Oesophageal motor changes in diabetes mellitus

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Stewart, I. M., Hosking, D. J., Preston, B. J., and Atkinson, M. (1976). *Thorax*, **31**, 278–283. **Oesophageal motor changes in diabetes mellitus.** Radiography and manometry have been used to study oesophageal motor function in a group of 31 diabetics, 23 of whom had alimentary or genitourinary symptoms attributed to autonomic neuropathy. Peristalsis was of diminished amplitude and oesophageal emptying in the 15° Trendelenburg position was delayed. The lower oesophageal sphincter pressure was reduced. The changes seldom caused symptoms and they were not confined to those diabetics with alimentary or genitourinary symptoms attributable to autonomic neuropathy. They suggest that autonomic neuropathy in diabetes is widespread and often subclinical.

Degeneration of the ganglion cells of the oesophageal myenteric plexus is associated with hypersensitivity of the oesophageal smooth muscle to cholinergic agents. Bethanecol, a cholinergic drug with muscarinic actions, accelerated oesophageal emptying and increased the lower oesophageal sphincter pressure to normal levels in our diabetics but the hypersensitivity to this drug found in the presence of ganglion cell degeneration was not seen. This implies that in diabetic autonomic neuropathy the predominant lesion is in the preganglionic fibres of the vagus rather than in the myenteric plexus of the oesophageal wall.

Disturbance of gastrointestinal motility in diabetes is well recognized and may cause nausea, vomiting (Kassander 1958; Dotevall, 1961), constipation, and diarrhoea (Rundles, 1945; Malins and Mayne, 1969; Whalen, Soergel, and Geenen, 1969). Oesophageal symptoms are much rarer but oesophageal manometric abnormalities in diabetes have been reported by Mandelstam *et al.* (1969) who found diminution in the amplitude of peristalsis and reduction in the lower oesophageal sphincteric pressure. Tertiary contractions were common, but, when present, peristalsis was properly coordinated. In contrast, Silber (1969) found incoordination of oesophageal peristalsis in diabetic patients which did not correlate with the presence of peripheral neuropathy, and indeed similar changes were noted in non-diabetics with no oesophageal symptoms.

The present study was undertaken to determine whether specific oesophageal motor changes occur in diabetes and, if so, to clarify their nature and to determine whether they are associated with impairment of vagal function.

PATIENTS

Thirty-one diabetic patients were studied (Table I).

Of these 13 had alimentary symptoms thought to be due to autonomic neuropathy, 10 had impotence or bladder symptoms attributed to autonomic neuropathy, and eight had no autonomic symptoms. Because it contained many patients with impotence the second group had a higher proportion of male patients but otherwise the three groups were of comparable age and sex. None of the diabetics complained of oesophageal symptoms but one patient, who suffered from diarrhoea, admitted to mild dysphagia on questioning. Five diabetics had mild heartburn and all had autonomic symptoms (3 alimentary, 2 genitourinary).

For comparative purposes a group of 14 (10 male, 4 female) staff and patients without alimentary disease was studied. In all cases informed consent to the investigations was obtained.

METHODS

RADIOLOGY Patients swallowed 20 ml of Micropaque and if the oesophagus was not cleared 'dry' swallows at 30-second intervals were made up to a time limit of 4 minutes. This examination was first done with the patient in the supine oblique position and was then repeated with the table

TABLE I
CLINICAL FEATURES IN DIABETICS STUDIED

| | No. of Patients | | | Mean Age (yr) | Mean Duration of Diabetes (yr) | Treatment | | Diarrhoea | Vomiting | Impotence | Bladder Symptoms | Peripheral Neuropathy | Retinopathy | Vascular Disease |
	Total	M	F			Insulin	Oral Agents							
Diabetics with autonomic alimentary symptoms	13	5	8	50·8	16·0	9	4	11	4	4	0	8	8	2
Diabetics with non-alimentary autonomic symptoms	10	9	1	46·2	10·2	8	2	0	0	9	2	8	5	1
Diabetics with no autonomic symptoms	8	4	4	47·5	10·7	5	3	0	0	0	0	3	3	2

tilted 15° head down. The procedures were screened intermittently and video tape recordings were made so that motility and rate of clearance of contrast from the oesophagus could be assessed. Films of the oesophagus using the undercouch tube were taken, and the maximum diameter of the oesophagus at any level between the aortic arch and the phrenic ampulla was measured.

Patients whose emptying time exceeded 1 minute in the head down position had the studies repeated 15 minutes after a subcutaneous injection of 2·5 mg bethanechol, a cholinergic agent with muscarinic actions.

Oesophageal Manometry Oesophageal intraluminal pressure was measured in the fasting state through two open-ended water-filled polyethylene tubes (1·5 mm internal diameter) with constant water perfusion at a rate of 0·5 ml/min. The tips of the tubes were 5 cm apart. With the patient in the left lateral position, pressure in the lower oesophageal sphincter was recorded by withdrawing the tube through the cardia in steps of 1 cm. Thereafter swallows of 10 ml water were given and peristalsis was recorded from all levels of the oesophagus.

Studies were repeated 15 minutes after 2·5 mg bethanecol, given subcutaneously to determine whether hypersensitivity to this agent, as occurs in achalasia (Kramer and Ingelfinger, 1951) and

Chagas' disease (Heitmann and Espinosa, 1969) was present.

RESULTS

RADIOLOGY The findings in 26 diabetics and 14 non-diabetics without oesophageal symptoms studied are shown in Tables II and III where it will be seen that in all the non-diabetics oesophageal emptying took less than 1 minute. In contrast 19 of the 26 diabetics showed delayed oesophageal emptying, and in 14 of these, contrast medium remained in the gullet for more than 4 minutes. This delay was present in a greater proportion of diabetics with symptoms attributable to autonomic neuropathy than in those without such symptoms. Bethanecol was given to those patients with delayed oesophageal emptying, and oesophageal emptying times were reduced in all groups of patients (Table III).

The mean diameter of the barium-filled oesophagus was slightly greater in the diabetic patients than in the non-diabetics but the difference was only significant in the group with bladder symptoms and impotence.

Tertiary contractions were seen much more frequently in the diabetics than in the non-diabetics and their frequency was greater in diabetics with symptoms attributable to autonomic neuropathy than in those without such symptoms.

TABLE II
RADIOGRAPHIC FINDINGS

	No.	Mean Age (yr)	Oesophageal Emptying Time > 1 min.	Mean Oesophageal Diameter (mm) (±ISD)	Tertiary Contractions Present	Gastro-oesophageal Reflux Present
Normal subjects	14	49	0	28·1 ± 3·8	3	0
Diabetics with alimentary autonomic symptoms	11	49	10	31·3 ±10·9	9	3
Diabetics with genitourinary autonomic symptoms	8	43	6	33·6± 4·9	5	3
Diabetics with no autonomic symptoms	7	52	3	33·7± 9·0	2	0

TABLE III
EFFECTS OF BETHANECOL ON OESOPHAGEAL EMPTYING TIME

	Bethanecol	No. of Patients	Oesophageal emptying Time		
			< 1 min	2–4 min	> 4 min
Diabetics with alimentary autonomic symptoms	Pre	10	0	4	6
	Post	7	3	3	1
Diabetics with genitourinary autonomic symptoms	Pre	8	2	1	5
	Post	6	1	4	1
Diabetics with no autonomic symptoms	Pre	7	4	0	3
	Post	3	1	1	1

Gastro-oesophageal reflux of contrast medium was seen in six diabetics with autonomic symptoms but in none of those without such symptoms and in none of the non-diabetic patients.

Oesophageal Manometry Although tertiary contractions were commoner in diabetics with autonomic symptoms than in those without and in non-diabetics, oesophageal peristalsis remained coordinated in the majority. In those diabetics with alimentary and genitourinary autonomic symptoms 70% of swallows were followed by a coordinated peristaltic wave, which was only a slightly lower percentage than that for non-diabetics and diabetics without autonomic symptoms (Table IV). The maximum amplitude of the peristaltic wave was slightly lower in diabetics with autonomic symptoms than in the other groups but this difference was not significant.

The lower oesophageal sphincter pressure was significantly reduced in all groups of diabetics compared with the non-diabetic and normal group but did not differ between those diabetics with and those without autonomic symptoms. When detectable the sphincter showed normally coordinated relaxation on swallowing.

Effect of Bethanecol Bethanecol caused a slight increase in the maximum amplitude of oesophageal peristalsis in normal and non-diabetic subjects and also in all three groups of diabetic patients.

Lower oesophageal sphincteric pressure rose slightly after bethanecol in the normal group and more strikingly in each of the three groups of diabetics (Figure). The magnitude of the pressure increase was significantly greater in the diabetics than in normal subjects but did not differ between those with alimentary or genitourinary autonomic symptoms and those without (Table IV).

Although the increase in lower oesophageal sphincter pressure after bethanecol was greater in the diabetics than in normal subjects the final pressures obtained were comparable because of
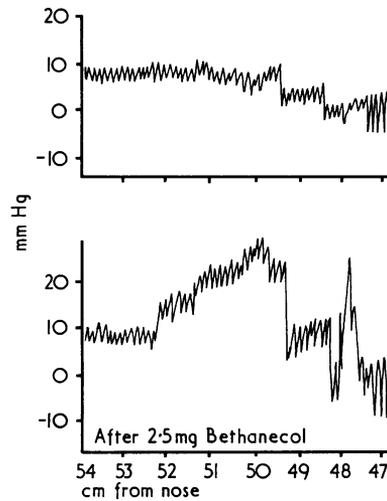

FIGURE *Pressure recordings at the gastro-oesophageal junction in a diabetic with diarrhoea. The increase in pressure resulting from contraction of the lower oesophageal sphincter is inconspicuous (upper record) but becomes prominent 15 minutes after 2·5 mg bethanecol given subcutaneously (lower record).*

the lower initial pressures recorded from the diabetics. In only one diabetic, a man of 45 suffering from impotence, did the post-bethanecol lower oesophageal pressure reach a level (40 mmHg) comparable with those found in Chagas' disease by Heitmann and Espinosa (1969) who used the same technique.

DISCUSSION

Our findings indicate that asymptomatic abnormality of oesophageal motility is common in diabetes. The radiological and manometric abnormalities detected agree well with those described by Mandelstam and his colleagues (Mandelstam

T A B L E   I V

	No. of Patients	Mean Amplitude of Peristaltic Wave (mmHg) ($\pm$ISD)	Mean Percentage of Swallows followed by Coordinated Peristalsis	Tertiary Contractions	Mean Lower Oesophageal Sphincter Pressure (mmHg) ($\pm$ISD)	
					Pre Bethanecol	Post Bethanecol
Normals and non-diabetics	11	25·8± 8·3	88	3	15 ±4·7	16·2±3·9
Diabetics with alimentary autonomic symptoms	12	22 ± 6·7	70	8	8·4±5·2	18·8±2·8
Diabetics with genitourinary autonomic symptoms	9	17·4±10·2	70	6	7·5±4·5	18·8±6·4
Diabetics with no autonomic symptoms	8	25 ± 4·6	89	4	8·8±5·7	18·0±5·4

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and Lieber, 1967; Mandelstam *et al.*, 1969) and consisted of diminution of the amplitude of peristalsis, resulting in delayed oesophageal emptying in the recumbent position, frequent tertiary contractions, and loss of tone of the lower oesophageal sphincter which often led to gastro-oesophageal reflux. Oesophageal peristalsis, albeit of reduced amplitude, remained properly co-ordinated in almost all our patients.

Degeneration of truncal vagal nerve fibres might well account for oesophageal motor changes in diabetics. In the dog, bilateral vagotomy at hilar or cervical level causes oesophageal dilatation with abolition of peristalsis and loss of tone in the lower oesophageal sphincter (Carveth *et al.*, 1962; Higgs and Ellis, 1965). When truncal vagotomy is carried out for the treatment of duodenal ulcer the level of section is too low to affect peristalsis but the operation may lead to loss of tone of the lower oesophageal sphincter (Woodward, Alexander-Williams, and Atkinson, 1966). Furthermore, the gastric secretory response to insulin-induced hypoglycaemia was subnormal in many of our patients, suggesting that vagal impairment was indeed present (Hosking *et al.*, 1975).

Our findings suggest that in the diabetic the intramural myenteric plexus of the oesophagus is not severely damaged and the clinical, radiological, and manometric abnormalities are quite different from those seen in achalasia and Chagas' disease. Degeneration of the ganglion cells and post-ganglionic nerve fibres of the myenteric plexus leads to hypersensitivity of the oesophageal muscle to the cholinergic agents (Kramer and Ingelfinger, 1951). Heitmann and Espinosa (1969) demonstrated hypersensitivity to bethanecol in Chagas' disease, but, using the same dosage of this drug, we were unable to detect this in diabetic patients. Although bethanecol produced a greater increase in lower oesophageal sphincter pressure in diabetics than in normal subjects, since the initial levels were low in the diabetics those after bethanecol were not significantly higher in diabetics than in normals. In Chagas' disease Heitmann and Espinosa (1969) found a mean rise of 15·9 mmHg in lower oesophageal sphincter pressure but the mean post-bethanecol sphincter pressure (25·4 mmHg) was much higher than that of their normal subjects and exceeded that of our diabetics. The absolute level of lower oesophageal sphincter pressure after bethanecol seems a better criterion to use than does the pressure increase expressed as a percentage of the basal value. If the latter is low, even a small rise will represent a considerable percentage increase and furthermore

there is evidence that the exaggerated response seen after denervation may be related to the development of muscle hypertrophy which would cause higher absolute pressures to be generated. Hence we conclude that hypersensitivity to bethanecol is not characteristic of diabetes and it therefore seems likely that the myenteric plexus is functionally intact.

Histopathological changes have been found in the autonomic nervous system in diabetics (Hensley and Soergel, 1968; Kristensson *et al.*, 1971), and in the vagus patchy degeneration of myelin sheaths with fragmentation and granular change in the axon have been noted. The significance, extent, and frequency of these changes in diabetics is unknown and further studies, including ganglion cell counts for the oesophageal myenteric plexus, are needed.

The clinical significance of the oesophageal motor changes we have found remains uncertain. None of our patients had severe dysphagia and although in six gastro-oesophageal reflux was demonstrated radiologically, and five had associated symptoms, these were all mild. Gastric secretory studies reported elsewhere (Hosking *et al.*, 1975) indicated that many of our patients had vagal impairment and the consequent reduction in acid secretion might protect against the development of reflux oesophagitis.

We found no correlation between the severity of the oesophageal motor disturbance and the presence of alimentary autonomic symptoms in this group of diabetics. In the same group of patients parallel studies of gastric vagal function assessed by the gastric secretory response to insulin-induced hypoglycaemia, also indicated that vagal impairment was not greater in those with alimentary than in those with genitourinary autonomic symptoms (Hosking *et al.*, 1975). Two possible explanations for this apparent discrepancy are that the vagal fibres supplying different parts of the gut may be affected in differing degree or that other factors such as bacterial overgrowth in the intestine may precipitate symptoms.

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