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# Chronic mesenteric ischemia.
## What should the general practitioner know?

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**Summary**

*This review article observes the problems of chronic mesenteric ischemia. It is difficult for general practitioners to diagnose this condition correctly due to lack of specific symptoms. This article discusses the questions of etiology, classification of this condition made by several authors, clinical manifestations depending on localization of vascular lesions and covers the issues of chronic mesenteric ischemia. Aortic angiography, abdominal aorta and mesenteric arteries duplex scanning, computer angiography and magnetic resonance angiography, spiral computer tomography can be used for the diagnostics of visceral artery stenosis. Chronic mesenteric ischemia can be treated conservatively and surgically, considering both urgent and planned operations. The tactics of conservative treatment depends on clinical manifestations' intensity, disease's functional class and should include lipid-lowering therapy.*

**Key words**

*Chronic mesenteric ischemia, ischemic gastropathy, ischemic pancreatopathy, ischemic hepatopathy.*

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Chronic mesenteric ischemia (CMI) is a collective term including different aclinical syndromes and digestive organs' disorders caused by impaired blood supply of abdominal aorta and its unpaired visceral branches inadequate to provide normal tissue functioning due to insufficient oxygen delivery that leads to ischemia development, cell damage and necrosis.

There are more than 20 terms describing this pathology: "angina abdominalis", "chronic mesenteric arteries' obliteration", "mesenteric arterial insufficiency", "chronic mesenteric ischemia", and "abdominal ischemic syndrome". The following codes are included in the International Classification of Diseases: I70.0 – abdominal aorta atherosclerosis, I71.4 abdominal aorta aneurism, I74.0 – abdominal aorta embolism and thrombosis, I77.4 – the syndrome of celiac trunk compression, K55 – intestinal vascular disorders.

The frequency of CMI occurrence is high enough. For example, the study of A.V.Pokrovsky (188) revealed that the lesions of abdominal aorta's unpaired visceral branches appear in 75.5% of autopsies of patients with atherosclerosis of coronary arteries and brain arteries and with arterial hypertension (AH). Atherosclerosis of unpaired visceral branches of abdominal aorta can be detected in 54% of patients undergoing angiography: 45% of general population have isolated celiac trunk atherosclerosis, 18.4% of patients have atherosclerosis of upper mesenteric artery, 1.2% of patients have atherosclerosis of gastroduodenal artery, common hepatic artery atherosclerosis occurs in 1% of cases, splenic artery – in 1% of cases, inferior mesenteric artery – in 15.4% of cases. 66.3% of patients having occluding lesions of unpaired visceral branches of abdominal aorta verified with angiography develop asymptomatic course of this pathology, CMI is diagnosed in 3.2% of patients undergoing in-patient treatment of chronic pancreatitis [2]. Difficult diagnostics of CMI could be explained by the lack of specific symptoms. In general, clinical manifestations of CMI are related to other gastroduodenal zone disorders like gastroduodenitis, hepatitis, pancreatitis, etc. Mesenteric ischemia is detected the most frequently only in case of development of acute mesenterial circulation disturbance that is intestinal infarction.

## Etiology

Acute ischemia of gastrointestinal organs could be caused by thrombosis, embolism, and trauma. Chronic ischemia is caused by intravascular lesions (inherited, acquired) and extravascular compression of visceral arteries. Intravascular lesions occur more frequently than extravascular ones (62-90% of cases comparing with 10-38% of cases, respectively). Atherosclerosis occurring in 52.2-88.3% of cases is the most important cause of acquired intravascular lesions of visceral arteries, the second most frequent cause is Takayasu's arteritis (22-31% of cases). The most common congenital diseases leading to CMI are fibromuscular dysplasia, hypoplasia, visceral arteries; development anomalies, and angiodysplasia. The most frequent cause of extravascular compression is arcuate ligament of diaphragm or its medial crux (40.8-72.5% of cases) [3].

## Classification

There is no common classification of mesenteric ischemia. O.Sh.Oinotkinova and Yu.V.Nemytina (2001) had developed a pathogenetic classification of CME [9].

1. Forms:
- ✓ celiac;
- ✓ mesenteric;
- ✓ celiac-mesenteric

2. Stages of disease:
- ✓ compensated;
- ✓ subcompensated;
- ✓ decompensated;

3. Clinicopathologic variants:

Visceralgia:

abdominal ischemic visceralgia (AIV):
- ✓ stable abdominal visceralgia;
- ✓ progressive abdominal visceralgia;
- ✓ abdominal ischemic visceropathy (AIVP).

Gastroduodenopathy:
- ✓ atrophy;
- ✓ erosions;
- ✓ ulcers (gastric, duodenal).

Hepatopathy:

✓ hepatocellular insufficiency with impairment of protein-synthetic function;

✓ hepatocellular insufficiency with impairment of absorbing and excretory function;

Pancreatopathy:
- ✓ algesic;
- ✓ latent;

with impaired exocrine secretion

with impaired endocrine function

Enterocolopathy:
- ✓ proximal entropathy;
- ✓ terminal colonopathy.

**Complications:**

✓ gastrorrhaggia, perforation;

✓ hepatocellular insufficiency (hepatic coma);

✓ pancreatic insufficiency, diabetes mellitus, pancreonecrosis;

✓ bowel gangrene;

The classification of L.B. Lazebnik and L.A. Zvenigorodskaya (2003) reflects clinical forms and functional classes of CMI [7].

**Ischemic gastroduodenopathies**

- atrophic gastritis, atrophic duodenitis;
- erosive gastritis, erosive duodenitis (acute, chronic);
- ischemic stomach ulcer, ischemic duodenal ulcer;

Complications:

- chronic ischemic gastric ulcer, chronic ischemic duodenal ulcer;
- acute gastrorrhaggia;
- penetrating stomach ulcer, penetrating duodenal ulcer;
- perforated stomach ulcer, perforated duodenal ulcer;.

**Ischemic lesions of pancreas (ischemic pancreatopathies):**

- acute ischemic pancreatitis;
- chronic ischemic pancreatitis;
- pancreatic lipomatosis.

Complications:

- secretory and incretory pancreatic insufficiency;
- diabetes mellitus;
- pancreatic cyst;
- pancreatic sclerosis;
- pancreatonecrosis.

**Ischemic lesions of liver (ischemic hepatopathies):**

- acute ischemic hepatitis;
- chronic ischemic hepatitis;
- non-alcoholic steatohepatitis;

Complications:

- hepatic fibrosis;
- liver cirrhosis;
- hepatocellular insufficiency;
- hepatic coma.

**Ischemic lesions of intestine (enterocolopathies):**

- ischemic enteropathies (mesenteric ischemia);
- ischemic enteropathy with the syndrome of impaired absorption;
- chronic ischemic ulcers of small intestine;
- ischemic colopathies with mucous membrane atrophy;
- ischemic colitis;
- schemic ulcers of large intestine;

Complications:

- large intestinal strictures;
- acute intestinal obstruction;
- acute enterorrhagia;
- intestinal infarction;
- bowel gangrene;
- fecal peritonitis.

## Functional classes

✓ Functional class I (FC I) – no evident clinical symptoms. These patients have no impaired blood supply at rest and develop abdominal pain only after stress testing.

✓ Functional class II (FC II) – signs of impaired blood supply at rest and their aggravation after stress testing, evident clinical symptoms: pain and indigestion syndromes, weight loss, impaired pancreatic function, impaired secretory and absorptive function of intestine;

✓ class III (FC III) – patients with constant pain syndrome, weight loss and dystrophic changes of digestive organs.

Blood supply of digestive organs is provided by three unpaired visceral branches of abdominal aorta: celiac trunk (CT), superior and inferior mesenteric arteries (SMA and IMA). Three independent arterial pools mentioned above are tightly linked between each other with collateral vessels. The most important collateral vessels are celiacomesenteric and intermesenteric anastomoses. Straight intermesenteric anastomosis is also known as Riolan's arcade normally present in 2/3 parts of population. Marginal artery of Drummond is an important vessel connecting superior and inferior mesenteric arteries. Left colic branch of middle colic artery from the system of superior mesenteric artery makes anastomosis with left colic artery from the system of inferior mesenteric artery at the splenic flexure of the colon. This so-called Triffitt point is a critical segment of large intestine. 5% of people have open-loop blood supply at this point, which predisposes splenic flexure of the colon to ischemia in case of any decrease of perfusion pressure in the system of mesenteric arteries.

Localization of ischemic damage of digestive organs depends on visceral artery responsible for their blood supply. CT lesions result in damage of the organs of the upper part of abdominal cavity: liver, pancreas, stomach, duodenum and spleen. SMA occlusion or stenosis lead to abnormal function of small

intestine, and IMA lesions cause large intestine's (LI) ischemia. At the same time, well-developed system of collateral vessels between visceral arteries provides long-term functional compensation in case of impaired main blood supply; due to this lesions of visceral branches of abdominal aorta do not always lead to the development of chronic ischemic symptoms in digestive organs. Clinical symptoms manifest in the most evident way in case of lesions of 2-3 visceral arteries [4, 6].

According with the opinion of M.V. Tarbaeva (A.V. Vishnevsky Institute of Surgery), in case of atherosclerotic lesions of visceral arteries, atherosclerotic plaques are the most likely to be found in the proximal segment of the artery within the distance of 1-2 cm. Normally this process spreads from the aortic wall. Usually IMA is involved, TC lesions occur less frequently. Isolated lesions of single visceral arteries are not typical for Takayasu's arteriitis, normally both abdominal aorta and several visceral branches are involved. Arteries' lesions are usually more extensive. Takayasu's arteriitis is characterized with good collateral blood supply and big diameter of involved vessels, in particular, Riolan's arcade. In case of extravascular compression of celiac trunk with falciform ligament of diaphragm stenosis leads to abnormal laminar blood flow and facilitates thromb formation and embolism development. Thus, acute visceral ischemia can be a possible consequence of CMI syndrome.

## Clinical syndromes of CMI

Gastroduodenal (erosive and ulcerous) syndrome appears in 46.2% of cases and is the most frequent clinical form of CMI of digestive organs, according with the results of the study that had been hold in Central Research Institute of Gastroenterology.

Erosive and ulcerous lesions of gastroduodenal zone in CMI are characterized by disease manifestation as a bleeding episode, lack of seasonal disease exacerbations, atypical clinical symptoms, high frequency of concomitant cardiovascular diseases, relapses, big dimensions of ulcers, low efficacy of antiulcerant therapy [5].

The frequency of ischemic pancreatopathy in CMI is 33.9% [6]. The main feature of pancreatic circulation is the lack of its own major arteries. Blood supply of pancreas is provided by the branches of common hepatic artery, SMA and lienal artery. The frequency of development of pancreonecrosis and ischemic pancreatopaties in CME is determined by these anatomic features.

Ischemic pancreatopathy can manifest as acute ischemic pancreatitis and fatal ischemic chronic pancreatitis. V.T. Ivashkin and coauthors [3] investigated clinical features of chronic pancreatitis with evident atherosclerotic lesions of mesenteric vessels and found out the following characteristics of this pathologic condition: older age of patients, less evident pain syndrome, high frequency of coronary heart disease (CHD) and AH, combination of chronic pancreatitis and erosive changes of gastroduodenal zone resistant to pharmacological treatment.

It is also necessary to take into account the fact that pancreatic ischemia appears very rarely as a single ischemic lesion and more frequently is combined with ischemic lesions of other abdominal cavity organs.

According with the results of L.A.Zvenigorodskaya and coauthors [2], ischemic lesions of intestine have the third position between the other forms of CME.

Ischemic colitis (IC) is characterized with restricted lesions of large intestine combined with the development of ischemia, inflammatory edema of mucosa, ulcers, bleeding, and fibrous strictures of colon, IC manifests more frequently in elderly and old patients with CHD, AH and diffused atherosclerosis.

IC development is characterized with impaired blood supply in the systems of CT, SMA an IMA. Typical feature of colon blood supply is the presence of collateral vessels connecting it with SMA and Riolan's arcade – parallel or marginal vessel passing along its mesenteric edge. IMA constriction causes segmentary ischemic lesions in the area of colon's splenic flexure, its ileocecal and rectosigmoid parts. Rectum blood supply is mediated by superior and inferior rectal arteries. Due to the presence of numerous intramural anastomoses between them rectum is rarely involved in CMI development. Mucosal lesions of large intestine are also inhomogenous because colon's free edge receives less blood supply than its mesenteric edge [2].

L.A. Zvenigorodskaya and coauthors notice that microscopic IC is more common than traditionally described IC forms. Microscopic ischemic signs (superficial epithelial necrosis, reduction of goblet cells' number, local lymphocyte infiltration, abnormal microcirculation with the development of stasis, thrombosis and plasmorrhagia in lamina propria of large intestinal mucosa) appear before macroscopic changes. Typical symptoms of microscopic ischemic colitits include postprandial abdominal pain mostly in left ileac region, constipation, abdominal discomfort, and flatulence. Abdominal palpation results in pain

and spasm in sigmoid colon, blind intestine is dilated, the psoas sign is positive [2, 3].

## Diagnostics

CMI diagnostics is based on detalization of patient's complaints, history taking, physical examination and instrumental/laboratory tests. Patient's history details reveal the presence of cardiovascular diseases, obliterating endarteritis, metabolic syndrome, diabetes mellitus and allow selecting risk groups for possible abdominal aorta atherosclerosis development (78% sensitivity). Postprandial abdominal pain is the main symptom in the majority of patients. Pain features may be different; initially it is discomfort in epigastrium, it changes to dull pain when circulatory lesions start to be more severe. Intestinal dysfunction is the second frequent sign of abdominal ischemia manifesting as abnormal secretory and absorptive function of small intestine (flatulence; unstable, frequent, watery stool) and evacuative function of large intestine with persistent constipation. Progressing weight loss is the third frequent symptom of CMI, and it is related both to patients' refusal to take food because of pain and impaired secretory and absorptive function of small intestine, which becomes particularly evident in the late stage of the disease [2, 3].

During auscultation systolic murmur can be heard in the projection of abdominal aorta's visceral branches. In case of TC stenosis murmur's epicenter is localized 2-4 cm below xiphoid process, in case of SMA lesions it can be found 2-3 cm below the previous position. Murmur indicates possible arterial lesions (the frequency of its detection is around 14-92.6%), but its absence does not allow excluding ischemia. Additional diagnostic tests should be directed on estimation of digestive organs' functional condition, detection of atherogenic dyslipidemia, abnormal blood rheological characteristics.

The following techniques can be used for the diagnostics of visceral arteries' stenosis [4, 11, 12]:

- aortoangiography;
- color Doppler ultrasonography of abdominal aorta and its visceral branches;
- computer angiography, magnetic resonance angiography, spiral computer tomography;

## Treatment

CMI treatment is based on conservative and surgical techniques. It is possible to use planned surgery: reconstructive surgery eliminating occlusion and restoring circulation (endoscopic resection of plaques, vascular grafting), creation of vascular bypasses around a diseased artery – vascular bypass operations, percutaneous endovascular angioplasty, laser recanalization. Urgent surgical interventions in acute mesenteric ischemia usually result in bowel resection [12].

Conservative treatment tactics depends on severity of CMI clinical manifestations, thus its FC, and should include hypolipidemic therapy. Clinical guidelines and published articles shed almost no light on treatment of atherosclerotic lesions of unpaired visceral branches of aorta. Nevertheless, experts think that statins are indicated to patients with atherosclerosis of abdominal aorta and its branches (Class and level of evidence IIaC) [10].

Dozens of randomized clinical trials that have proved the efficacy of statins and their role in cardiovascular risk reduction have been conducted within the last 15 years.

According with the guidelines [1, 8, 10], dyslipidemic therapy of visceral branches' atherosclerotic lesions does not differ from the therapy of patients with high cardiovascular risk. But it is necessary to take into account the fact that more frequent control of drugs' safety is required in case of abnormal hepatic and pancreatic function common for TC atherosclerosis, and also in case of elevated blood levels of liver enzymes.

The most rational strategy considers prescription of the last generation statins like atorvastatin and rosuvastatin with well-proved impact on prognosis and good patients' tolerability. Results of numerous clinical studies demonstrate that statins significantly reduce CVD morbidity and mortality if being used for primary and secondary prevention. In clinical studies statins slowed down progression and even caused regression of coronary arteries' atherosclerosis [10].

The MIRACL and SPARCL studies have proved the efficacy of atorvastatin in acute cardiovascular catastrophes (unstable angina and stroke). The REVERSAL study of atorvastatin and the ASTEROID study of rosuvastatin demonstrated the important ability of statins not only to modify lipid blood spectrum (reduce the low density lipoproteins' (LDL) levels) but also to have direct impact on atherosclerotic plaques, stabilizing and reducing the volume of atheroma.

Statins were presented as the first line drugs for atherosclerosis treatment in the last European Guidelines on cardiovascular disease prevention in clinical practice (2016) [15].

It is necessary to reach target levels of LDL in order to reach the desired effect during statins' therapy.

Table 1. **LDL cholesterol target levels (mmol/L) depending on risk category**

| Lipid parameters | In population (low risk) | Patients with moderate risk | Patients with high risk | Patients with very high risk |
|---|---|---|---|---|
| TCh | ⩽5.5 | ⩽5.0 | ⩽4.5 | ⩽4.0 |
| LDL cholesterol | ⩽3.5 | ⩽3.0 | ⩽2.5 | ⩽1.8 |
| HDL cholesterol | males.>1.0 females.>1.2 | males>1.0 females.>1.2 | males >1.0 females >1.2 | males >1.0 females>1.2 |
| TG | ⩽1.7 | <1.7 | <1.7 | <1.7 |

Patients belonging to the very high risk group have LDL cholesterol target levels <1.8 mmol/L (< ~70 mg/dL), if this value is impossible to reach it is recommended to reduce LDL cholesterol levels by 50% of its initial levels. The patients of the high risk group have LDL cholesterol target levels <3.0 mmol/L (<~100mg/dL). The patients of the moderate risk group have LDL cholesterol target levels <3.0 mmol/L (<~115 mg/dL).

LDL cholesterol target levels depending on risk category are present in Table 1.

It is necessary to evaluate the blood levels of lipids, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), creatine-phosphokinase (CPK). 4-6 weeks after the start of the therapy it is necessary to evaluate treatment's safety and tolerability (repeat blood tests for ALT, AST and CPK) and the presence of muscular symptoms. For dose titration it's necessary pay attention at first on treatment's safety and tolerability, at second – on reaching target level of lipids. If transaminases' activity levels are elevated more than 3 times above the reference levels and/or CPK levels are 4 times higher than normal ones and if they are elevated less than 10 times in respect to reference values, it is necessary to cancel statin therapy or reduce their dose, to repeat blood test in 4-6 weeks, and to perform the monitoring of patient's condition and kidney function. Apart from this, it's necessary to exclude other causes of elevated enzymes' levels and evaluate all bilirubin fractions. Elevated levels of conjugated bilirubin are more significant than ALT and AST activity, if there is no biliary tracts' obstruction. If AST/ALT levels are ⩽ 3 values of upper reference level, it is possible to continue the treatment with regular (after each 4-6 weeks) control of enzymes' blood concentration. If there are the signs of active hepatic lesions, hyperbilirubinemia or CPK levels elevation more than 10 times above upper reference level, statins therapy should be cancelled in order to find out the cause of abnormal blood tests.

Several options are possible for patients intolerant to one statin drug: change of one statin for another, reduction of initial dose, taking statins once for 2 days or twice for a week, ezetimibe prescription and maximal lifestyle change. Combined use of statins and ezetimibe can be considered as a variant of treatment for patients with severe hypercholesterolemia who are intolerant to high doses of statins or haven't reached the target levels of LDL cholesterol. If these drugs are not effective, PCSK9 inhibitors prescription can be discussed [15].

Chronic liver diseases, non-alcoholic steatohepatitis or steatohepatosis with normal levels of liver enzymes are not considered to be contraindications for therapy with statins.

Statins are indicated to both young and elderly patients with verified CVD. From safety point of view, it's necessary to prescribe statins to elderly patients starting from the minimal dose with consequent monitoring of patient's condition. If statins are indicated for patients above 75 years, it is necessary to evaluate the correlation between risk and benefits. It is better to take into account the fact that elderly women of asthenic constitution receiving many drugs have elevated risk of myopathy, rhabdomyolisis and DM development in case of treatment with statins [15].

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