic evaluation (e.g. endoscopy) in all cases and targeting therapy based on the results,
* testing for H.pylori infection and reserving endoscopy for positive cases to look for ulcer disease or cancer or treating all positive cases with antibacterial therapy,
* empirical medical therapy (e.g. a prokinetic or antisecretory agent) with any subsequent investigation reserved for failures.

Based on the available evidence, prompt endoscopy is always indicated in elderly patients or in those with alarm features such as weight loss or anaemia. In patients without alarm features, the role of prompt endoscopy remains controversial. Initial empirical therapy for all patients may only delay diagnostic testing, will probably provide the least patient assurance and may promote inappropriate long-term medication use. For strategies relying on H.pylori testing, the benefits in functional dyspepsia are likely to be small.[4]

In terms of cost-effictiveness, empirical treatment seems to be a more useful pragmatic approach.

A number of decision analyses have been conducted to determine the most reasonable management approach.[2,15,16,17] The factors that one must consider in selecting a strategy include cost, patient and physician attitudes about having an uncertain diagnosis, ethics, patient satisfaction and prevalence of the disease.

After a thorough clinical evaluation and detailed history, conditions such as GERD, irritable bowel syndrome, biliary pain and medication-induced dyspepsia can most likely be confirmed or excluded.[6,7.] In about two-third of the cases it is attributed to functional dyspepsia since upon investigations, no organic lesion is found.

Non-pharmacological Management:

All patients with dyspepsia should be advised to stop smoking and, if their medical condition permits, to discontinue ulcerogenic medications. They should also avoid foods and other factors that precipitate their symptoms.

As dyspepsia may be aggravated by stress, anxiety or depression, it may be useful to explore these issues. Reassurance is a key step in managing dyspepsia but advice regarding stress reducing activities like exercise and relaxation is also important.

Pharmacological Management:

Treatment goals in dyspepsia and functional dyspepsia

The goal of treatment in patients with an underlying structural lesion should be to address the cause of the symptoms. This may involve permanent removal of a cause of symptoms (for example, eradication of a H. pylori colony in patients with peptic ulcer disease) or initiation of systematic treatment (for example, long-term antisecretory treatment in patients with reflux oesophagitis).

For practical reasons extensive screening for structural lesions is not always possible. The (empirical) therapy employed should be potent enough to clear up a structural lesion and eliminate the symptoms with a high level of probability.

Patients with functional dyspepsia (like those with reflux disorders) typically have chronically recurrent symptoms. Unlike peptic ulcer disease, functional dyspepsia still has no permanent cure, as such treatment is limited to achieving rapid improvement of symptoms.[18]

Classification of patients with functional dyspepsia

Patients with functional dyspepsia may present with very different symptoms. Patients with functional dyspepsia are classified on the basis of their dominant symptoms into ulcer type, reflux type or dysmotility type. The purpose of this type of classification is to help identify patient groups likely to respond particularly well to specific treatments, based on the theory that there is a correlation between the dominant symptoms and the underlying dysfunction. According to this theory, reflux-type or ulcer-type symptoms will respond well to antisecretories, while dysmotility-type symptoms will respond better to prokinetics.

However, strict discrimination is rarely possibly as there is considerable overlap between the various types of dyspepsia. Likewise, symptoms clash with those of irritable bowel syndrome, which is associated with lower abdominal symptoms and changes in the frequency of bowel movements, again in the absence of an objectifiable organic lesion as a cause of the symptoms. This overlap between functional dyspepsia and irritable bowel syndrome suggests a common pathophysiological basis.

There is no cure for functional dyspepsia based on what we know today. Drug therapy is therefore based on symptom control and improvement. Since the disease generally presents on an episodic basis, hence drug therapy is usually indicated when symptoms are severe. Therapy for chronic condition is not (yet) established. Management strategies for different stages will be as under:-

Stage 1 :

In stage one (on completion of diagnostic procedures) the patient is counselled on the possible causes of his or her symptoms. Patients often fear that their symptoms may be due to a life-threatening disease. It is important to address these fears through suitable counselling (and diagnostic procedures).

It is also important to explore potential changes in lifestyle and diet that may be responsible for the symptoms (eating habits, use of painkillers, alcohol consumption etc.).

Stage 2:

If this approach fails to provide any pointers or if modification of these factors fails to improve the symptoms, drug therapy should be considered which is the second step. Drug therapy is based on the clinical symptoms. For example:-

* Patients with ulcer-type symptoms are put on antisecretories.
* Those with dysmotility as the predominant system will receive prokinetics.
* Those with primarily reflux-type symptoms may receive prokinetics or antisecretories.

Stage 3 :

If there is no response to drug treatment, use of another therapeutic principle is recommended after around two weeks. This is stage three. If there is still no improvement, the diagnosis should be reconsidered. Further diagnostic procedures may need to be initiated, or it may be necessary to proceed to stage four, involving the use of measures of unproven efficacy. These include psychosomatic/psychotherapeutic treatment or H. pylori eradication therapy (some authors recommend H. pylori eradication as an initial therapeutic measure as this more or less rules out peptic ulcer disease as a cause of the symptoms).[19]

Treatment with tricyclic antidepressants is becoming common in some countries as a means of combating refractory dyspepsia. Extremely low doses appear to be effective in dyspepsia. The same doses would have no effect in the usual indications for tricyclic antidepressants. The efficacy of tricyclic antidepressants in dyspepsia probably has to do with modulation of visceral nociception at the level of the enteric nervous system or CNS.

Formal studies on the efficacy of proton pump inhibitors in functional dyspepsia have not been published until recently. Like earlier studies on the efficacy of H2-blockers, they indicate that pharmacological inhibition of acid secretion is an effective (compared with placebo) measure in patients with functional

dyspepsia. Their action is probably mainly related to inhibition of a symptom-triggering pathological reflux of acid into the oesophagus. It is also possible that reduction of acid secretion improves symptoms by affecting the interaction of mechanosensory and chemosensory afferent nerve fibres. However, this is not conclusively proven.

Inhibition of acid secretion is also effective in most of the organic diseases that cause dyspeptic symptoms. The use of proton pump inhibitors on an empirical basis in patients with dyspepsia without prior diagnostic elucidation improves reflux oesophagitis as reliably as it does in peptic ulcer. Proton pump inhibitors are superior to other drugs without causing more side effects.[20]

Functional dyspepsia is a chronic disease. These patients require treatment on a long-term or recurrent basis. Given the extensive experience in long-term treatment of patients with reflux disease, it can be assumed that long-term treatment without significant side effects will also be possible in patients with functional dyspepsia. Numerous studies on the efficacy of cisapride were conducted in the course of the drug's clinical development. On the whole, prokinetic therapy can be expected to improve the symptoms of functional dyspepsia.

However, it is important not to overlook the fact that there is no direct correlation between the size of the impact on gastrointestinal motility (e.g. degree of acceleration of gastric emptying) and improvement of symptoms. Therefore, prokinetics may operate on the basis of mechanisms other than acceleration of gastric emptying. The currently available prokinetic drugs (e.g. cisapride or metoclopramide) have clear limitations. For example, metoclopramide is frequently associated with central nervous side effects by virtue of its antidopaminergic effects.Cisapride treatment may (especially if used along with motilides or antihistamines) cause long QT syndrome with potentially fatal cardiac arrhythmia. The US-FDA has therefore recently issued a restriction on its use and the drug has been removed from the market.

One of the main misunderstandings about dopamine D2-antagonists – strongly encouraged by the competitive profiling of cisapride and related drugs – is that they unavoidably would have central nervous effects. This is true for metoclopramide. However, both domperidone and itopride (Ganaton®) have clinically relevant anti-dopaminergic effects but hardly penetrate the CNS. The fact that they have anti-emetic properties is not in conflict with the absence of CNS effects. The chemoreceptor trigger zone is part of the circumventricular organs that are not sealed-off by an anatomical blood-brain barrier. The anti-dopaminergic effects of domperidone and itopride are truly 'peripheral'.

On the other hand, prolactin secretion is also regulated at circumventricular level. Domperidone and itopride are both not unlikely to stimulate prolactin secretion. This may be bothersome as it may cause relevant adverse effects. However, it is very rarely observed with itopride, whereas it is quite common for domperidone. This probably relates to the fact that the prokinetic properties of domperidone rely exclusively on the anti-dopaminergic action, whilst for itopride both anti-dopaminergic actions and inhibition of acetylcholinesterase play a role. This synergistically dual mode of action allows to take benefit at both levels without needing excessive i.e. prolactin enhancing anti-dopaminergic actions. This is also evident by the fact that the anti-emetic actions of domperidone and metoclopramide tend to be predominant compared to the prokinetic properties: they are highly effective against emesis induced by powerful dopaminergic stimulation (as with drugs used for the treatment of Parkinson's disease) and chemotherapy. For itopride, the prokinetic action is predominant[21] and the anti-emetic action is an attractive but ancillary feature.

CONCLUSIONS

Many questions about the evaluation and management of dyspepsia remain unanswered. So far little consensus data is available to guide physicians in the diagnosis and management of patients presenting with dyspepsia in the

primary care setting. The situation is further complicated by the need to have a cost-effective, yet rational approach to dyspepsia.

Primary care physicians must determine when to treat empirically and when to arrange endoscopy for patients. Patients at high risk for malignancy should have early endoscopy. In young patients without signs or symptoms of a serious underlying disorder, the most evidence-based initial management strategy appears to be *H. pylori* testing followed by eradication of the organism when the test is positive.[9,15,22] A gastric acid suppressant or prokinetic agent can be used in patients with nonulcer dyspepsia who do not have *H. pylori* infection and in patients with *H. pylori* infection who do not respond to anti*H. pylori* agents (probably a large number of such patients, if not the majority[16]). If symptoms still do not improve, endoscopy and more specialized testing are indicated.[22]

If, after endoscopy and all other specialized testing, the diagnosis is functional or nonulcer dyspepsia and the symptoms do not respond to all previous treatments, dietary, environmental and emotional triggers should be evaluated and addressed.[16] Additional treatments can include antidepressant drug therapy, stress management, relaxation therapy, hypnotherapy or psychotherapy.[17]

In the next few years we may have new in-sight which will contribute to a better understanding of the pathogenesis of functional gastrointestinal diseases such as functional dyspepsia. However, it remains to be seen whether these new insights will lead to cure of this condition.

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