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SNAPSHOT ON A POSSIBLE THERAPEUTIC EFFECT OF ANTI-DIABETIC DRUGS IN GASTRIC ULCER

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Diabetes mellitus is a chronic metabolic disease that has increased blood glucose level as a defining feature which eventually causes multiple complications including gastrointestinal problems. Type 2 diabetes mellitus (T2DM) represents a risk factor for stomach inflammation and gastrointestinal problems including ulcer diseases. Gastrointestinal symptoms include functional dyspepsia, abdominal pain, diarrhea and gastric ulcers that could be severe and progressed to bleeding and perforation. Gastric ulcer in T2DM has many causes but the most important of them is higher possibility of Helicobacter pylori infection. However, the current mini-review correlates T2DM and gastric ulcer as one of its complications in susceptible individuals. Yet, specific treatments for gastric ulcer are histamine-H_2 blockers, proton pump inhibitors, antacids and antibiotics that aimed to reduce discomfort, treat the ulcer, and prevent a recurrence. In addition, many experimental studies provided a protective role for many anti-diabetic drugs in gastric ulcer during T2DM such as metformin, pioglitazone and glucagon-like peptide-1analogues. Many of these anti-diabetic drugs may promote tissue generation and the healing of ulcerative wounds by producing anti-inflammatory and anti-oxidative effects in the tissue around the ulcer of diabetic rats. The presence of sufficient clinical studies concerning this effect and the development of novel strategies are warranted in the near future

Keywords: *Type 2 diabetes mellitus; Gastric ulcer; Anti-diabetic drugs; Metformin; Pioglitazone; Rosiglitazone; Glucagon-like peptide-1*

INTRODUCTION

Prevalence of diabetes mellitus

The World Health Organization (WHO) describes diabetes mellitus as a chronic metabolic illness that has increased blood glucose level as a defining feature, which over time causes damage to the heart, vasculature, eyes, kidneys and nerves[1] . Numerous individuals of different ages, races and socioeconomic backgrounds suffer from diabetes mellitus[2] . Due to the aging of the population, urbanization and sedentary lifestyle, the high global prevalence of diabetes mellitus is quickly rising. Within the last 30 years, the number of people with diabetes mellitus was doubled. According to estimates, 285 million individuals worldwide had diabetes mellitus in 2010. By 2030, it is expected to increase to 439 million[3] . Around 90–95% of diabetic patients suffers type 2 DM[4].

Pathogenesis of type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM), that also called adult diabetes or obesity-related diabetes or non-insulin dependent diabetes**,** is referred to a multisystem illness that has become a major public health concern[5]. It is manifested in high level of glucose, decline of antioxidants and abnormalities in lipid metabolism[6].

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T2DM is more prevalent to develop in people with history of high blood pressure, dyslipidemia, or any sort of pregnancy-related diabetes [7]**.** Furthermore, there are concerns that genetic and/or beta-cell cytotoxic factors may lead to decreased beta-cell mass, which could be a danger sign for glucose intolerance[8].

There are several environmental and genetic risk factors for T2DM, including obesity, poor diet and sedentary lifestyles, which all cause multiple pathophysiological issues that result in a defective glucose equilibrium[9].

T2DM occurs by insufficient capacity of insulin-sensitive tissues to respond to insulin and impaired insulin production by pancreatic-cells, resulting in hyperglycemia[1]. T2DM's pathogenic factors has been associated with mutations in mitochondrial DNA (mtDNA) and declines in mtDNA copy number[10].

Hyperglycemia can result in oxidative stress in a variety of ways, including the generation of free fatty acids, advanced glycation end products (AGE) and glucose autoxidation and also blood MDA significantly increased in T2DM[11,12] . As well, stimulation of protein kinase C (PKC) and overproduction of superoxide are considered mechanisms in T2DM[10] .

Although the pathophysiology of diabetic dyslipidemia is unknown, a vast body of research proves that insulin resistance plays a major factor in the development of T2DM. Diabetic dyslipidemia stimulates the release of unrestricted fatty acids from fat cells that resistant to insulin. In the presence of appropriate glycogen stores, triglyceride production is triggered by an increase in the flow of free fatty acids into the liver, which in ultimately encourages the release of VLDL cholesterol and Apo-lipoprotein B (ApoB). Increased hepatic VLDL cholesterol production as a result of insulin's impaired ability to inhibit free fatty acid release correlates with the degree of hepatic fat accumulation as a result of increased levels of VLDL cholesterol, triglyceride, and small dense LDL-cholesterol, with decreased HDL cholesterol levels **(Fig. 1)**[13, 14].

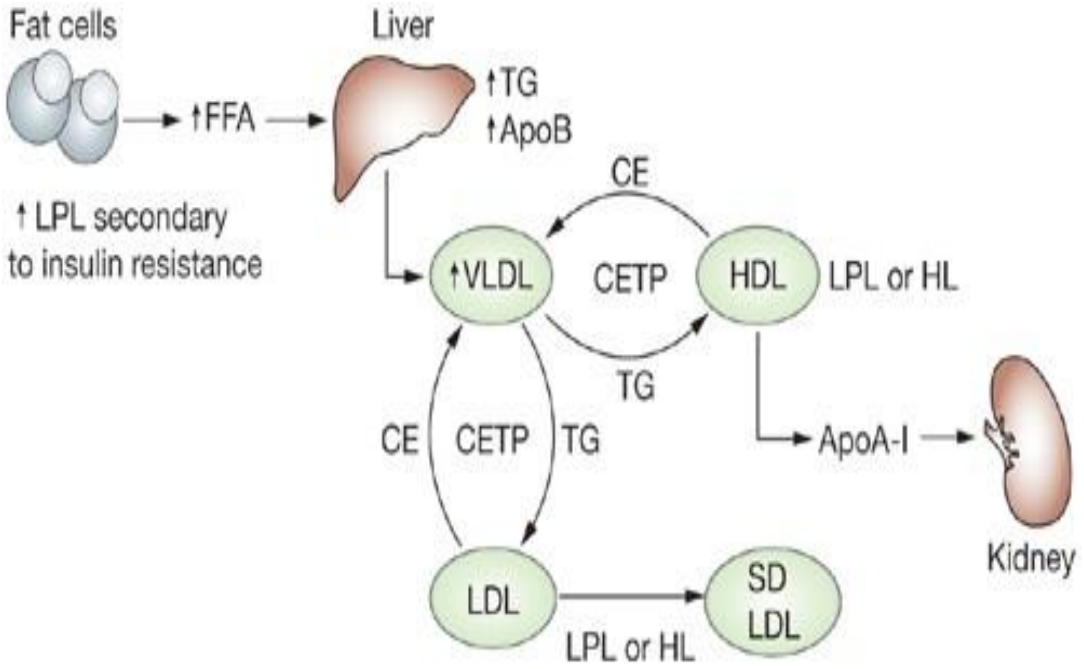

Fig. 1 : Mechanisms of dyslipidemia in T2DM [13].

Abbreviations: ↑, increased level; ApoA-1, apo-lipoprotein A-1; ApoB, apo-lipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HL, hepatic lipase; LPL, lipoprotein lipase; SD LDL, small dense LDL cholesterol; TG, triglyceride**.**

Complications of T2DM

It is commonly acknowledged that unregulated glucose level leads to continued hyperglycemia, which causes diabetic complications[10]. T2DM macro-vascular consequences include peripheral artery disease, cerebrovascular disease, cardiomyopathy, arrhythmias, coronary heart disease which is considered the main factor of sudden death[15]. Chronic hyperglycemia damages the microvasculature, leading to diabetic retinopathy, neuropathy, and diabetic nephropathy, all of which have a major harmful influence on quality of life and lifespan[6] **.** Hence, it is essential to regulate blood glucose levels in diabetic patients. Certain drugs can have the opposite effect and cause hypoglycemic episodes, as well as, potentially catastrophic side effects such as comas, seizures, life-threatening arrhythmias, and myocardial infarctions[16].

Diabetic gastropathy

Gastrointestinal problems in T2DM include: Vomiting, diarrhea, constipation, severe indigestion, and slow gastric emptying[17,18]. Patients with T2DM have a significant risk for acute stomach inflammation and ulcer disease[19, 20] . The full thickness of the mucosa as well as the muscle mucosa are both affected by the regional deep ischemic lesion[21]. Gastric ulcers are examples of micro-vascular complications of diabetes mellitus that are more severe, have a slower healing rate and are frequently accompanied by other problems such as gastrointestinal hemorrhage[19] . It is responsible for bleeding and perforation in 55% of T2DM patients[22, 23]. Gastric ulcer considered a significant cause of morbidity in T2DM patients[24, 25] .

Pathogenesis of peptic ulcer in diabetes mellitus

The autonomic neuropathy is one of the mechanisms supporting a greater susceptibility to multifactor damage in diabetes[26], anti-oxidative system dysfunction[25, 27, 28], gastric mucosal inhibition of basic fibroblast growth factor synthesis[29], insufficient duodenal secretion of bicarbonate[30], inhibition of NO synthase and decrease prostaglandin E_2 levels[31], malfunction of the capsaicin-sensitive afferent neurons that are responsible for protecting of the stomach mucosa[32], attenuation of gastric secretion[25, 26, 33], stimulation of acid output[34, 35] . Moreover, slow gastric motility in diabetes, enhances the stomach mucosa's exposure to ulcerogens and hinders the healing of gastric ulcers[17, 32]. In addition**,** there is a high incidence of Helicobacter pylori (H. pylori) infection in people with T2DM, which can result in autonomic neuropathy causing bleeding and perforation[16, 23, 25, 36] .

Regarding diabetic patients with gastric ulcer disease, large number of patients require *H.pylori* eradication for peptic ulcer treatment of triple therapy involving amoxicillin, clarithromycin, and a proton pump inhibitor (PPI). Several individuals who already take diabetes medication have reported experiencing hypoglycemia episodes within 30 days of receiving triple therapy for H. pylori eradication[16] . After the antibiotic therapy for H. pylori eradication is finished, the gut flora is affected, which affects metabolism[37]. Because. PPIs can cause hypoglycemia by increasing the risk of serum gastrin concentration and altering glucose metabolism by stimulating B-cell growth and renewal. Omeprazole may raise the risk of hypoglycemia especially if used in combination with clarithromycin and sulfonylurea[38] .Omeprazole raises the pH of the stomach by increasing the absorption of clarithromycin[39] .Also, omeprazole induces hypoglycemia in gliclazide-treated individuals, according to another study[40]. So, it may be advisable to decrease the dose of antidiabetic drugs when used with triple therapy of H.pylori eradication.

An**o**ther important factor is reduction numbers of circulating endothelial progenitor cells (EPCs)[41] . Since EPCs are crucial for vascular recovery, angiogenesis and are biological indicators for vascular function. Yet, peripheral vascular dysfunction in T2DM patients has been linked to low EPC levels[42] . Therefore, in patients with T2DM who have

peptic ulcers, EPCs are considerably diminshed[23]. Also, drugs may contribute to gastric ulcer in diabetic patients receiving acetylsalicylic acid on a daily basis of 100 mg for the prevention of cerebrovascular stroke which ,in turn, elevates the risk of developing severe acute gastric ulcer disease[43, 44]. Additionally, there are reports that link free radicals, a low level of mucosal glycoprotein, the breakdown of epithelial basement membrane components, a DNA damage and a total disruption to cell metabolism to the pathogenesis of gastric ulceration in diabetes mellitus **(Fig. 2)**[45] .

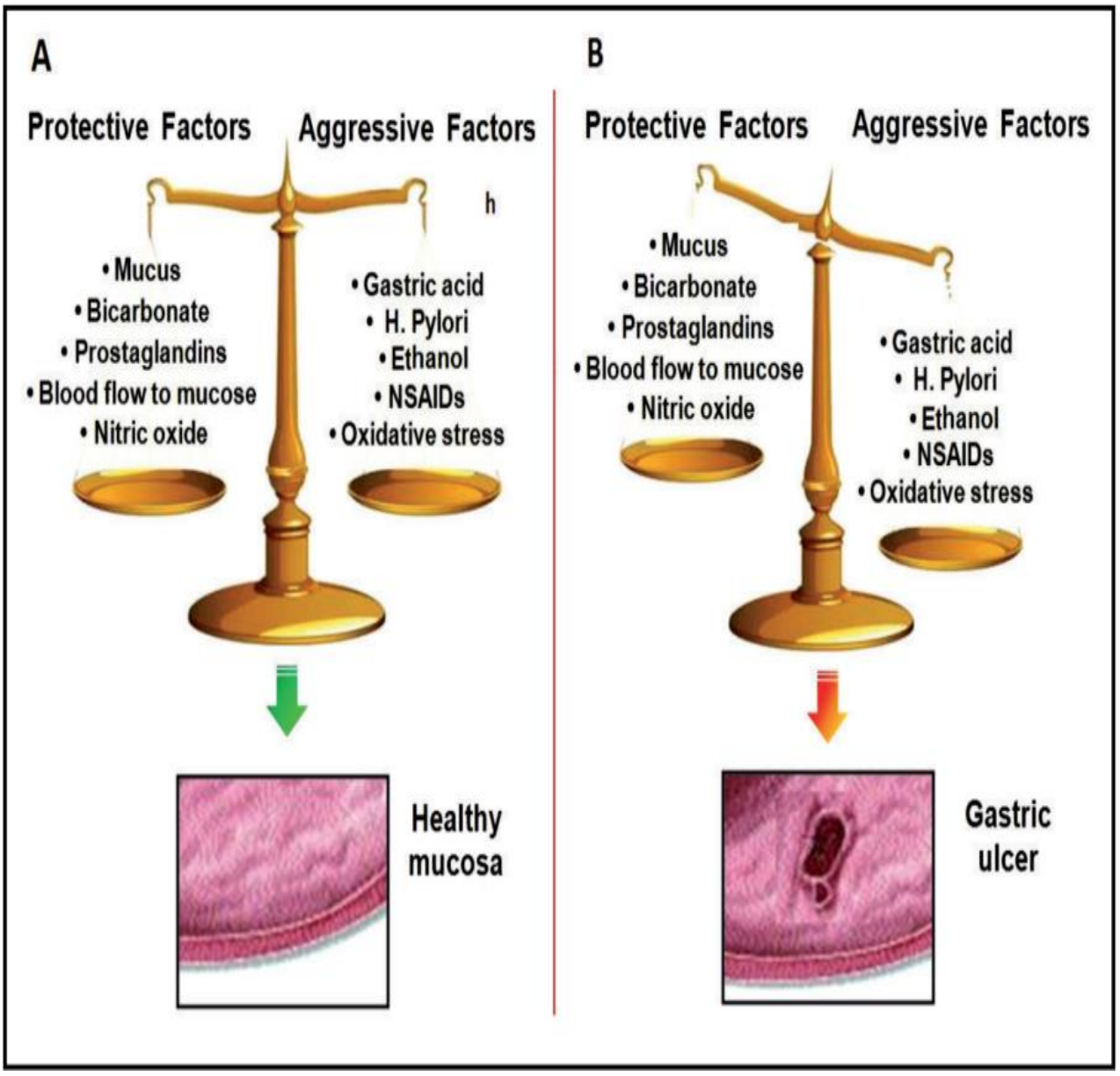

Fig. 2: Protective and aggressive factors on gastric mucosa in healthy and ulcer state [46].

Management of gastric ulcer in diabetes mellitus

Proton pump inhibitors (PPIs), histamine type-2 receptor antagonists (H2 blockers), antacids and antibiotics for treatment of H. pylori infections are among the treatments for gastric ulcers that are often used in clinical practice. Their objectives are to reduce discomfort, treat the ulcer, and prevent a recurrence[47] . PPIs medication and histamine-H2 blockers therapy are the two main options for treating peptic ulcers, respectively[48].

Proton pump inhibitors (PPIs)

Act by irreversible blocking the gastric H^+K^+ ATPase[49] . PPIs are potent medications that restrict the production of acid, have simplified the treatment of disorders connected to acidity and reduced the need for surgery. PPIs also used with antibiotics for elimination of Helicobacter pylori infection[50] . They act on last stage of acid production results in more efficient symptom alleviation and recovery[51].

Histamine-H_2 receptor antagonists (H_2 blockers)

Drugs such as (cimetidine, famotidine, ranitidine and nizatidine) are common H_2 blockers. They act by reversible inhibiting of H-2 receptor in gastric parietal cells and so reduce the level of stomach acid secretion[47] . Therefore, they are beneficial in preventing and treating gastric and duodenal ulcers[52] .

Potassium-competitive acid blockers (P-CABs)

Vonoprazan, is a new and diverse category of medications used to treat peptic ulcers. They work by competitively blocking the potassium binding site of the stomach H+/K+ ATPase, which may help them overcome the drawbacks of proton-pump inhibitors[53].

Antacids

Antacids are available for self-prescription. They are composed of diverse compounds or mixtures of calcium carbonate, magnesium, and aluminum salts. The effect of antacids on the stomach is due to partial neutralization of gastric hydrochloric acid , inhibition the proteolysis of enzyme such as pepsin[54]. Also, stimulating bicarbonate and mucus secretion to enhance the mucosal blood circulation[47].

Role of anti-diabetic drugs in management of gastric ulcer in T2DM

Many previous studies provided a protective and treatment role for many anti-diabetic drugs in gastric ulcer during T2DM.

Metformin

A previous work demonstrated that metformin can be used in treatment of indomethacin-induced stomach ulcers[47]**.** In non-diabetic ulcerative rats, metformin was administered orally as a single dose at three different concentrations (200, 100, and 50 mg/kg). The most potent gastro-protective effect was observed at 200 mg/kg, which was very effective against gastric ulcer induced by indomethacin. This included increased gastric defense factors (higher mucin concentration in gastric juice), decreased gastric acid output, ulcer index, and decreased levels of TNF-α, IL-6, and Rho associated protein kinases (ROCK-1), which is crucial for NF-κB activation and inflammatory degradation[47]. Additionally, a single oral dose of metformin (500 mg/kg) one hour before indomethacin (30mg/kg) injection has anti-secretory effects, improved anti-oxidant and mucosal protection properties. Also, it produced important reductions in the ulcer index, total and free acid output and malondialdehyde in gastric juice. As well, it causes a rise in mucin, nitric oxide and catalase concentrations in the gastric mucosa[55] .

Pioglitazone

Pioglitazone is anti-diabetic drug with a gamma-agonist of the peroxisome proliferator-activated receptor (PPAR-γ). It achieves its gastro-protective effects in T2DM by repairing and preserving the stomach mucosa, with hyperemic effects on the gastric mucosa including endogenous prostaglandins (PGs) and nitric oxide (NO)[20,56]. Intragastric administration of pioglitazone (40 mg/kg/day)

enhances the blood flow to the stomach mucosa, which considerably speeds up the healing process of ulcers. Additionally, pioglitazone increases the protein level of HSP70 that has a potent cytoprotective effects[20]. Pioglitazone is known to boosts the protein expression of leptin which, in turn, results in reduction of stomach acid output[55]. Also, it decreases the expression and production of pro-inflammatory cytokines like IL-1β and TNF-α[20, 57-60] . Pioglitazone helps in acceleration the recovery of pre-existing stomach ulcers by reducing the location of stomach ulcers, stimulating the blood flow to the stomach at the ulcer edge, down-regulating cyclooxygenase-2 and increasing the production of PPAR-γ mRNA in the inflamed stomach mucosa[61]. A previous study reported that, on prolonged use of pioglitazone, it enhances expression of nitric oxide synthase that plays an important role in gastro-protection and stimulates the generation of catalase, which is in charge of the intracellular breakdown of H_2O_2 in the stomach mucosa of rats with diabetes[56].

Rosiglitazone

It is another gamma-agonist of the peroxisome proliferator-activated receptor (PPAR-γ) that is anti-diabetic medication with reported gastro-protective effects; it guards against indomethacin induced ulcers reducing NO, raising PGE2 and enhancing mucus secretion. Administration of rosiglitazone (10 mg/kg, orally, for 1 weeks) before giving intrapritoneal injection of indomethacin (30mg/kg), in non diabetic group, diminished the inflammed area and lessened the severity of ulcer. This could be attributed to the fact that rosiglitazone caused a significant rise in stomach juice mucin concentration and a decrease in TNF-α level[62]. Additionally, a nother study reported that a single oral dose of rosiglitazone (3 mg/kg), one hour before indomethacin (30mg/kg) injection, elevated the PH, decreased ulcer index, mucosal malondialdehyde level, and free and total acid output[55].

Glucagon-like peptide-1 (GLP-1) analogues

GLP-1 belongs to a category of bioactive peptides. Previuos reports demonsterated that GLP-1 analogues are drugs that play a major role in the prevention of gastric mucosal ulcers[63,64] **.** Intracerebroventricularly injection of Exendin-4 (1 μg/kg), a GLP-1 analogue, in rats reduced the damage of the gastric mucosa caused by ethanol[63]. Also, intraperitoneal injection of Exendin-4 (0.5 μg/kg/day) for 7 days induced pro-angiogenic, anti-inflammatory and anti-oxidative reactions in the peri-ulcer tissue of diabetic rats that eventually enhances tissue granulation and closure of ulcerative wounds[64]**.** In accordance, this study support the potential clinical application of Glp-1 analogues as supplementary hypoglycemic agents in the antipeptic ulcer medication in diabetes.

Conclusion

Type 2 diabetes mellitus is a chronic metabolic disease with increased blood glucose level and eventually could lead to different complications. Patients with T2DM have a significant risk for acute stomach inflammation and ulcer diseases. This mini-review focused on diabetic gastropathy and pathogenesis of gastric ulcer in diabetes mellitus. Slow gastric motility in diabetes, enhances the stomach mucosa's exposure to ulcerogens and hinders the healing of gastric ulcers. Previous experimental studies provided a protective and treatment role for many anti-diabetic drugs in gastric ulcer during T2DM. The lack of clinical studies concerning the effects of anti-diabetic drugs in gastric ulcer during T2DM is important to be considered in the future.

REFERENCES

1. U. Galicia-Garcia,A. Benito-Vicente,S. Jebari,A. Larrea-Sebal, *et al.*, "Pathophysiology of type 2 diabetes mellitus", ***Int J Mol Sci,*** 21(17), 6275 (2020).
2. Y. Gorelik, E. Anis and M. Edelstein, "Inequalities in initiation of COVID19 vaccination by age and population group

in Israel-December 2020-July 2021", ***Lancet Reg Health Eur,***12, 100234 (2022).
3. L. Chen,D. J. Magliano and P. Z. Zimmet, "The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives", ***Nat Rev Endocrinol,*** 8(4), 228-236 (2012).
4. A. Artasensi,A. Pedretti,G. Vistoli and L. Fumagalli, " Type 2 diabetes mellitus: a review of multi-target drugs", ***Molecules*** 25(8), 1987 (2020).
5. R. A. DeFronzo, E. Ferrannini, P. Zimmet and G. Alberti, *"International textbook of diabetes mellitus*", ***John Wiley & Sons,*** (2015).
6. C. Faselis,A. Katsimardou,K. Imprialos, P. Deligkaris *et al.,* "Microvascular complications of type 2 diabetes mellitus", ***Curr Vasc Pharmacol,*** 18(2), 117-124 (2020).
7. S. Karmakar, M. Bhowmik, B. Laha and S. Manna, "Recent advancements on novel approaches of insulin delivery", ***Med Nov Technol Devices.*** 19, 100253 (2023).
8. J. L. Leahy, "Pathogenesis of type 2 diabetes mellitus", ***Arch Med Res,*** 36(3), 197-209 (2005).
9. R. A. DeFronzo, E. Ferrannini, L. Groop, R. R. Henry, *et al.,* "Type 2 diabetes mellitus", 1(1), 1-22 (2015).
10. A. P. Rolo and C. M. Palmeira, "Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress", ***Toxicol Appl Pharmacol,*** 212(2), 167-178 (2006).
11. D. Jay, H. Hitomi and K. K. Griendling, "Oxidative stress and diabetic cardiovascular complications", ***Free Radic Biol Med,*** 40(2), 183-192 (2006).
12. S. Menon and G. Rajalekshmi, "Role of Oxidative Stress In Type 2 Diabetes Mellitus", ***J Evol Med Dent Sci,*** 6(88), 6127-6132 (2017).
13. A. D. Mooradian, "Dyslipidemia in type 2 diabetes mellitus", ***Nat Rev Endocrinol,*** 5(3), 150-159 (2009).
14. B. E. Dunning and J. E. Gerich, "The role of α-cell dysregulation in fasting and postprandial hyperglycemia in type 2 diabetes and therapeutic implications", ***Endocr Rev,*** 28(3), 253-283 (2007).
15. M. Viigimaa, A. Sachinidis, M. Toumpourleka, K. Koutsampasopoulos, *et al.,* "Macrovascular complications of type 2 diabetes mellitus," ***Curr Vasc Pharmacol.*** 18(2), 110-116 (2020).
16. A. Chang,A. Chang,W.-T. Chen,L. Chan et al., "Triple therapy for Helicobacter pylori eradication and the risk of hypoglycemia in patients with diabetes: A population-based cohort study", ***BMC Public Health***, 23(1), 1772 (2023).
17. D. U. Owu, A. O. Obembe, C. R. Nwokocha, I. E. Edoho, *et al.,* "Gastric ulceration in diabetes mellitus: protective role of vitamin C", ***Research Notices IS,*** 2012362805, (2012).
18. R. K. Campbell, "Type 2 diabetes: where we are today: an overview of disease burden, current treatments, and treatment strategies", ***J Am Pharm Assoc***, 49(5), S3-S9 (2009).
19. A. A. Fouad, A. I. Al-Sultan, M. T. Yacoubi and W. Gomaa, "Ameliorative effects of telmisartan in diabetic rats with indomethacin-induced gastric ulceration", ***Eur J Pharmacol,*** 637(1-3), 162-170 (2010).
20. P. Konturek, T. Brzozowski, G. Burnat, A. Szlachcic, *et al.,* "Gastric ulcer healing and stress-lesions preventive properties of pioglitazone are attenuated in diabetic rats", ***J Physiol Pharmacol,*** 61(4), 429 (2010).
21. G. Khoder, A. A. Al‐Menhali, F. Al‐Yassir and S. M. Karam, "Potential role of probiotics in the management of gastric ulcer", ***Exp Ther Med,*** 12(1), 3-17 (2016).
22. M. M. Yaseen, S. A. Alkubaisy,W. T. Mohammad, A. T. Jalil, *et al.,* "Cancer and Comp ***Med Chem Sci,*** 6(335-345 (2023).
23. Z. Nie, L. Xu, C. Li, T. Tian, *et al.,* "Association of endothelial progenitor cells and peptic ulcer treatment in patients

with type 2 diabetes mellitus", 11(5), 1581-1586 (2016).
24. P. Bytzer, N. J. Talley, J. Hammer, L. J. Young, *et al.*, "GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications", ***Am J Gastroenterol,*** 97(3), 604-611 (2002).
25. Z. Inas,A. Hala and H. H. Gehan, "Gastroprotective effect of Cordia myxa L. fruit extract against indomethacin-induced gastric ulceration in rats", ***Life Sci,*** 8(3), 433-445 (2011).
26. M. Buysschaert, J. Donckier, A. Dive, J.-M. Ketelslegers, *et al.*, "Gastric acid and pancreatic polypeptide responses to sham feeding are impaired in diabetic subjects with autonomic neuropathy", ***Diabetes***, 34(11), 1181-1185 (1985).
27. E. Goldin, E. Ardite, J. I. Elizalde, A. Odriozola, *et al.*, "Gastric mucosal damage in experimental diabetes in rats: role of endogenous glutathione", ***Gastroenterology***, 112(3), 855-863 (1997).
28. M. A. Morsy, G. H. Heeba, S. A. Abdelwahab and R. R. Rofaeil, "Protective effects of nebivolol against cold restraint stress-induced gastric ulcer in rats: role of NO, HO-1, and COX-1, 2", ***Nitric Oxide***, 27(2), 117-122 (2012).
29. K. Takeuchi, K. Takehara, K. Tajima, S. Kato, *et al.*, "Impaired healing of gastric lesions in streptozotocin-induced diabetic rats: effect of basic fibroblast growth factor", ***Pharm Exp Therap***, 281(1), 200-207 (1997).
30. K. Takehara, K. Tashima and K. Takeuchi, "Alterations in duodenal bicarbonate secretion and mucosal susceptibility to acid in diabetic rats", ***Gastroenterology,*** 112(2), 418-428 (1997).
31. G. H. Heeba, M. K. Hassan and R. S. Amin, "Gastroprotective effect of simvastatin against indomethacin-induced gastric ulcer in rats: role of nitric oxide and prostaglandins", ***Eur J Pharmacol,*** 607(1-3), 188-193 (2009).
32. I. A. Harsch, T. Brzozowski, K. Bazela, S. J. Konturek, *et al.*, "Impaired gastric ulcer healing in diabetic rats: role of heat shock protein, growth factors, prostaglandins and proinflammatory cytokines", 481(2-3), 249-260 (2003).
33. M. B. Saltzman and R. W. McCALLUM, "Diabetes and the stomach", ***Yale J Biol Med*** 56(3), 179 (1983).
34. E. Kuipers, "Helicobacter pylori and the risk and management of associated diseases: gastritis, ulcer disease, atrophic gastritis and gastric cancer," ***Aliment Pharmacol Ther.*** 11(S1), 71-88 (1997).
35. F. Chang,T. Chen, S. Lee, M. Doong, *et al.*, "Pentagastrin-induced gastric acid secretion in the diabetic rats: role of insulin", ***Chin J Physiol,*** 47(4), 175 (2004).
36. S. Gentile, S. Turco, B. Oliviero and R. Torella, "The role of autonomic neuropathy as a risk factor of Helicobacter pylori infection in dyspeptic patients with type 2 diabetes mellitus", ***Diabetes Res Clin Pract,*** 42(1), 41-48 (1998).
37. G. M. Martín-Núñez, I. Cornejo-Pareja, L. Coin-Aragüez, M. D. M. Roca-Rodríguez, *et al.*, "H. pylori eradication with antibiotic treatment causes changes in glucose homeostasis related to modifications in the gut microbiota", ***PLoS One*** 14(3), e0213548 (2019).
38. T. M. Parekh,M. Raji,Y. L. Lin,A. Tan, *et al.*, "Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas", ***JAMA Intern Med***, 174(10), 1605-1612 (2014).
39. H. Zojaji, E. Ataei, S. J. Sherafat, M. Ghobakhlou, *et al.*, "The effect of the treatment of Helicobacter pylori infection on the glycemic control in type 2 diabetes mellitus", ***Gastroenterol Hepatol Bed Bench,*** 6(1), 36-40 (2013).
40. T. Dujic,S. Cvijic,A. Elezovic,T. Bego, *et al.*, "Interaction between Omeprazole and Gliclazide in Relation to CYP2C19 Phenotype", ***J Pers Med***, 11(5), 367 (2021).

41. N. Werner,S. Kosiol,T. Schiegl, P. Ahlers, *et al.*, "Circulating endothelial progenitor cells and cardiovascular outcomes", 353(10), 999-1007 (2005).
42. C. Urbich and S. Dimmeler, "Endothelial progenitor cells: characterization and role in vascular biology", ***Circ Res,*** 95(4), 343-353 (2004).
43. M. Boehme,F. Autschbach,C. Ell and U. J. H.-g. Raeth, "Prevalence of silent gastric ulcer, erosions or severe acute gastritis in patients with type 2 diabetes mellitus--a cross-sectional study", 54(74), 643-648 (2007).
44. G. H. Heeba,M. A. Morsy, M. E. Mahmoud and R. Abdel-latif, "Gastro-protective effect of L-arginine against nitric oxide deficiency-related mucosal injury induced by indomethacin: Does age matter?", ***J Biochem Mol Toxicol,*** 37(11), e23479 (2023).
45. A. Ige,E. Adewoye,N. Okwundu,O. Alade, *et al.*, "Oral magnesium reduces gastric mucosa susceptibility to injury in experimental diabetes mellitus", ***Pathophysiology,*** 23(2), 87-93 (2016).
46. M. I. G. Silva,F. F. J. P. u. d. de Sousa, ***Gastric ulcer etiology,*** (2011).
47. E. Y. AbdelAziz,M. G. Tadros and E. T. Menze, "The effect of metformin on indomethacin-induced gastric ulcer: Involvement of nitric oxide/Rho kinase pathway", ***Eur J Pharmacol,*** 892,173812 (2021).
48. T. Kamada,K. Satoh,T. Itoh, M. Ito, *et al.*, "Evidence-based clinical practice guidelines for peptic ulcer disease 2020", ***J Gastroenterol,*** 56(4), 303-322 (2021).
49. K. S. Jain,A. K. Shah,J. Bariwal, S. M. Shelke, *et al.*, "Recent advances in proton pump inhibitors and management of acid-peptic disorders", ***Bioorg Med Chem,*** 15(3), 1181-1205 (2007).
50. V. Savarino,P. Dulbecco, N. de Bortoli, A. Ottonello, *et al.*, "The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal", ***Eur J Intern Med.*** 37,19-24 (2017).
51. K. Andersson and E. Carlsson, "Potassium-competitive acid blockade: a new therapeutic strategy in acid-related diseases", ***Pharmacol Ther,*** 108(3), 294-307 (2005).
52. R. J. Lipsy, B. Fennerty,T. C. Fagan, "Clinical review of histamine2 receptor antagonists", ***AMA Arch Intern Med,*** 150(4), 745-751 (1990).
53. E. Marabotto, S. Ziola,V. Savarino, E. G. Giannini, *et al.*, "Vonoprazan fumarate for the treatment of gastric ulcers: a short review on emerging data", ***Clin Exp Gastroenterol.*** 99-104 (2020).
54. P. N. Maton and M. E. Burton, "Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use", ***Drugs***, 57(6), 855-870 (1999).
55. M. A. Morsy, O. M. Ashour, A. A. Fouad and S. A. Abdel-Gaber, "Gastroprotective effects of the insulin sensitizers rosiglitazone and metformin against indomethacin-induced gastric ulcers in Type 2 diabetic rats", ***Clin Exp Pharmacol Physiol,*** 37(2), 173-177 (2010).
56. L. Moezi, R. Heidari, Z. Amirghofran, A. A. Nekooeian, *et al.*, "Enhanced anti-ulcer effect of pioglitazone on gastric ulcers in cirrhotic rats: the role of nitric oxide and IL-1β", ***Pharmacol Rep,*** 65(1), 134-143 (2013).
57. T. Brzozowski,P. C. Konturek,R. Pajdo,S. Kwiecień, *et al.*, "Agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ: A new compound with potent gastroprotective and ulcer healing properties", ***Inflammopharmacology***, 13, 317-330 (2005).
58. K. Wada,A. Nakajima,H. Takahashi,M. Yoneda, *et al.*, "Protective effect of endogenous PPARγ against acute gastric mucosal lesions associated with ischemia-reperfusion", ***Am J Physiol Gastrointest Liver Physiol,.*** 287(2), G452-G458 (2004).
59. L. Moezi, Z. Janahmadi, Z. Amirghofran, A. A. Nekooeian, *et al.*, "The increased

gastroprotective effect of pioglitazone in cholestatic rats: role of nitric oxide and tumour necrosis factor alpha", ***Int J Exp Pathol,*** 95(1), 78-85 (2014).

60. S. Lahiri,T. Sen and G. Palit, "Involvement of glucocorticoid receptor and peroxisome proliferator activated receptor-γ in pioglitazone mediated chronic gastric ulcer healing in rats", ***Eur J Pharmacol,*** 609(1-3), 118-125 (2009).
61. P. C. Konturek,T. Brzozowski,J. Kania,S. J. Konturek, *et al.,* "Pioglitazone, a specific ligand of peroxisome proliferator-activated receptor-gamma, accelerates gastric ulcer healing in rat", ***Eur J Pharmacol,*** 472(3), 213-220 (2003).
62. A. Taye and A. H. Saad, "Role of rosiglitazone as a gastroprotective agent against indomethacin-induced gastric mucosal injury in rats", ***Gastroenterology Res,*** 2(6), 324 (2009).
63. N. Isbil-Buyukcoskun and G. Gulec, "Investigation of the mechanisms involved in the central effects of glucagon-like peptide-1 on ethanol-induced gastric mucosal lesions", ***Regul Pept,*** 128(1), 57-62 (2005).
64. Y.-C. Chen,C.-C. Ho, C.-H. Yi, X.-Z. Liu, *et al.,* "Exendin-4, a glucagon-like peptide-1 analogue accelerates healing of chronic gastric ulcer in diabetic rats", ***PloS one*** 12(11), e0187434 (2017).

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لمحة سريعة عن التأثير العلاجى المحتمل للأدوية المضادة للسكرى فى قرحة المعدة

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يعتبر مرض السكرى من الامراض المزمنة حيث يحدث ارتفاع فى مستوى الجلوكوز في الدم مما يؤدي إلى مضاعفات عديدة بما في ذلك المشاكل المعوية. يمثل مرض السكري من النوع الثاني عاملاً من عوامل خطر المشاكل المعوية والتهاب المعدة الذى يظهر في صورة سوء الهضم الوظيفي، وآلام البطن، والإسهال، والقرحات المعوية التي يمكن أن تكون شديدة ومتقدمة لدرجة النزيف وحصول ثقب في جدار المعدة.

إن امراض الجهاز الهضمي التي تحدث اثناء مرض السكرى من النوع الثاني لها اسباب كثيره ولكن اهم هذه الاسباب هي زياده احتمالية الاصابة بجرثومة المعدة و على ذلك، فإن الاستعراض المصغر الحالي يربط بين مرض السكري من النوع الثاني والقرحة المعوية كإحدى مضاعفاته في الأفراد المعرضين للخطر.

تعتبر موانع الهيستامين-٢، ومثبطات مضخة البروتون، ومضادات الحموضة هي العلاجات المحددة لعلاج قرحة المعدة حتى الان والتي تهدف إلى تخفيف الألم، ومعالجة القرحة وتجنّب تكرارها. وبالإضافة إلى ذلك، اثبتت دراسات بحثية كثيرة دوراً وقائياً للعديد من العقاقير المستخدمة في علاج مرض السكرى من النوع الثاني مثل الميتفورمين، البيوجليتازون ، الروسيجليتازون وجلوكاجون شبيه البيبتيد-١ في الوقاية من الاصابة بالقرحة المعدية.