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Pathophysiological mechanisms of type 2 diabetes mellitus involved in acute mesenteric ischemia

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ABSTRACT

Type 2 diabetes mellitus is a complex condition with high prevalence in the global population, implying multiple complications for the entire organism. It is essential to understand its implications in the development and evolution of other pathologies in order to manage efficiently their complications thus decreasing overall mortality. A surgical pathology potentially associated with type 2 diabetes is acute mesenteric ischemia. Although it has a decreased prevalence in the global population, mesenteric infarction is related to an extremely high mortality rate due to its elusive clinical presentation and rapid progression. The difficult diagnosis emphasizes the need to make associations between acute mesenteric ischemia and other pathologies involved in its evolution, such as type 2 diabetes mellitus. This metabolic disease raises the risk of macro and microvascular complications, therefore disturbing the vascularization of the bowel. The purpose of this review is to describe how diabetes is particularly involved in all four types of mesenteric infarction by modulating different physiopathological mechanisms based on the process of atherosclerosis and other endothelial molecular processes.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease with a significant prevalence in the global population, being found in 1 out of 10 adults with age between 20 and 79 years, and in 3 out of 4 adults living in low and medium-income countries [1]. Due to its high incidence and its multiple complications, T2DM was considered in 2016 the seventh cause of death worldwide [2]. Therefore, it is necessary to study its effects on the entire organism in order to understand the development and the outcome of the eventual complications. This will potentially allow for prompt and efficient treatments for decreasing its mortality.

A potential complication of T2DM is acute mesenteric ischemia (AMI) [3], a surgical pathology defined as a sudden interruption of blood perfusion on a part of the bowel, which leads firstly to ischemia and then to intestinal necrosis [4]. Even if it is a rare cause of hospitalization, with a prevalence between 0.09% to 2%, the mortality of AMI is significant, being approximated between 60 to 80% [5]. Because an increased time length from the onset of symptoms is linked with a greater extension of intestinal necrosis, the survival rate is associated with the rapidity of diagnosis. The study of Kassahun et al. reports that 50% of the patients diagnosed within the first 24 hours survived, while the survival rate tends to decrease to below 30% for those diagnosed in over 24 hours [6]. This data is relevant because it highlights the need of a rapid diagnosis of AMI, a process that necessitates the connection with other pathologies that predispose to its development, such as T2DM.

The link between T2DM and AMI is highlighted by previous studies showing a prevalence of 64% of diabetes in 83 patients who needed surgical intervention as a treatment for mesenteric infarction [7]. Moreover, 26% of

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patients diagnosed with acute or chronic mesenteric ischemia associated diabetes [8]. Furthermore, the study of Chiu et al. demonstrated that T2DM raises the risk of developing AMI by 1.31-fold, compared with patients without diabetes [3].

T2DM is not only involved in the development of AMI, but also in the outcome of this disease, raising the incidence of perioperative complications [9] and decreasing the cumulative survival postoperative rate [10]. In a study made on a cohort of 1525 patients with T2DM who underwent orthopedic and general surgery interventions, it was found that 7.7% had adverse events such as delayed extubating (34.4%), circulatory disorder (36.4%), increased time of wound healing (9.3%), infections (12.7%) and death (2.5%) [11]. This data highlights the importance of being aware of T2DM as a risk factor in the development and outcome of other diseases and as a major component in the general mortality rate, raising it by 35% compared to a non-diabetic person [12].

Discussions

For this review there were used articles selected through search engines such as PubMed, Web of Science and Scopus, using the formula: (diabetes) AND (type 2 or type two) AND (acute mesenteric ischemia) AND (mesenteric infarction) AND (physiopathological mechanism).

Considering the Prisma guidelines, in the stage of identification, a number of 91 articles generated by the engines were selected. Removing the duplicates, 3 articles were excluded, remaining a number of 88 articles that were screened by title and abstract. We eliminated the articles written in other language than English, Clinical cases, articles with only abstracts available and letters to the editor. The 85 remaining articles were assessed for eligibility in full text, and a number of 5 articles were eliminated due to their topic focused mainly on type 1 diabetes mellitus, chronic mesenteric ischemia and mesenteric infarction treatment. All these processes led to 80 full-text articles included in augmenting the topic of this review (Figure 1).

Even if AMI can be caused by other pathologies not related to T2DM, it is obvious that this metabolic disease has a negative impact on the development and outcome of AMI. T2DM raises the risk of macro and microvascular complications, which also disturb the vascularization of the bowel [13]. The study of Sheleme et al. analyzed a cohort of 330 participants diagnosed with T2DM and found that 38.5% of them had one or more chronic complications [14]. In comparison, similar studies conducted in Saudi Arabia [15] and China showed a prevalence of complications associated with diabetes in a proportion of 42.7%, respectively 52% [16]. These studies have in common a significant rate of complications, which suggests that T2DM should be further investigated in order to understand and treat these side effects.

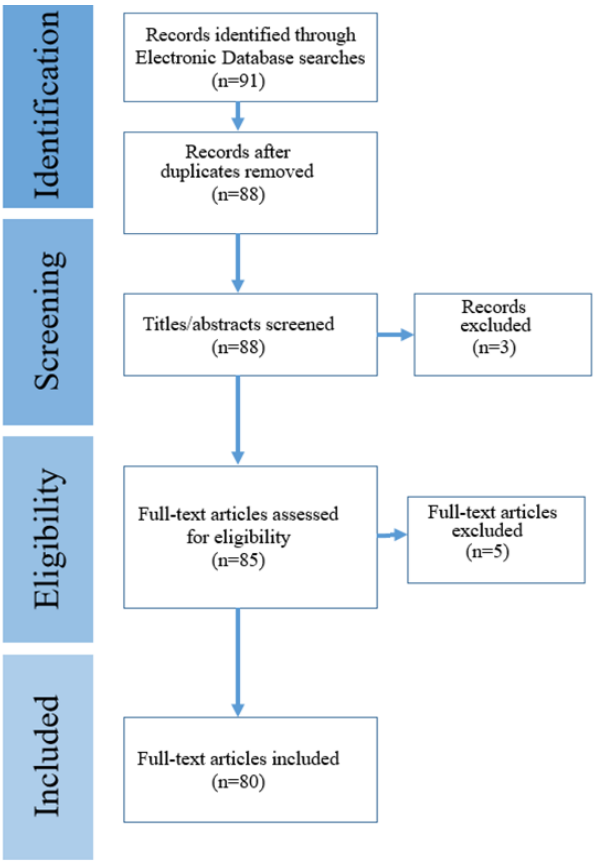

Figure 1. Review flow diagram. Caption: the PRISMA flow diagram for the review detailing the database searches, the number of abstracts screened and full-text articles assessed

The macrovascular complications are based on atherosclerosis, which predisposes to thrombosis and stenosis of arterial vessels [17] while the microvascular complications involve more complex physiopathological mechanisms such as formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC), altered expression of hypoxia-inducible factor-1α (HIF-1α), oxidative stress and modification of thrombus [18]. Taking into consideration these different mechanisms of production, it is reasonable to study the particular pathway in which T2DM can influence every type of AMI.

AMI is classified by its cause into four particular types: arterial embolism, arterial thrombosis, nonocclusive mesenteric ischemia (NOMI) and venous thrombosis [19]. Every type associates a specific physiopathological mechanism that can be individually influenced by diabetes.

Arterial embolism

The most frequent cause of AMI is arterial embolism, representing approximately 50% of all cases [20]. Usually, the superior mesenteric artery is the most affected vessel by the embolism [21], fact explained by the parallel arrangement to the abdominal aorta, enabling the embolus to enter along with blood flow. However, just 15% of emboli can be found at the origin of the superior mesenteric

artery, 50% being located distally, at the origin of the middle colic artery, its first major branch [22].

The presence of embolus in mesenteric vascularization is determined, in the majority of cases, by cardiac pathology [22]. AMI is commonly found in patients with valvular dysfunction, coronary disease and atrial fibrillation [23]. There are also unusual cases of mesenteric embolism caused by the rupture of atherosclerotic plaque or mural thrombus from an aneurysmal part of the vessel [24].

Even if the emboli are usually caused by a cardiac pathology [23], the lack of vascular compliance to this event can be associated with T2DM through distinctive physiopathological mechanisms. One of them involves the impaired expression of hypoxia-inducible factor-1α (HIF-1α). HIF-1α is a dimeric protein involved in the cellular response to decreased concentration of oxygen by modulating the expression of genes linked to the maintenance of oxygen homeostasis [25]. Activated by the lack of oxygen, HIF-1α promotes angiogenesis and synthesis of vascular endothelial growth factor (VEGF) which intensifies the migration of endothelial cells to deprived oxygen areas [26]. Studies display that hyperglycemia can alter the function and activation of HIF-1α, explaining the multiple ischemic complications in patients with T2DM [27]. As evidence, the biopsy made from ulcerated tissue from patients diagnosed with T2DM exposed diminished levels of HIF-1α [28]. Because diabetes disturbs this compensatory pathway to oxygen deficiency, it implies an accelerated progression of ischemia in the case of vascular occlusion through arterial embolism [29].

In addition, T2DM is involved in decreasing vascular compliance also through the alteration of collagen structure by excessive production of AGEs [30]. AGEs modify the structure of collagen by decreasing its solubility, increasing the resistance to collagenases and cross-linking the molecules of collagen, which determines a stiffer structure of vascular wall with diminished compliance [31]. Normally, in the case of hypoxia generated by embolic occlusion, vasodilation is a compensatory mechanism, but when the structure of collagen is altered, this mechanism is insufficient, accelerating further ischemic injuries [32].

Arterial thrombosis

Approximately 25% of AMI cases are caused by arterial thrombosis which is usually associated with a previous chronic atherosclerotic disease [20]. Due to the gradual progression of atherosclerosis, there is enough time for compensatory mechanisms to deal with oxygen deficiency by promoting collateral vascularization. In such manner, the patient can easily tolerate the disease due to the progressive onset of symptoms, resulting in a form of chronic mesenteric ischemia [19]. AMI appears when the collateral vascularization is obstructed and associates a poor prognosis due to the absence of symptoms and the belated diagnosis. The perioperative mortality is roughly 95% due to extensive ischemia and the complexity of the surgical approach [33].

Arterial thrombosis usually occurs following an atherosclerotic complication of visceral vascularization [34] by the rupture of atheroma plaque [35]. As mentioned before, because T2DM intensifies the atherosclerotic process, it can be the cause of AMI through arterial thrombosis [36]. A population-based autopsy study demonstrated this fact by investigating coronary atherosclerosis in diabetic and nondiabetic individuals, concluding that 75% of diabetics have high-grade coronary atherosclerosis, compared to only 55% of non-diabetics [37].

An essential factor involved in the development of atherosclerotic plaques is the high level of low-density lipoprotein (LDL) [38]. Normal values of LDL do not influence the intracellular accumulation of lipids and do not contribute to atherosclerosis, but T2DM modifies lipid structure making them become atherogenic [39]. Participating in a desialylating process, the LDL particles achieve increased density, diminished volume and become negatively charged [40]. These modifications provide them a greater capacity to migrate to subendothelial space because of the reduced size. They also become prone to oxidation which makes them easily ingested by macrophages in the pathway of forming foamy cells [41].

Another physiopathological mechanism in which T2DM induces atherosclerosis is explained by the excessive production of AGEs [42]. These irreversible products accelerate the migration of monocytes to subendothelial space and also their conversion to macrophages by the overexpression of adhesion molecules [43,44]. Moreover, these macrophages are predisposed to easier conversion into foamy cells because of the glycation of LDL-cholesterol after its interaction with AGEs [45]. They also stimulate the AGEs receptors found on the surface of macrophages, activating them in order to synthesize the nuclear factor-κB (NF-κB) [46]. This is responsible for modulating the genetic transcription for endothelin-1, thrombomodulin and other cytokines, such as interleukin-6 and tumor necrosis factor-α (TNF-α), which have a chemotactic role for recruiting monocytes to the atheroma plaque [31].

Nonocclusive mesenteric ischemia (NOMI)

Nonocclusive mesenteric ischemia (NOMI) is a critical condition characterized by splanchnic vasoconstriction leading to intestinal hypoperfusion without occlusion. It is difficult to diagnose due to nonspecific clinical presentations and requires early detection to effectively manage its high mortality rate. The diagnosis is most reliably confirmed through mesenteric angiography. Treatment focuses on the rapid correction of predisposing factors and combating mesenteric vasoconstriction, primarily using papaverine infusion into the superior mesenteric artery and, in some cases, prostaglandin

analogues via intra-arterial infusion, which have been shown to relieve symptoms and restore blood flow. Despite the challenges in diagnosis, these therapeutic approaches are crucial in preventing intestinal necrosis and improving outcomes in NOMI patients. NOMI is found in just 20% of cases of AMI as a consequence of excessive vasoconstriction of the superior mesenteric artery and its branches [47]. Although it is difficult to diagnose this type of disease, its accuracy is essential because NOMI does not require surgical treatment and this approach can worsen its prognosis [48,49].

As mentioned before, NOMI is caused by excessive vasoconstriction of intestinal vascularization [47], a mechanism also intensified by T2DM through many physiological pathways. In the first place, a complication of T2DM that affects intestinal blood flow is overreactive vasoconstriction due to the increased secretion of endothelin-1 [50]. A physiopathological mechanism in which T2DM can mediate the overproduction of this molecule is determined by protein kinase C activation [51]. Overexpression of protein kinase C is proved by experimental procedures that provide 5 and 18-fold higher levels of PKC in cells overexpressing the insulin receptor [52]. Intracellular hyperglycemia leads to the formation of intermediate products such as glycerol-3-phosphate, the substrate for de novo synthesis of diacylglycerol, a molecule that stimulates protein kinase C [53]. The study of Geraldes et al. [54] proved that the increasing protein kinase C induces many morphological and functional modifications on the endothelium, the most significant being related to the overexpression of the vasoconstrictor molecule, endothelin-1, a fact demonstrated by overexpression of its mRNA in cultured retinal endothelial cells exposed to hyperglycemia [55]. Additionally, when insulin resistance progresses, hyperinsulinemia develops, which influences the vascular branches by oversecretion of endothelin-1, a molecule with a potent vasoconstrictive effect [56]. The increased level of endothelin-1 in diabetic patients is demonstrated in the study of Seligman et al. by having a value of 1.62 pg/ml compared with only 0.91 in patients with hypercholesterolemia and 0.69 in control subjects [57].

On the other hand, T2DM can alter the compensatory mechanism of vasodilatation by decreasing the nitric oxide (NO) synthesis, resulting in an imbalance between vasoconstriction and vasodilatation in favor of the first one [58]. NO is produced from the amino acid L-arginine with the contribution of endothelial enzyme oxide synthase (eNOS) and NADPH [59]. The overproduction of AGEs found in T2DM is responsible for the increased level of reactive oxygen species (ROS) [60] and the study of Masha et al. demonstrated at least 3 ways in which ROS diminish the NO bioavailability: 1) the reactions are derived to peroxynitrites synthesis, 2) BH4, an essential cofactor, is oxidized by ROS, 3) it leads to decreased intracellular thiols which associate the reduction of S-nitrosothiols production, used in the synthesis and the transport of NO [61].

Venous thrombosis

The rarest type of AMI is caused by venous thrombosis, being found in under 10% of cases. Generally, thrombosis is based on the Virchow triad that includes the presence of three factors: endothelial damage, hypercoagulability and altered blood flow in the vessels [20].

The thrombus in venous mesenteric vascularization implies a segmental injury associated with edema and hemorrhage in the intestinal wall. The thrombus usually originates in venous arcades and spreads across intramural vessels until it clogs a vessel. The venous thrombus can also be palpated where the superior mesentery vein is projected [62]. As a specific feature, the venous thrombus leads to gradual ischemia in contrast with the arterial thrombus [20] involving a decreased mortality rate, of approximately 44%, in comparison with the common prognosis of AMI [63].

AMI caused by venous thrombosis is induced by an endothelial injury that involves a local inflammatory response by promoting the synthesis of proinflammatory cytokines, adhesion molecules and hemostatic factors inducing a prothrombotic state [64]. All these factors connected to venous thrombosis in mesenteric vascularization can be influenced by T2DM by modifying different physiopathological mechanisms [65].

Diabetes induces the hypercoagulable state by platelet overactivation, a fact observed by studying the thromboxane B2 increase in patients with T2DM [66,67]. The platelet's hyperactivity is triggered by many complex mechanisms, one of them being explained by the connection between AGEs and their receptors found on the surface of platelets [68]. Another pathway of their overactivation is related to the inhibitory role of insulin on the P2Y12 receptor, responsible for the activation and aggregation of platelets [69]. In the case of T2DM, insulin resources are diminished and the insulin inhibitory effect on platelets is altered, which leads to excessive overactivity [70].

Furthermore, it is common to find in patients diagnosed with T2DM an increased level of molecules involved in a hypercoagulability state, such as fibrinogen, prothrombin, pre-kallikrein, factor V, factor VII, factor VIII, factor X and factor XI [71]. The study of Bembde et al. showed that the mean plasma fibrinogen level in diabetic patients was 656+/-130 mg/dl while in the control group was 324 +/-139 mg/dl, which is a significant increase [72]. Besides these hypercoagulability molecules, the study of Vaidya et al. revealed a decreased level of other anticoagulant factors such as antithrombin, protein C and protein S [73,74]. In addition, the inflammation produced by hyperglycemia can affect the endothelium by increasing the von Willebrand factor, essential in the aggregation of platelets [75].

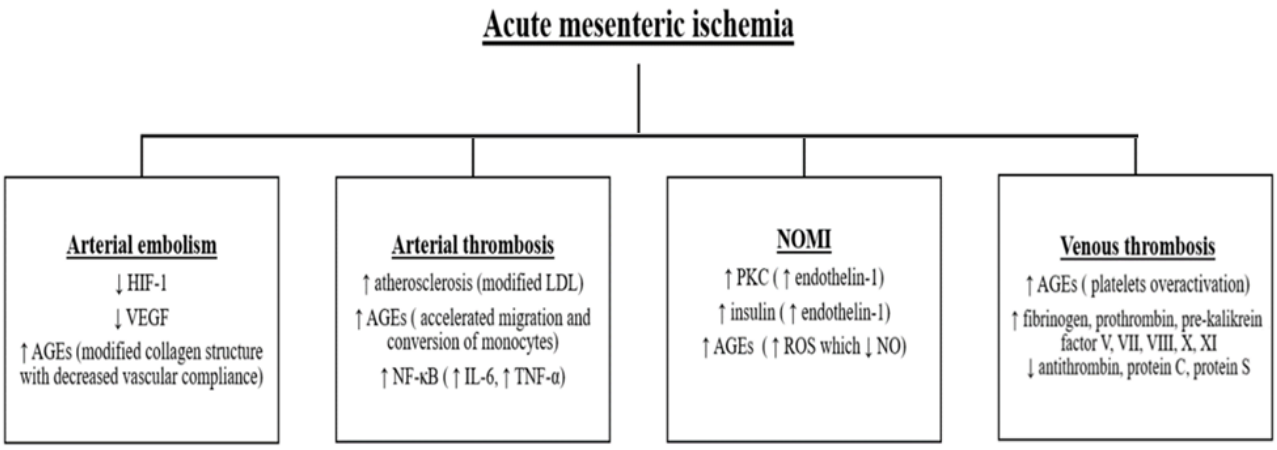

Figure 2. Mechanisms of development and evolution of every type of acute mesenteric ischemia in diabetic patients. The diagram illustrates the physiopathological pathways in which type 2 diabetes mellitus affects the protective factors of vessels and induces injuries that promote ischemia in mesenteric vascularization. Abbreviations are as follows: HIF-1, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; AGEs, advanced glycation end-products; LDL, low-density lipoprotein; NF-κB, nuclear factor-κB; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; NOMI, nonocclusive mesenteric ischemia; PKC, protein kinase C; ROS, reactive oxygen species; NO, nitric oxide.

Acute mesenteric infarction outcome in diabetic patients

This intestinal disease is associated with a high risk of morbidity and mortality, including peri-operative complications such as failure to wean off the ventilator for more than 48 hours, blood transfusion needed, septic shock, pneumonia, unplanned intubation, acute renal failure, cardiac arrest requiring CPR, infectious complications, a greater hospital length of stay, unplanned return to operating room [76,77]. It is important to identify how T2DM influences AMI outcome, not only to analyze its implication to the development and evolution of this disease. For example, a diabetic patient is more prone to acquire a postoperative nosocomial infection [78], a fact that can negatively affect the treatment of AMI. The study of Pomposelli et al. observed that a level of glycemia greater than 220 mg/dl is associated with a 2.7 times higher risk of developing nosocomial infection compared to a glycemia lower than 220 [79]. Overall, the hospital mortality caused by T2DM, regarded the cause of hospitalization, is increased along with the glucose values. The study of Krinsley showed that the group with normal glycemia (80-99 mg/dl) had the lowest mortality rate, 9.6%, in comparison with the value of 27% in patients with glycemia between 100 and 119 mg/dl and 42.5% for those with a glucose level greater than 300 mg/dl [80].

Conclusions

Type 2 diabetes mellitus is a complex pathology that can cause or intensify acute mesenteric ischemia by modulating different physiopathological mechanisms, being involved particularly in all four types of mesenteric infarction. Diabetes includes a great range of macro and microvascular complications which are based on the process of atherosclerosis, the decreased response to hypoxia due to HIF-1 alteration, the diminished vasodilatory response by influencing the NO synthesis, the excessive vasoconstriction induced by the increased level of endothelin-1, the overactivation of platelets and the promotion of a prothrombotic state.

Acute mesenteric ischemia is a disease difficult to recognize because of its elusive clinical presentation, with a significant mortality rate increasing along with diagnosis time. This is why it is important to understand the development mechanism and its risk factors because it enables the physician to make a correlation between the mesenteric ischemia and other pathologies that interfere, such as type 2 diabetes mellitus, in order to accelerate the diagnostic process.

Highlights

- ✓ Type 2 diabetes mellitus is a complex disease with major complications in systemic vascularization.
- ✓ Affecting the vascularization of the small intestine, diabetes can lead to acute mesenteric ischemia.

Abbreviations

AMI : acute mesenteric ischemia
T2DM : Type 2 Diabetes Mellitus

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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