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Angiología

Review

Update on biomarkers for the early detection of intestinal ischemia

Actualización de biomarcadores para la detección precoz de la isquemia intestinal

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Abstract

Intestinal ischemia associates high mortality rates mainly due to delayed diagnoses. Although computed tomography angiography (CTA) remains a sensitive and specific tool, it often takes a long time to perform it in the presence of unspecific clinical presentations. In this time lapse, intestinal ischemia may progress into an irreversible stage with signs of systemic failure. The acquisition of precise and early detection biomarkers of the disease would shorten time to diagnosis and hence its associated mortality. It is widely accepted that the molecules that have traditionally been used —lactate among them— do not have proper diagnostic capabilities. Nevertheless, the D-stereoisomers of lactate and procalcitonin have shown high sensitivity rates for the detection of ischemic colitis after open aortic surgery while D-dimer measurement is recommended to rule out acute mesenteric ischemia in patients with abdominal pain. Other molecules with a potential for diagnostic yield that are still in the pipeline are intestinal fatty acid binding protein (i-FABP) and glucagon-like peptide-1 (GLP-1).

Keywords:
Intestinal ischaemia. Mesenteric ischemia. Ischemic colitis. Biomarkers. D-lactate. I-FABP. GLP-1.

Resumen

La isquemia intestinal asocia una elevada mortalidad debida principalmente a un retraso en el diagnóstico. Si bien el angio TC es una herramienta sensible y específica, suele transcurrir demasiado tiempo hasta su realización debido a una presentación clínica poco específica. En este tiempo la isquemia intestinal puede progresar a estadios irreversibles con afectación sistémica. La obtención de biomarcadores precisos y de elevación precoz acortaría el tiempo diagnóstico de esta patología, lo que disminuiría su mortalidad asociada. Se sabe que las moléculas usadas tradicionalmente, entre ellas el lactato, no tienen buena capacidad diagnóstica. No obstante, se ha observado una elevada sensibilidad con el uso del esteroisómero D del lactato y la procalcitonina para detectar colitis isquémica tras cirugía de aorta, al tiempo que se recomienda valorar los niveles de dímero D para descartar isquemia mesentérica aguda en pacientes con dolor abdominal. Otras moléculas con un potencial rendimiento diagnóstico son la proteína ligadora de ácidos grasos intestinales (I-FABP) y el péptido similar al glucagón de tipo 1 (GLP-1), aún en investigación.

Palabras clave:
Isquemia intestinal. Isquemia mesentérica. Colitis isquémica. Biomarcadores. D-lactato. I-FABP. GLP-1.

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INTRODUCTION

Acute mesenteric ischemia (AMI) is due to a deficit of perfusion at bowel level. Vascular dysfunction is mainly due to the acute occlusion of the superior mesenteric artery (SMA). However, in 15 % of the cases, non-occlusive hypoperfusion due to low cardiac output has been reported while in another 15 % of the cases it is due to mesenteric venous thrombosis (1). Mortality rate can be as high as 75 % to 90 % and is mainly due to a delayed diagnosis with the corresponding development of a large bowel infarction, often in elderly patients with multiple comorbidities (2). Occlusion due to in situ thrombosis can occur on a previously diseased artery with calcification and atheromatous plaques giving rise to symptoms of chronic mesenteric ischemia before the acute episode like postprandial abdominal pain and ponderal loss due to abdominal angina. In these cases, lesions are often found at the origin of the artery, and bowel infarction is often large. On the other hand, embolic occlusion often damages the artery most distal sectors with less extension of the infarcted area, and often associating synchronically embolic processes in different places (1).

Compared to thin bowel damage due to SMA occlusion, we should remember cases of ischemic colitis following damage to the inferior mesenteric artery (IMA), which are especially relevant in the aortic pathology setting. Therefore, the rate of ischemic colitis after infrarenal aortic aneurysm repair surgery is around 3 % and 36 % for elective and emergency procedures, respectively, with mortality rates as high as 90 % in cases of transmural damage (3). The use of routine colonoscopy shows even higher rates (7.4 % in cases of elective repair of abdominal aorta aneurysm), and as high as 60 % in cases of rupture (4). In these cases, ischemic colitis predominantly damages the sigmoid colon, and hypoperfusion, embolization, and reperfusion damage are some of the triggering causes involved in the pathogenesis of both macro- and microcirculation. Macrocirculation can be affected by AMI or hypogastric artery ligation if enough collaterality is lacking. Regarding microcirculation, perioperative hypotension or the administration of catecholamines can cause perfusion deficit (4).

We should mention that if the mortality rate of intestinal ischemia has been somewhere around 60 % to 80 % over the past few decades despite de advances made in imaging modalities and treatment, it is mainly due to delayed diagnoses where clinical suspicion plays a crucial role (5). Classical clinical presentation consists of diffuse periumbilical pain often disproportionate in relation to physical examination. Also, in 25 % of the cases, there is no abdominal pain (6). If we agree that revascularization should be performed when ischemia is still reversible —ideally before transmural damage has occurred— then early diagnosis is necessary to reduce the mortality rate. Although CTA is the most sensitive and specific imaging modality available today (5) often too much time passes by before his imaging modality can be accessed since clinical presentation is non-specific in relation to its actual severity (6). In addition, there are times that exploratory laparoscopy should be used to confirm clinical suspicion. Also, it is not uncommon to find healthy bowels that require no procedures at all. Therefore, a marker —not only of early elevation but also an accurate one— would help us prevent the morbidity associated with the surgical technique in cases where clinical suspicion turns out negative (7).

The objective of this study is to review the current evidence available on the biochemical markers used in the early detection of intestinal ischemia, and those that are still in the pipeline although with possible clinical potential.

DEVELOPMENT

Pathophysiology

Splanchnic circulation requires nearly 25 % of the cardiac output at rest and can require an additional 10 % in the postprandial state. Over two thirds of this blood go directly to the mucosa and submucosa layers of the GI tract to facilitate nutrient exchange (6). Therefore, cellular damage associated with ischemia starts with peeling and bleeding of the mucosa villi that are highly sensitive to hypoperfusion and hypoxia. With longer ischemia times, the intestinal barrier starts to degenerate. This epithelial degeneration promotes the passage of endoluminal structures like bacterial

endotoxins to systemic circulation, which makes us think that certain parameters of bacterial translocation are useful to detect tissue necrosis in the early stages. This bacterial translocation can trigger the systemic inflammatory response syndrome (SSIR) with the corresponding recruitment of inflammatory mediators that enhance bowel hypoperfusion and tissue damage (8). Therefore, although ischemic damage to the intestinal mucosa can be reversed, transmural damage results in inflammation, necrosis, sepsis, and multiorgan failure (5). In advanced stages of ischemia, the decision to revascularize these patients can be controversial since, although reperfusion is key to avoid disease progression into necrosis and the need for bowel resection, we should consider that the oxygen supply that follows proper revascularization can be associated with more cellular damage and hemodynamic instability by promoting the formation of free radicals that stimulate recruitment and leukocyte activation, thus increasing microvascular patency due to loss of integrity at endothelial level (6) and create greater oxidative stress that accelerates necrosis, multiorgan failure, and death (8).

Biochemical markers

Compared to the early and accurate markers of myocardial or hepatic damage for the diagnosis of ischemia in these organs, serological markers of intestinal ischemia provide poorer, less accurate, and maybe less useful information. The complexity of the GI tract made up of several tissues (mucosa, submucosa, and muscular layers) is one of the possible explanations to this phenomenon that alters the blood concentration of different molecules. Secondly, we should remember that the molecules released by the intestine pass on to the portal system being many of them cleared by the liver without ever reaching systemic circulation. Finally, also in association with the liver, several markers of intestinal damage are also expressed by hepatic tissue being the origin of the molecule difficult to spot when detected in peripheral blood (7). Therefore, in the search for new markers to achieve early diagnoses, the ideal molecule should be tissue-and-ischemia specific, metabolically stable, indicate actual damage, and highly sensitive (5). The structural integrity of the protein should be kept during portal circulation and after hepatic metabolism in such a way that it can be analyzed in samples of peripheral venous blood. Also, since ischemia starts in the mucosa and spreads towards the serosa, a protein derived from the mucosa layer will be a better early marker compared to a different protein derived from the seromuscular layer (1). Also, high sensitivity is required to rule out diagnosis plus enough specificity to perform the CTA.

Also, we should mention that the practical utility of markers to detect intestinal ischemia depends on the prevalence of this entity in the different clinical settings. Therefore, in low prevalence settings, the use of highly specific markers can be useful to discriminate false positives. Where the prevalence of intestinal ischemia is higher (surgeries with prolonged clamping, use of inotropes at high doses), the use of very sensitive markers (D-dimer, D-lactate) can be appropriate to minimize the rate of false negatives (7).

Bottom line is that, up until now, none of the traditional markers used to detect intestinal ischemia (lactate, lactate dehydrogenase, creatine kinase, leukocyte count, base excess) has good diagnostic capabilities (5) since they are associated with systemic inflammation and macrophage activation, which is indicative of advanced disease progression into visceral ischemia (6). Also, it has been quite demonstrated that markers of muscular damage: lactate dehydrogenase (LDH), and creatine kinase (CK) are equally high in patients with and without intestinal ischemia (5, 9). Therefore, we should really look for other alternatives.

Lactate

Serum lactate has been used as a marker of bowel damage for the last 50 years. This molecule is produced in states of anaerobiosis due to the action of lactate-dehydrogenase (LDH) enzyme on the pyruvate generated in glycolysis, thus obtaining cells their energy (ATP). This resulting lactate is collected from peripheral tissues and transformed into pyruvate and glycose in the liver through the Cori cycle. In states of shock and sepsis, liver failure explains why lactate

accumulates in blood due to lack of use rather than an increased production in the tissue hypoxia setting (10). Therefore, it is currently widely accepted that lactate is a non-specific marker of tissue hypoperfusion and is only elevated in advanced stages of intestinal ischemia (10). Therefore, we should mention that, to this date, lactate has prognostic value since low levels are suggestive of success after treatment (6).

All in all, recently, attention has been brought upon the differentiation between L- and D-stereoisomers, molecules with the same chemical composition that vary in the 3D arrangement of atomic groups in space (6). On the one hand, L-lactate is present in all cells as the product of glycolysis in conditions of hypoxia. Early elevation is rarely assessed because it is subject to intense hepatic metabolization, which explains its absence at systemic level even in processes of extensive intestinal ischemia. When detected, it is often indicative of advanced hypoperfusion with transmural infarction, and metabolic acidosis (6). Therefore, it should not be used as an early diagnostic marker (1). Its functional increase works as an unfavorable prognostic marker rather than as a diagnostic marker (11).

On the other hand, D-lactate, a product of bacterial fermentation performed by the gut microbiota accumulates in blood when it escapes through an intestinal barrier weakened by ischemia. Also, its half-life —longer compared to other compounds like lipopolysaccharide released into the blood flow following mucosal disruption— make it a good candidate as a marker of intestinal ischemia. However, although it is a molecule of intestinal origin only, it is found elevated in several settings like gastric bypass surgery, the short bowel syndrome, and in people with abundant glycose intake, and those who use probiotics (11). Therefore, while some studies indicate that it has a scarce discriminatory value to detect intestinal ischemia (2, 5), others have demonstrated its utility in the aortic surgery setting with highly elevated D-lactate levels within the next 2 hours after surgery in patients who developed ischemic colitis confirmed on the histopathological exam. Also, these elevated levels were maintained two days after surgery compared to patients who didn't develop this complication (3). Sensitivity rates > 80 % have been reported for values > 0.2 mmol/L (7).

D-dimer

D-dimer —well known marker of fibrinolysis— is used to detect thrombotic processes. Highly sensitive rates (96 % to 100 %) for the detection of mesenteric ischemia have been reported. Also, it is a marker for early elevation. (1) However, its specificity is low (40 %), and even though its sensitivity is high, its utility to discard ischemia when it tests negative is still controversial (6). However, the European Society of Vascular Surgery (ESVS) recommends its measurement as a way to rule out acute mesenteric ischemia in patients with acute abdominal pain (12) since it has confirmed 90 % sensitivity and 23 % specificity rates for the detection of D-dimer levels > 0.2 mg/L (2). However, determining D-dimer is irrelevant for the diagnosis of postoperative intestinal ischemia since it is always high due to surgical trauma.

Procalcitonin

Procalcitonin (PCT) marker also seems like a promising prognostic marker of acute mesenteric ischemia. It is a precursor of calcitonin, and it is thought to be released from hepatic parenchyma in pathological situations before the stimulation of bacterial endotoxins, tumor necrosis factor, and interleukin-6 (IL-6). It is used as a marker of bacterial infection because its secretion through hepatic parenchyma is stimulated by endotoxins. As a matter of fact, when PCT is not used, the distinction between bacterial infection and non-bacterial inflammation can be difficult to make since leukocyte count and the level of C-reactive protein appear elevated in both conditions. In the case of intestinal ischemia, endotoxin elevates in blood due to an impaired intestinal barrier showing elevated levels of PCT. (4) Its capacity to discriminate patients with intestinal ischemia has been demonstrated. Also, it is marker of necrosis, lesion spread, and mortality (5,13,14). It has a high negative predictive value (> 80 %) to rule out ischemic colitis after aortic surgery. As a matter of fact, PCT levels > 2.0 ng/mL two days after surgery are associated with 100 % sensitivity and 83.9 % specificity rates for the detection of ischemic colitis. Colonoscopy is advised for the early detection of ischemic complications in patients treated with aortic surgery with serum PCT levels > 2.0 ng/mL two days after surgery (4).

Glutathione S-transferase

Glutathione S-transferase (GST) is a cytosolic enzyme involved in detoxification processes. It acts as a marker of oxidative stress and is released by several tissues as a response to ischemia, among them, the intestine, and the liver. Although some studies conducted with animals show encouraging data, the same promising results have not been seen in human cohorts. Therefore, its clinical utility is still controversial, and more research is required on this regard (6,7).

Intestinal fatty acid-binding protein

Specific to intestinal tissue, the intestinal fatty acid-binding protein (i-FABP) is, maybe, the most promising marker of all (5). This is a cytosolic protein of enterocytes of intestinal villus. The loss of cellular membrane integrity as a response to malperfusion is associated with the quick release of this protein into systemic circulation and since it is excreted by the kidney, it can be detected both in plasma and urine. Favorable sensitivity (90 %) and specificity (89 %) rates for the early detection of acute mesenteric ischemia have been reported (6). In addition, it has been proposed that measuring i-FABP in urine can improve diagnostic accuracy (1).

In the context of open repair of aortic aneurysm, elevated levels of plasma i-FABP at the end of surgery demonstrated a 100 % sensitivity and 98.1 % specificity rates for the detection of intestinal ischemia (15). In such study, during aneurysm repair surgery, the i-FABP was elevated in all the patients reaching its highest peak at the end of the procedure. Kidney function was not associated with changes to plasma levels. However, in patients who developed intestinal necrosis, the i-FABP reached peak levels and plasma concentration remained high one day after surgery compared to those who did not develop necrosis, in whom the i-FABP levels came back to baseline values 1 day after surgery. These results are indicative that measuring i-FABP levels 1 day after surgery can help us identify patients who would benefit from re-laparotomy or exploratory laparoscopy anticipating the indication 24 to 48 hours vs the decision based on exploratory clinical criteria only. On the other hand, the use of i-FABP plus hypoxia parameters like elevated lactate levels and reduced serum pH contributes to defining the intestinal origin of hypoxia in these patients (15).

Glucagon-like peptide 1

Finally, we should mention the glucagon-like peptide 1 (GLP-1) intestinal hormone produced by enteroendocrine L-cells from distal ileum and colon epithelium. The clinical interest triggered over the past few years lies in its therapeutic potential against diabetes type 2 since it is an incretin hormone that plays an insulinotropic role on pancreatic beta cells, thus stimulating insulin biosynthesis and inhibiting the production of glucagon. Also, it delays gastric emptying and induces satiety, thus reducing food intake. Its secretion is basically stimulated by the nutrients absorbed after contact with membranous receptors on the surface of L-cells. However, it has been reported that postprandial elevation of plasma GLP-1 precedes the arrival of food to distal intestine where L-cells can be found. This discrepancy triggered the discovery of other mechanisms involved in the secretion of this hormone finding receptors capable of recognizing neurotransmitters, other hormones, and inflammatory molecules in L-cells. Therefore, beyond its role in the metabolism of glucose, the GLP-1 could have other functions, especially in association with enteral inflammation. As a matter of fact, lipopolysaccharides —proinflammatory molecule present on the surface of gram-negative bacteria— stimulate the secretion of GLP-1 directly by activating the Toll-like receptor (TLR-4) of enteroendocrine L-cells, a phenomenon that occurs rapidly after the onset of intestinal ischemia (8). Therefore, as the intestinal barrier disintegrates due to ischemia, endoluminal lipopolysaccharides start gaining more access to the enteroendocrine cells of the epithelium, thus stimulating the secretion of GLP-1. This is a process that would take place even before the necrosis of the mucosa, being, the physiological response of epithelial cells when they contact with the contents of intestinal lumen that are often kept at a distance from the epithelium due to the glycocalyx secreted by these cells. The secretion of GLP-1 is, therefore, different compared to other study markers that are only released after cellular death (i-FABP) or when systemic inflammation is already happening (D-lactate, procalcitonin).

CONCLUSIONS

1. Intestinal ischemia is still a diagnostic challenge that vascular surgeons face.
2. Among the aforementioned markers, at least, L-lactate does not contribute to early diagnosis because it is non-specific and elevated levels occur in advanced stages.
3. D-lactate, however, has demonstrated some diagnostic utility together with D-dimer and procalcitonin on whose utility there is evidence with established cut-off values to take measurements in the routine daily practice.
4. Finally, i-FABP and GLP-1 —more promising and specific— are still far from being incorporated to the routine clinical practice. Research should be encouraged to improve the diagnostic timing of this disease that is associated with high morbidity and mortality rates.

Table I below includes the biomarkers analyzed with their corresponding degree of validity based on current evidence available.

Table I. Biomarkers analyzed and current validity

Biomarkers for the early detection of intestinal ischemia	Degree of validity
Lactate dehydrogenase (LDH)	+
Creatine kinase (CK)	+
L-lactate	+
D-lactate	+++
D-dimer	+++*
Procalcitonin (PCT)	+++
Glutathione S-transferase (GST)	++
i-FABP	++
GLP-1	++

*Degree of validity: + non-specific; ++ under study; +++ in experimentation. GLP-1, glucagon-like peptide 1; i-FABP, intestinal fatty acid binding protein. * It has validity in the context of patients with acute abdominal pain without previous surgeries since in the postoperative period, D-dimer levels are often high due to the activation of fibrinolysis (false positive).*

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