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Review Article

Temperature

# Role of Low Environmental Temperature in Peptic Ulcer Development

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Peptic ulcers are described as acid-induced lesions found in the stomach and duodenum caused by the imbalance between the defending factors of the mucosa and the attacking factors such as hydrochloric acid in gastric juice, with Helicobacter Pylori (H. Pylori) and Non-Steroidal Anti-Inflammatory Drugs NSAIDs. They exhibit seasonal patterns in their occurrence, with higher occurrence in winter and spring and a low occurrence in summer. Temperature plays a major role in their occurrence, some of which have resulted in increased morbidity in some number of diseases, such as gastrointestinal bleeding, caused by an increase in air pressure, dry air (relative humidity) occurring from cold air, and also its actions on the protective effect helicobacter pylori in the human body. Their actions excite the adrenal gland marrow and the sympathetic nerve, causing rapid secretion of adrenaline and non-adrenaline, angiotensin II and endothelin, resulting in damage to the mucosa epithelial, caused by the contraction effect of the adrenal agents on the duodenal mucosa and blood vessel. It causes low expression of Epidermal Growth Factor Receptor (EGFR), Epidermal Growth Factor (EGF), Heat Shock Protein (HSP) 70, Occludin, Nitric Oxide Synthase (NOS), in the gastric mucosa, in extremely cold temperature than those in extremely hot temperature, increasing the gastric acid secretion in extremely cold temperature than in extremely hot temperature. Therefore, this review aims to give general insight into the role of low temperature in peptic ulcer development and further consideration in the treatment of peptic ulcer diseases.

**Keywords:** Peptic Ulcer, Temperature, Helicobacter Pylori (H. Pylori)

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# Introduction

Peptic ulcers are described as acid-induced lesions found in the stomach and duodenum, characterized by denuded mucosa with its defect extending into the sub-mucosa or muscularis propria, [1]. These diseases tend to share a common pathway of acid-pepsin pathogenesis, [2]. The major ones are Duodenal Ulcer (DU) and Gastric Ulcer (GU), [2]. This is due to the imbalance between the defending factors of the mucosa and the attacking factors such as hydrochloric acid in gastric juice [3]. The main risk factors for these diseases are Helicobacter Pylori (H. Pylori) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [1,4]. Ulcerations in the gastro-duodenal tract are seen as defects of the mucosal lining resulting from the epithelial cell damaged brought into play by caustic agents such as acid and pepsin, [5]. These caustic agents prevail over the defensive mechanisms of the gastroduodenal mucosa, observing from a pathophysiological standpoint, [6]. They are not classified as a single entity, rather they are group according to their lesion site, i.e., stomach or duodenum, and presence or absence of complications, i.e., hemorrhage or perforation,[7].

Non-steroidal anti-inflammatory drugs are the most common drugs, used for pain and inflammation reduction, with proven efficacy, [8]. However, they have been said to account for over 90% of ulcers with substantial implications and complications associated with gastro-intestinal toxicities, [9,10]. Its mechanism of action is through COX-1 inhibition in the gastrointestinal tract, leading to a reduction in prostaglandin secretion and gastric mucosa cytoprotective effect, [11]. These all together increases the risk of damage to the mucosa, [11]. Peptic ulcer remains an important cause of morbidity and health care cost, [12]. The natural history of peptic ulcers ranges from healing without intervention to the development of complications such as bleeding and perforation, [12]. In a review study, the pooled incidence of uncomplicated peptic ulcer disease (PUD) was approximately one case per 1000 person-years in the general population and the incidence of ulcer complication was about 0.7 cases per 1000 person, [13]. The cases of PUD vary based upon the presence of *Helicobacter pylori.* Higher rates are found in countries where *Helicobacter pylori* infection is higher with approximately 1 percent per year, a case that is 6-10 fold higher in uninfected individuals, [14,15,16,17].

A population-based one-year prevalence of PUD of 0.1 to 1.5 percent based on physician diagnosis and 0.1 to 0.19 percent based on hospitalization data was recorded by Sung *et al*., (2009), [18]. In the unitedstates, a study by Anand *et al*., (1996), [19] reported an endoscopic point prevalence for peptic ulcers in asymptomatic, *H. pylori*-positive adults of 2 percent. Ulcer incidence increases with age for both duodenal and gastric ulcers, [19].

**Role of temperature on helicobacter pylori (H. Pylori)**

Helicobacter pylori, a gram-negative bacterium, infesting more than 50% of the world population [20], has its home in the human gastric mucosa, causing stomach injury, [21]. Its communication with the receptors of epithelial cells accompanied by endogenous pathways stimulation and its actions on soluble bacterial components alters or destroys the gastric barrier, [22, 20]. Its ability to survive and endure in an organism has been said to be mediated by the production of catalase by bacteria. [23,24]. Vitamin-D and D-receptors in target tissues such as the intestine, immune cells, has also been identified to play an important protective role in H. Pylori infection, [25,26,27]. Its synthesis which is in response to sunlight and ultraviolet radiation is affected by season, temperature, latitude, and daily sunshine duration,[28]. A recent study revealed that lower H. pylori infection rates were associated with higher average annual temperature while average daily sunshine time correlated positively with H. pylori infection, [29]. It also revealed that, individuals dwelling at high latitude showed a high H.Pylori infection rates, [29].

Although the mechanism of action of H. Pylori hasn't been understood fully, it has been said to be associated with acute and chronic inflammatory responses with a resultant infection in gastric/duodenal ulcers or the development of gastric cancer, [30]. It was said that, the excessive damage done to the barrier by inflammation allows the movement of H. Pylori-virulence-factors into the circulation resulting in the development of a systematic inflammatory response, [30]. Studies also revealed that, lower decrease in the body immunity functions during the cold season, such as a decrease in the number of outer lymph cells and B lymph cells, makes the duodenal mucosa subjected to attack easily by Helicobacter Pylori resulting in the inhibition of the mucosa growth factors, and the rapid development of a peptic ulcer, [31,32,33].

**Role of Temperature in the Occurrence of Peptic Ulcer**

Large numbers of medical conditions have been observed to exhibit seasonal patterns in their occurrence. Examples are; gastrointestinal diseases and cardiovascular diseases, both occurring with high frequency in winter months, [34,35,36,37]. It is characterized by seasons, with a higher occurrence in winter and spring and a low occurrence in summer, [3]. Although H. Pylori and NSAIDs are the major factors responsible for the onset, development, and occurrence of peptic ulcers, only a few studies have been carried out to determine the role of extreme weather and climatic conditions in the development and treatment of peptic ulcer diseases, [1]. Few studies have observed that, temperature plays a major in the occurrence of peptic ulcers, some of which have resulted in increased morbidity in some number of diseases, such as gastrointestinal bleeding, [36, 38, 39], which exhibit a higher frequency in the winter than in the summer, [40].

The actions of temperature on ulcer development have been also said to be caused by an increase in air pressure and dry air relative humidity occurring from cold air, [41,42,43,44]. A series of stress actions have been observed to occur when meteorological factors such as temperature violently change into a severe cold atmosphere i.e., change in temperature, [40,43]. These actions excite the adrenal gland marrow and the sympathetic nerve, causing rapid secretion of adrenaline and non-adrenaline, angiotensin II, and endothelin, [31], resulting in damage to the mucosa epithelial, caused by the contraction effect of the adrenal agents on the duodenal mucosa and blood vessel as a result of insufficient oxygen supply, [42.45.46,47]. The stress caused by cold reduces the secretion of inhibitable growth factors, increasing the secretion of hydrochloric acid in gastric juice, accelerating the onset of peptic ulcers, [31].

A recent study examined gastric mucosal damage and its barrier function (through associated barrier factors) under an extremely hot temperature at an average of >30$^{0}$c and an extremely cold temperature at an average of < 10$^{0}$c, [48]. Their results revealed low expression of epidermal growth factor receptor (EGFR), epidermal growth factor (EGF), heat shock protein (HSP) 70, occludin, nitric oxide synthase (NOS), in the gastric mucosa, in extreme cold temperature than those in extreme hot temperature, whereas the gastric acid secretion Was higher in extreme cold temperature than in extreme hot temperature, [48].

**Role of Temperature on Mucosa Barrier Proteins**

Mucosal barrier functions are defined by tight junctions, [49]. Tight junctions comprise multiple proteins, including; occludin, heat shock protein, epidermal growth factor, and claudins, which have been characterized as barrier enhancing or pore-forming, [48, 49]. They are the most important structural component for the formation of constitutive barrier function in epithelial cells, present on the apical end of the lateral membrane surface in epithelial cells therefore forming a barrier against paracellular transport and maintaining apicobasal cell polarity through their fence function, [50]. Changes to these components that regulate and maintain distinct permeability pathways as well as the mucosal immune stimuli can result in barrier loss,[49].

**Nitric Oxide (NO)**: is a highly reactive molecule playing an important fundamental role in the maintenance of normal vasomotor tone,[51]. It has been said that its degree of expression in the gastric mucosa membrane reflects gastric mucosa blood volume, therefore playing a defensive role in the protection of gastric mucosa, [51]. Its level of expression has been revealed to be low during cold temperatures,[48].

Nitric oxide is a gaseous molecule with autocrine and paracrine effects on many cell types. Nitric oxide is synthesized from the amino acid l-arginine by NO synthase (NOS) and is involved in a myriad of cellular functions including muscle relaxation, neuronal signaling and immune function. It is one of the smallest molecules in nature,[52].

In the gastrointestinal tract, NO participate in the modulation of smooth musculature tone such as regulation of intestinal peristalsis, gastric emptying, antral motor activity, [53]. It also regulates acid and gastric mucus secretion, alkaline production and is involved in the maintenance of mucosa blood flow and also demonstrates gastro-protective properties against different types of aggressive agents. However, a high concentration of NO is related to numerous pathological processes of gastrointestinal tract (GIT. Nitric oxide is produced in the GIT by enzymatic, non-enzymatic or bacteria production mechanisms. For example, xanthine oxidoreductase is an enzyme that under hypoxic conditions can produce NO by reduction of nitrate ($NO_3^-$) and

Nitrite ($NO_2^-$).

Nitric oxide can also be formed from dietary nitrate which is in the oral cavity and is reduced by bacterial reductases to nitrite, [54], yielding NO gas after acidification in the gastric lumen, [55]. Nitric oxide production from the reaction of hydrogen peroxide with arginine is an example of the non-enzymatic production of NO, [56]. Nitric oxide is produced by anaerobic bacteria in the colon using nitrite and nitrate as substrate, [57,58].

Some important roles of NO in GIT functions include;

01. Motility: the motility of the GI tract is controlled by enteric inhibitory and excitatory motor neurons that innervate the smooth muscle layer. Distention of the gut by a food bolus is detected by local enteric afferent neurons. About 50% of the nerves in the enteric nervous system contain NOS which are located in the myenteric and muscle fibres, [59].

02. Secretion and Absorption: Nitric oxide is involved in intestinal water transport by acting directly on the epithelium and blood flow or indirectly by stimulating neuronal reflexes or interactions with other agents. For example, NO activates soluble guanylate cyclase and this result in cGMP generation which is a potent activator of the intestinal secretion, [60].

03. Intestinal inflammation, carcinogenesis and apoptotic processes: nitric oxide is important in maintaining mucosal integrity of the GI tract by several mechanisms. Nitric oxide plays a pivotal role in protecting the GI mucosa from a variety of noxious stimuli through the maintenance of mucosal perfusion,[61,62]. It also plays a critical role in modulating the defensive mechanisms in the GI tract due to its anti-inflammatory action and improvement of mucosa integrity. Nitric oxide functions in apoptosis in two ways based on its concentration, low concentration protect B lymphocytes against viral infections whereas high concentrations induce apoptosis,[63,64].

04. Gastrointestinal diseases: impaired NO release is indicated in disease with non-relaxing sphincters or bowel segments like achalasia, [67], and infantile hypertrophic pyloric stenosis, [66].

**Heat shock proteins (HSP):** They have been said to play a major role in the gastroduodenal defense Mechanism with their expressions activated by heat shock, an example of which is HSP 70 induced by molecular chaperones,[67,68]. It is also said to be involved in various biological activities, such as apoptosis prevention, protection from cytotoxic damage, e.g. from NSAIDs or H. pylori infection, and the facilitation of ulcer healing, [67,68]. It has also been revealed to have low expression in the gastric mucosa during cold temperatures,[48].

**Epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) protein:** They have both been revealed to be involved in peptic ulcer healing and re-epithelialization, which has also been found to be associated with gastric mucous surface epithelial cells differentiation, proliferation and migration [69], with their expression significantly low during the cold season, [48].

Epidermal growth factor (EGF) is a 53-amino acid peptide, it plays an important role in regulating and maintaining cell growth or development, survival, migration, apoptosis, proliferation and differentiation by binding to epidermal growth factor receptor (EGFR), [70]. It is an effective intestinal regulator helping to protect intestinal barrier integrity which is important in the absorption of nutrients and health in humans and animals[70]. According to Zeng and Harris (2014),[71], it has been detected in a variety of body fluids such as saliva, milk, amniotic fluid, urine, plasma, and intestinal fluid.

Epidermal Growth Factor also functions as a gastrointestinal tract (GI) mucosal protective factor, which associates with intestinal maturation and maintenance of epithelial cell homeostasis in the small intestine, [72]. Some importance of EGF on stomach and duodenal function include the following;

01. Regulation of Tight Junction: tight junction regulates the passage of ions, water and solute and solutes and acts as a fence to maintain cell polarity by blocking the free diffusion of proteins and lipids between the apical and basolateral domains of the plasma membrane, [73].The epidermal Growth Factor is a key regulator of epithelial permeability,a property that depends on Tight Junctions, [74,75]. Epidermal Growth Factor has been shown to protect intestinal barrier function by preventing early-weaned, [76], hydrogen peroxide, [77,78,79], ethanol [80], acetaldehyde,[81,82,83] and intestinal ischemia-reperfusion [84,85], induced disruption of Tight Junctions and permeability.

Xu *et al*.(2015) [76], indicated that the oral administration of EGF could improve the gene expression of tight junction proteins such as ZO-1, claudin-1, and occludin, thus enhancing the intestinal barrier function of early-weaned piglets. Hydrogen peroxide-induced intestinal barrier disruption was prevented by Epidermal Growth Factor through Mitogen-activated Protein Kinase (MAPK) and Protein Kinase C(PKC) pathways.

Epidermal Growth Factor induces changes in the composition of Tight Junctions (TJ) through activating several signalling pathways such as Protein Kinase C (PKC),[78], Mitogen-activated Protein Kinase (MAPK),[74] and Signal Transducers and Activators Transcriptions (STATs) in different types of cells, [86].

**PKC pathway**: Protein Kinase C is a family of serine/threonine protein kinases that plays an important role in controlling the function of other proteins and in several signal transduction cascades, [87,88]. Protein Kinase C enzymes are activated by signals including the increased concentration of diacylglycerol (DAG) or calcium ion, [89]. The PKC family consists of fifteen isoenzymes in humans, [90]. These isoenzymes are divided into three subfamilies of conventional, novel and atypical, [91]. Protein Kinase C is transported to the plasma membrane after activation and it helps in the contraction of smooth muscles in the GIT,[92,93].

**MAPK pathway:** This pathway is also known as the Ras-Raf-MEK-ERK pathway, it is a chain of proteins in the cell that relates information within the cell through the communication of signals from a receptor on the surface of the cell to the DNA in the nucleus of the cell which leads to some changes in the cell such as cell division, [94].

The MAPK pathway plays a major role in integrating and relating external signals from the presence of mitogens such as epidermal growth factors (EGF) into signalling events thereby promoting cell growth and proliferation in many mammalian cell types, [95].

Activated MAPK can phosphorylate a wide range of substrates and thereby affecting a broad array of cellular functions including motility and proliferation. It was shown in a recent study that the MAPK pathway is involved in the regulation of TJ proteins in mouse epididymis, [96].

The contradictory effect of MAPK activation is more pronounced in TJ integrity where its activation leads to disruption of TJs in some epithelial monolayers and prevention in other epithelia, this was observed in Caco-2 cell monolayers by Aggarwal *et al*., (2011), [97].

**STATs pathway:** it is a chain of interactions or communication between proteins in a cell that is involved in processes such as immunity, cell division, cell death and tumor formation. This pathway communicates and relates information from chemical signals from outside of a cell to the cell nucleus resulting in the activation of genes transcription, [98]. Disruption to this pathway can cause serious diseases such as cancers, immune system disorders and skin conditions, [98].

01. EGF Promotes Mucin Secretion: The EGF protects and separates itself physically from exogenous stress by secreting mucins to form a thick protective layer of mucus over the intestinal mucosa which are important for intestinal lubrication, limiting bacteria adhesion and maintaining proper intestinal permeability, [99,100,101].
02. EGF Reduces Bacterial Colonization: The intestinal microbiota profile plays an essential role in intestinal integrity. EGF can reduce colonization of the intestinal epithelium by entero-pathogens, such as *Escherichia coli (E.coli),*[102,76,103,104] *Campylobacter jejuni (C.jejuni)*,[105], and *Enterococcus.*[102].
03. EGF and intestinal development: EGF plays a significant role in intestinal development, including increasing villous height and crypt depth, enhancing enterocyte proliferation, and stimulating secretion of digestive enzymes such as trypsin, chymotrypsin, alkalinephosphatase, sucrase, maltase, and lactase, which is important for improving nutrition absorption, feed utilization, and growth performance of animals,[76,99, 102,106,107,108].
04. Other importance includes inhibition of acid secretion, protects gastric mucosa against injury, mediates inflammation, mediates mucosa adaptation and accelerates ulcer healing.

The biological functions of EGF a remediated through binding to EGFR and subsequent activation of various signal transduction pathways to regulate intestinal development, Tight Junctions expression and mucins secretion which is important for the formation of intestinal barrier functions, [99,106,

107]. The epidermal Growth Factor acts as a key epithelial mucosa regulator to regulate intestinal permeability and intestinal barrier integrity.

# Conclusion

In summary, the cold temperature has been identified to be one of the major factors in the occurrence of peptic ulcer, performing its functions by directly acting on the adrenal glands to increase the secretion of endothelin, adrenaline, which exerts their contracting effect on the duodenal mucosa and blood vessel resulting in mucosa damage. It also plays a major role by limiting the expression of mucosa barrier proteins; which are the major defence proteins against helicobacter pylori and non-steroidal anti-inflammatory drugs. Therefore, giving the dearth knowledge of the role of temperature in the treatment of peptic ulcer diseases, it is very important to consider temperature as one of the major factors in the treatment of peptic ulcer diseases.

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