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Review of the Possible Role of the Stomach in the Gut–Joint Axis in Osteoarthritis: Avicenna's Perspective Versus Modern Medicine

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Abstract

Osteoarthritis (OA) is the most common debilitating chronic joint disorder with no definitive treatment. Avicenna considers a strong relation between the Gastrointestinal Tract (GIT), with other body organs, including the joints. Specifically, he regards disorders of the stomach as the most important underlying cause of arthritis. The present review study aims to collect the available scientific evidence on the role of the stomach in OA in order to provide a new insight of the gut-joint axis based on Persian Medicine (PM) theory. In this narrative review, the term "vajae-al-mafasel" was searched (the equivalent term for arthritis) in Avicenna's medical masterpiece, Canon of Medicine. Additionally, PubMed, Web of Science and Google Scholar databases were queried with keywords including OA, gut, stomach, PM, and systems biology. After gathering data, they were classified, coded, analyzed, and compared. Mechanisms that play a role in the GUT-OA axis include: 1) Gut Microbiota (GM) dysbiosis; 2) contribution of GM metabolites; 3) leaky gut syndrome; 4) bacteria transfer phenomenon; and 5) Metabolism disturbance. Growing evidence shows the pivotal role of the stomach, as part of the GIT, in the balance of metabolic functions and gut-joint axis. the role of the stomach is discussed in OA in the four sections: maintaining the metabolic balance by stomach, bone metabolism and gastric acid, controlling cartilage homeostasis by gastric hormones, gastric microbiota dysbiosis and OA.

Keywords: Dysbiosis, Gastrointestinal microbiome, Osteoarthritis, Persian medicine, Stomach, Systems biology

Introduction

Osteoarthritis (OA) is the most common form of arthritis and the fourth cause of disability and loss of function globally (1), affecting 18% of women and 10% of men over 60 years of age worldwide (2). The growing trend of aging and sedentary life has turned OA into one of the biggest challenges of the health system (2). OA is a multifactorial disease with unknown etiology, for which there is no definitive pharmacological treatment available (3). Traditionally, management includes pain reduction and joint replacement for end-stage cases, neither of which target the pathogenesis of the disease (4, 5). Considering the gastrointestinal, cardiovascular, and renal complications of Non-Steroidal Snti-Inflammatory Drugs (NSAIDs) (4), the limited lifespan of prosthesis (5), and estimating more than 130 million people whom suffering from OA by the year 2050 (6), there is an emphasis to focus on disease prevention and treatment in the early stages (7), and identifying the risk factors to elucidate the etiology of OA (5). Regarding pathophysiology, systems biology endeavors to express the communicative mechanisms of the components of organ systems in a comprehensive view, and to present an integrated picture of molecular, cellular and tissue interactions (8,9).

In Persian Medicine (PM), the human body is regarded as an integrated system with closely related components (10). A renowned Iranian philosopher and physician, Avicenna (Ibn Sina: 980-1037 AD), deemed a relation between the Gastrointestinal Tract (GIT), especially the stomach, with other organs, including the joints, using the concept of "*mosharekat*" and "*amraaz sherki*", *i.e.,* participation and participatory diseases which is similar to the concept of systems biology in modern medicine (11). According to Avicenna, the stomach and upper GI plays a key role in the whole body's health, including the joints (12,13).

In PM, paying attention to the underlying causes of disease is of particular importance in taking the best approach to treatment (13,14). In Avicenna's renowned book, Canon of Medicine, several mechanisms have been proposed for arthritis, most of which result from the stomach and upper GI dysfunction (14). The axis between the GIT/musculoskeletal system and Metabolic Syndrome (MetS) has been of interest in recent years (Figure 1) (15). Although majority of studies have investigated the role of hormones and the intestinal microbial community in the pathophysiology of metabolic diseases, including OA, studies on the role of the stomach are lagging behind (16). Hence, focusing on the upper digestive system, especially the stomach in the MetS-Gut-Joint axis, may be a promise for new preventive and therapeutic strategies for OA (16). In this study, the role of the stomach was explored in OA based on Persian medicine (PM) theory and current scientific evidence to propose a potential new clinical approach for OA prevention, treatment, and symptom management. By understanding the stomach's role in the gut-joint axis, the aim was to suggest novel strategies that could complement existing treatments and contribute to better control of OA the symptoms.

Materials and Methods

This study is a narrative review based on content analysis to evaluate OA etiology in PM sources and modern medicine. The theoretical sampling method was followed which is a special type of criterion-based sampling that follows the gradual selection rule. In this method, the researcher takes a primary source, analyses the data, and then retakes more samples to refine his emerging categories and theories. This process continues until the researcher reaches the stage of data saturation; that is, the stage where no new insights and ideas are obtained from further expansion of examples. Initially, Avicenna's Canon of Medicine (Qanun fi al-Teb), was searched for "vajae-al-mafasel" (a term for arthritis in Arabic). Subsequently, PubMed, Web of Science, and Google Scholar databases were searched for OA in combination with gut, stomach, PM, and systems biology for preclinical and clinical evidence of the role of the stomach in OA. After collecting the data, open coding, and then central coding (phenomenon, causes, contexts, contexts, intervening conditions, strategies, and consequences) were done. Finally, the obtained results underwent the content analysis.

Results and Discussion

The gut-joint axis from Avicenna's point of view

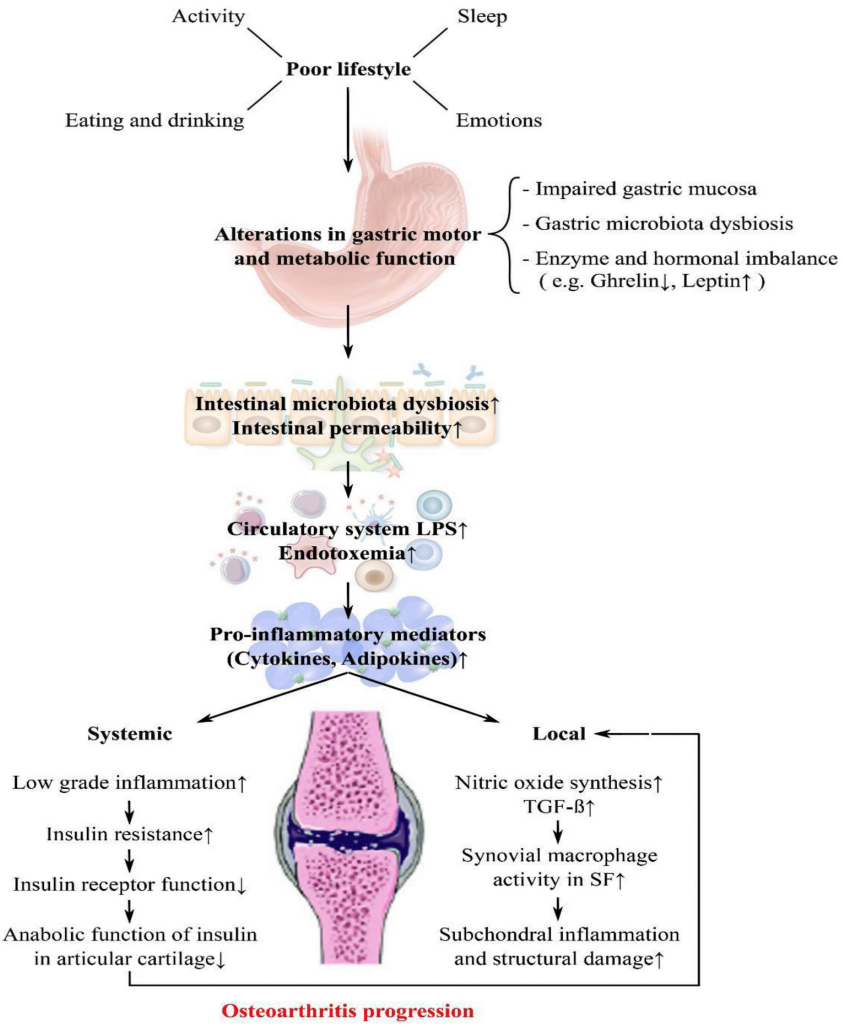

Figure 1. Proposed paradigm for the role of stomach in osteoarthritis.

The relationship between organs, especially the stomach and upper GI, with other body systems has been emphasized and paid attention to in PM (17). Accordingly, from the viewpoint of PM authors, the stomach plays a key role in the whole body's health, and the health of all body organs depends on the health of the stomach (18). Therefore, PM physicians emphasize improving the GIT function, especially the stomach, in order to maintain health, prevent and treat various diseases (19). Avicenna also considers the stomach as the main underlying cause of disease (20). In Canon of Medicine, he proposed three general causes for arthritis, which include a weak joint that admit pathetic fluids from a faulty sewer. Many of the underlying causes proposed for arthritis in this book are related to digestive disorders, especially gastric disorders (Table 1) (21). Any disturbances in digestion lead to the production of abnormal substances in the body and affects the health of the whole body, and the joints (20). Avicenna believes that to maintain health and treat joint diseases, special attention should be paid to the function of the GIT and stomach as an important underlying cause of diseases (17).

Physiopathology of OA

In recent years, the pathophysiological concept of OA has changed from an exclusively degenerative and mechanical disorder to a more complex concept with multiple mechanisms (22). Anabolism and catabolism phases are regulated in healthy individuals, so that any destruction and repair of the cartilage is in balance. By secreting growth factors such as transforming growth factor-β (TGF-β), chondrocytes prevent calcification and vascularization of the cartilage matrix to maintain the integrity of the Extracellular Matrix (ECM) (22). In OA, there is imbalance at the cellular level (23). In

Table 1. A selection of scientific evidence on selected etiologies of arthritis (osteoarthritis) proposed by Avicenna

OA factor according to Avicenna		Modern evidence				
		Study design	Population	Assessed variable	Result	Authors (Date) References
Eating habits	Overeating; eating a variety of foods in one meal	Longitudinal cohort	Labrador retriever dogs	The effect of diet restriction on development of radiographic evidence of hip joint OA	Lifetime preservation of 25% diet restriction delayed onset and reduced severity of hip OA	Huck *et al* (2009)
		Animal	Domestic dogs	The effect of diet restriction on OA	25% diet restriction decreased hip joint laxity and OA in a dog breed that is genetically susceptible to obesity and OA	Keal.y RD *et al* (1992)
	Eating before complete digestion of the previous meal	Cross-sectional	7972 Adults (18–65 years old)	Speed of eating as a risk factor of MetS	Eating speed was significantly associated with a high risk for MetS and its components	Lixin Tao *et al* (2018)
		Medical examination and health interview	24,173 individuals aged ≥50	Correlation between chewing difficulty and OA	High prevalence of OA was seen in females aged 50 years and older with mastication discomfort	Hwang, Su-Hyun *et al* (2015)
	Not following the correct order of eating	Animal	Mouse model	Correlation between altered eating habits and OA	Circadian rhythm disruption (feeding behavior) potentiated OA change	Ranjan Kc *et al* (2015)
		Animal	Male wild mice	Effect of feeding pattern on GM and host metabolism	Time-restricted feeding affected bacteria shown to influence host metabolism	Zarrinpar *et al* (2014)
		Case control	Female patients with RA	Detection of periodontopathogens DNA in synovial fluid	Oral bacterial DNA in synovial fluid may indicate its role in the pathogenesis of arthritis	Reichert S *et al* (2013)
Drinking habits	Alcohol	Cross-sectional	25,534 participants in Korea	Association between alcohol consumption and OA prevalence	Positive associations between alcohol consumption and radiological knee OA, rather than symptomatic knee OA	Kang *et al* (2020)
		Longitudinal cohort	Participants without hand OA at baseline	Progression of hand OA in relation to alcohol consumption	Moderate alcohol consumption was associated with hand OA severity, radiographic changes, and erosive hand OA	Haugen *et al* (2017)
		Meta-analysis		Association between alcohol consumption and OA	Results provided evidence to dispel notions that alcohol use may be protective against OA	To *et al* (2021)
Sleep pattern	Sleep duration more or less than needed	Case control	351,932 OA patients aged ≥18 yr	Association between sleep disorders and OA	Sleep disorders may play a role in the development of OA	Jacob *et al* (2021)
		Population-based	5268 Women aged ≥50 yr	Relationship between sleep duration and OA	Both long and short sleep durations were positively associated with OA	Park *et al* (2019)
		Descriptive	Adults (≥65 years) with OA	The association of self-reported sleep quality with joint pain and fatigue	Poor quality of night sleep affected OA symptoms	Whibley *et al* (2019)
		Cross-sectional observational	11,540 participants with OA	The association between OA and sleep duration	Prevalence of OA was lower in the participants who had 6–7 h of sleep and progressively increased with shorter sleep time	Jung *et al* (2018)

Contd. table 1.

Physical activity	Inactivity	Animal	Male mice model	Correlation of the OA pathophysiology and LPS release by GM	Moderate exercise ameliorated osteoarthritis by↓ LPSs	Kefeng Li *et al* (2020)
		Animal	Guinea pigs	The effect of sedentary lifestyle on OA	Physical inactivity promoted development of knee OA	Antunes *et al* (2019)
		Animal	Rat model	The effects of aerobic exercise and prebiotic on metabolic OA	Better protective effect of combined treatment with exercise and dietary intake on knee health was observed	Rios *et al* (2019)
		Animal	Mouse model	The effect of obesity due to HFD on knee OA	Exercise relieved OA development by ↓ fasting blood insulin levels	Griffin *et al* (2012)
	Intensive exercise after meals	Clinical study	19 healthy male volunteers	The effect of heavy exercise on OA	high intensity exercise seems as a proinflammatory factor increase the intestinal permeability and LPS level.	Antunes *et al* (2019)
Sex hormones	Amenorrhea (disturbance of sexual hormones)	Animal	Rat model	The role of estrogen in development of postmenopausal OA	↓Estrogen level was associated with the pathological changes of OA	Xiao Xu *et al* (2019)
		Animal	Mouse model	The role of the ERRs in OA pathogenesis	ERRs in articular chondrocytes directly caused expression of MMP3, 13, which play a crucial role in cartilage destruction and OA pathogenesis	Son and Soo Chun (2018)
		Case control	112 Women with generalized OA	Alteration of sex hormone status in postmenopausal women with generalized OA	↑ Circulating free androgens and estrogens presented suggesting a role in the etiopathogenesis of generalized OA	Spector *et al* (1991)
Climate and environmental conditions	Exposure to extreme weather conditions or polluted air	Animal	Rat model	The effect of exposure to ambient air pollution on OA	Exposure to particulate matter and gaseous pollutants significantly increased plasma cytokine levels compared to control	Nikolenko *et al* (2022)
		Time-series	Knee OA patients	The effects of air pollution on knee OA	Short-term exposure to particulate matter increased the number of outpatient visits for knee OA	Chen *et al* (2021)
		Systematic review		Associations between OA and pollutants	Pollutants were found to be a big new risk factor for OA	Deprouw *et al* (2022)

↑= Increased, ↓= Decreased, OA= Osteoarthritis, ERRs= Estrogen-related receptors, LPSs=Lipopolysaccharides, MetS= Metabolic syndrome.

the early stages of OA, chondrocytes try to deal with the destruction process by secreting Tissue Inhibitors of Matrix Metalloproteinase (TIMPs) (22). However, as the disease progresses, chondrocytes start to release chemical mediators such as Nitric Oxide (NO). *Via* inducing the production of Interlukin1 (IL-1), NO increases the expression of proteolytic enzymes such as Matrix Metalloproteinases (MMPs) and disintegrin and metalloproteinases with thrombospondin motifs (ADAMTS), leading to the degradation of ECM components such as aggrecan and type II collagen. These harmful structural changes disrupt tissue homeostasis and integrate function of the synovial joint and ultimately limit repair and regeneration with negative effects on biomechanics of the joint (24). OA is also associated with changes in the composition and function of the Synovial Fluid (SF). Together with an increase in the levels of catabolic and pro inflammatory cytokines, these alterations cause cartilage destruction and create a vicious circle. This

thick liquid has lubricating, metabolic, and regulatory functions, and facilitates the transport of nutrients, waste materials, and enzymes and metabolites to and from synovial tissues (23).

Potential mechanisms for the role of the digestive system in OA

Growing evidence shows an important connection between health of the gut and that of the whole body. The gut is the largest human organ system, where the interactions of digestive mucosal cells, immune system, food particles, and resident microbiota lead to a series of physiological processes (25). The Gut Microbiota (GM) is vital in maintaining health, digestion and absorption of nutrients, vitamin synthesis, and development of the central nervous system and immune system (26). In recent years, GM has been considered as a powerful factor in the pathogenesis of many chronic inflammatory and metabolic, digestive, and systemic disorders, including OA (26,27). Several mechanisms are proposed to cause OA. However, the exact role and contribution of each has not been elucidated (27,28).

Mechanisms that play a role in the GUT-OA axis include:

Gut Microbiota dysbiosis

High Fat Diet (HFD)-induced obesity, the most studied risk factor for OA, is associated with changes in the microbiome. Recently, a link between systemic inflammation and GIT M dysbiosis has been suggested. Evidence shows that via activating innate immune responses, the intestinal microbiota leads to increased serum titers of inflammatory mediators and low-grade inflammation in obese patients. This indicates a possible link with the onset and progression of metabolic OA (29). Evidence also indicates that obesity has a significant inflammatory component that may be important in the development of inflammation in OA. Obesity is associated with damage in the intestinal mucosa, displacement of microbiota and increased serum Lipopolysaccharides (LPSs). Obesity-related inflammation is caused by LPSs derived from the gut microbiota (30). In a study by Schott *et al*, the HFD was associated with a significant decrease in the diversity and number of specific species such as bifidobacteria and an increase in the frequency of pro-inflammatory species (31). In contrast, Ulici *et al* revealed the structural role of microbiota in OA independent of obesity. Using a mouse model, they showed that the progression of joint damage in axenic mice (mice that live in a sterile environment without microbiota) is less severe than in the control group. This indicates the key role of the microbiota in the progression of joint changes (32). An animal study demonstrated a decrease in some microbiota species such as Lactobacillus species and the abundance of Methanobrevibacter spp., which can be related to OA (33). Moreover, a study of 1444 patients with knee or hip OA identified a strong correlation between the frequency of Streptococcus A group as a gut microbiota and low grade inflammation in Knee OA (34).

Change in the contribution of Gut Microbiota metabolites

Studies have found an increase in the serum level of bacterial metabolites (including LPS) and its circulatory transfer to the joint can be effective in the development of metabolic OA (35). LPSs are responsible for most of the biological properties of bacterial endotoxins and have an exceptional ability to induce inflammation through Toll-Like Receptors (TLR- 2,4) (36). LPS-induced inflammation in adipose tissue can accelerate systemic changes in cytokines, adipokinase, and growth factors, including leptin and IL-1α, which ultimately stimulate the local innate immune system inside the joint and contribute to the progression of OA by activating chondrocytes and immune cells in synovial joints through TLRs (36). Experimental and clinical studies have shown a positive correlation between the severity of joint destruction, the severity of knee osteophyte formation, and the severity of pain with serum and joint LPS levels (29,37,38).

Leaky gut

There is a significant correlation between damage to the intestinal barrier and gastrointestinal and extra-gastrointestinal diseases (39). Under the influence of various factors, including HFD, eosinophils are depleted in the intestine, which is associated with increased intestinal permeability as well as GM dysbiosis. Overgrowth of pathogenic microbes along with reduction of protective bacteria, leads to activation of innate immune receptors in the intestine

by microbial products such as LPS, resulting in the production of proinflammatory mediators. Intestinal leakage causes more amounts of toxic metabolites, including LPS and inflammatory mediators, to enter the systemic circulation. These metabolites stimulate inflammation and initiate many OA processes. Identification of higher levels of LPS in plasma and synovial fluid of people with knee OA, as well as microbial DNA in OA cartilage, highlights the role of increased intestinal permeability in the development of OA (40).

Translocation of microbiota

Detection of bacterial DNA by PCR analysis of liquid and synovial tissue of rats with OA and in healthy human cartilage illustrates that bacterial fragments derived from GM and their metabolites can normally be transferred between GIT and epiphyseal bone marrow (41). Increased intestinal permeability allows the transfer of more bacteria or bacterial fragments into the bloodstream (42). This hypothesis is proposed that the presence of GM in human cartilage is not accidental, as they usually help repair it by suppressing the immune system and changing the composition of the deep matrix components of the cartilage. However, in dysbiosis, they cause inflammation and destruction of the cartilage (43). The metabolism of chondrocytes and DNA methylation are also different based on the type of cartilage and the residing microbiota. The type of microbiota is different in OA and healthy cartilage, and is also different in the cartilage of different organs joints (41).

Metabolism disturbance

Clinical research has shown that disruptions in the metabolism of carbohydrates, including Insulin Resistance (IR), can disturb the metabolism of the joints, like any other organ (44). The association found between OA and MetS in meta-analyses has caused studies of the last two decades to suggest the "metabolic OA" phenotype and propose GM as a hidden intermediary in this axis (45). It is hypothesized that a HFD is associated with intestinal mucosa dysfunction, which increases transfer of the LPSs component of the bacterial membrane to the blood circulation, resulting in endotoxemia. It also increases the serum titer of inflammatory cytokines, which leads to obesity and IR (30).

In the synovium of diabetic patients, IR can play a direct role in the development of OA by disrupting the secretion and protection of cartilage matrix (46). Several mechanisms contribute to this process. Firstly, insulin plays an anabolic role by inducing the production of type 2 collagen and proteoglycan in joint tissues, and reducing the activity of insulin receptors in OA reduces the positive effect of insulin (46). Second, AGEs (advanced glycation end-products) produced in type 2 diabetes, induce intracellular signaling cascades in chondrocytes; animal studies have shown that artificial increase of intra-articular AGEs leads to advanced OA (46).

OA is also associated with dyslipidemia and cholesterol accumulation in cartilage. A study by De Munter *et al* revealed that intake of cholesterol-rich foods leads to the accumulation of apolipoprotein B as the main compound of high oxidized-LDL in the synovial tissue. An increase in the ox-LDL level in serum and tissues under oxidative stress causes synovium inflammation to intensify following activation of macrophages and increases the formation of osteophytes through the activation of anabolic factors such as TGF-β (47). The study by Fernandez *et al* also demonstrated that inflammation caused by metabolic stress, not mechanical overload, is responsible for OA changes following HFD (48).

The role of stomach in the gut-joint axis

The stomach is the most important part of the GIT and a very complex multifunctional organ that plays an important role in the body (49). This organ plays the main role in regulating the food digestion process (50), and is hence important for the health of all body systems. Evidence represents the role of the stomach in the metabolic homeostasis of the body (51). High-fat food, hyperglycemia, insulin resistance, and dyslipidemia can disrupt the metabolism of the joints like any other organ (44). A number of these processes are under the special influence of the brain-stomach axis as part of the gut-brain axis, which leads to the regulation of glucose, fat metabolism, and eating behaviors, including satiety and appetite (52). The role of stomach in OA will be briefly discussed in the following sections.

Stomach and metabolism

Results of clinical studies have shown that there is a strong epidemiological relationship between metabolic syndrome and OA, especially in the Asian population. This raises the hypothesis of systemic regulation of joint tissue (53). As a part of GIT, the stomach plays an important role in maintaining the metabolic balance of the body (50). Diabetes is a serious risk factor for OA (54). Irregular emptying of the stomach can lead to poor blood sugar control, and hence, stomach dysfunction contributes substantially to impaired glucose tolerance in patients with long-term diabetes. Moreover, the stomach plays an important role in the integrated response to feeding by regulating the delivery of nutrients to the small intestine, where important hormonal responses control the processes of digestion and blood sugar control; hence, modulation of gastric function leads to improved blood sugar control in type 2 diabetes (55).

Moreover, stomach mucosa damage and mild inflammation can lead to metabolic endotoxemia (30). This is confirmed by the consequences of gastric bypass surgery. Roux-enY Gastric Bypass surgery (RYGB) causes changes in the microbiome composition and metabolic phenotype (56,57). Incomplete digestion of proteins in the small intestine as a result of deprivation of the distal stomach after surgery leads to increased colonic fermentation of proteins and higher concentrations of Short Chain Fatty Acids (SCFA). Samples of fecal water obtained in the second and eighth weeks after the operation showed significantly more cytotoxicity compared with samples obtained from animals with non-real surgery (57). Metcalfe's study proposed the hypothesis that metabolic endotoxemia can play a role in the onset and progression of OA in obese people by increasing the permeability of the intestinal mucosa and IR (30). In the laboratory studies, endotoxemia can cause articular cartilage destruction and OA by activating macrophages in synovial fluid and inducing NOS production (58,59).

OA and gastric acid

The stomach is constantly exposed to toxins. In addition to starting the digestion process, gastric acid secretion is the first line of defense against food-borne pathogens (51). *Via* preventing the invasion and colonization of pathogenic bacteria, gastric acid is a possible key factor in shaping the diversity and composition of microbial communities in the lower digestive tract (60). Gastric acid juice regulates gastric motor function, emptying rate of swallowed food, and mobility of the lower digestive tract (61). Moreover, accurate regulation of gastric acid secretion is of fundamental importance in bone metabolism. Calcium is one of the important factors in bone-intestinal signaling axis, which can only be absorbed by the human body in an ionized form. The low pH of the stomach is responsible for ionization of consumed calcium (62). The Calcium-Sensing Receptor (CaSR) in the stomach regulates the level of ionized calcium in the blood by stimulating gastric acid secretion (62).

OA and gastric hormones

Several digestive hormones produced in the stomach, including ghrelin, gastrin, leptin, and somatostatin, contribute in regulating systemic homeostasis in the gut-brain axis (63). There is increasing evidence for their vital role in controlling cartilage homeostasis and joint disorders (Table 2) (64).

Ghrelin is a hunger-sensing hormone mainly secreted from gastric oxyntic mucus, but also expressed in many other organs (65). Ghrelin is one of the key signals involved in human energy metabolism in the gut-brain axis (63). Currently, it is the only known hormone outside the CNS that is released during hunger to induce appetite (55,66). Ghrelin is also expressed in cartilage cells and plays an important role in the growth and differentiation of chondrocytes and regulation of cartilage metabolism (67). Increasing evidence shows the role of ghrelin in controlling inflammatory joint diseases such as osteoarthritis. *Via* reducing the expression and function of IL-1b and TNF-a, ghrelin inhibits the destruction of type II collagen and aggrecan and promotes cartilage growth (65). Several preclinical and experimental studies have demonstrated that ghrelin can play a protective role in the homeostasis of cartilage cells coping with apoptosis and OA progression by reducing the production of inflammatory cytokines and metalloproteinases, as well as maintaining the expression of joint anabolic factors including matrix,

Table 2. A selection of scientific evidence on gastric factors associated with osteoarthritis

Authors (Date) References	Study design	Population	Assessed variable	Main findings
			1- Gastric hormones	
			Ghrelin	
Wu J. *et al* (2017)	Cross-sectional clinical study	146 KOA patients (83.3% female)	Association between serum levels of ghrelin, knee OA symptoms (WOMAC Index)	Positive association of ghrelin with ↑ knee symptoms and ↑serum levels of MMPs suggests that ghrelin may have a role in knee OA
Ceriotti S. *et al* (2017)	*In vitro*	Joints from 6 different adult horses	The ability of ghrelin to counteract LPS-induced necrosis and apoptosis of chondrocytes and the involvement of GH secretagogue receptor (GHS-R)1a in the protective action of ghrelin	↓ Ghrelin concentrations increased necrosis and apoptosis and worsened LPS-induced cellular damage, whereas ↑ ghrelin protected against LPS-induced cellular damage
Zou Y. *et al* (2017)	*In vivo*	52 KOA patients (38/14) M/F and 52 healthy controls	Association between SFG levels and KOA symptoms	Independent and negative correlation of SFG levels with disease severity in KOA suggests that ghrelin might play a protective role in OA pathogenesis & progression
liu J. *et al* (2017)	*In vitro*	Human primary chondrocytes	The role of ghrelin on the pathological progression of OA	Ghrelin prevented articular cartilage matrix destruction in human chondrocytes by reduced IL-1β-induced expression of MMPs 3,13 and ADAMTs 4,5
Qu R. *et al* (2017)	*In vivo* and *In vitro*	Human chondrocyte and cartilage samples were collected from OA patients and C57BL/6 background age-matched male wild-type mice	The role of ghrelin in joint degeneration severity and levels of various inflammatory cytokines	Down-regulation of proinflammatory cytokines production and metalloproteinases, inhibition of apoptosis of chondrocytes and maintained critical matrix components expression by ghrelin, supports ghrelin as a potential therapeutic approach to OA
			Leptin	
Stannus P. *et al* (2013)	A prospective cohort (cross-sectional and longitudinal) study	163 humans (46% F), randomly selected subjects	The association between knee cartilage thickness, serum leptin levels, BMI, trunk and total body fat	Adiposity measures & cartilage thickness are mediated by leptin suggesting leptin may play a key role in cartilage thinning
Bao J. *et al* (2010)	*In vivo* study	Knee joints of rats	The rol of leptin on pathological process of OA	↑Both gene and protein levels of MMP-2,9, ADAMTS-4 ,5 AND ↓ proteoglycan in articular cartilage after treatment with leptin, strongly suggest that leptin plays a catabolic role on cartilage metabolism
Simopoulou T. (2007)	*In vitro* study	Articular cartilage samples of 17 patients (6/11) M/F	The effect of serum and SF leptin levels on chondrocyte proliferation	↑Leptin and leptin receptor in advanced OA cartilage suggested a pro-inflammatory and catabolic role of leptin on cartilage metabolism and a metabolic link between obesity and OA
Ding C. *et al* (2008)	Cross-sectional (prospective, population-based)	Sample of 190 randomly selected subjects (48% F)	Association knee cartilage volume, serum leptin levels, fat and lean mass	Negative association of serum levels of leptin with total cartilage volume, obesity and female sex was observed

Contd. table 2.

Dumond H. *et al* (2003)	*In vivo* and experimental	11 OA patients (3/8) M/F	The role of Leptin levels in SF obtained from OA patients in the pathogenesis of OA	The pattern and level of leptin expression were related to the grade of cartilage destruction and paralleled those of growth factors (IGF-1 and TGF 1). Leptin is a key regulator of chondrocyte metabolism by modulating chondrocyte functions & contributing to osteophyte formation
Stannus OP. *et al* (2010)	Cross-sectional study	193 (48% F) randomly selected subjects	The association between serum levels of leptin and (IL)-6, fat mass, BMI and JSN in radiography	This study suggested metabolic & inflammatory role of leptin in the etiology of hip OA and that the associations between body composition and hip JSN are mediated by leptin, particularly in women
Gastrin				
QING *et al* (2016)	*In vitro* study	36 OA patient & 10 healthy controls	The association of HIF1α levels in the SF and articular cartilage of KOA patients with the severity of disease	HIF1α in SF and articular cartilage is associated with progressive joint damage
Jiang *et al* (2020)	Animal	Adult Sprague-Dawley rats	Association between HIF-1α and apoptotic cell death following ischemic stroke	HIF-1α is acritical regulator of immunity and inflammatory response
Luo *et al* (2020)	*In vitro* and *In vivo*	Rat model	The protective role of gastrin against osteonecrosis	Gastrin prevents SAON with ↓ expression of HIF-1α, ↓ bone resorption and apoptosis, also ↑ bone formation
Drozdov N. *et al* (2012)	Randomized controlled study	43 patients with confirmed OA (knee and hip)	Influence of ginger on gastropathy conditions & pain joint in OA patients	The simultaneous anti-inflammatory & antioxidant and gastroprotective effects of ginger combined with↑ serum gastrin was more effective in reducing osteoarthritis symptoms
Somatostatin (SST)				
Silveri F. (1994)	Clinical study	20 patients with KOA	Evaluation the efficacy of SST intra-articular injection in OA patient	The results revealed a significant pain & joint function improvement after intra-articular SST
Shao *et al* (2020)	Animal	Rat model	The effects of capsaicin-induced sensory nerve denervation on OA progression in mice	Reduced expression of SST by application of capsaicin exacerbated the existing cartilage degeneration
Montjean *et al* (2020)	Animal study	Mature male Lewis rats	The effect of REG-O3 chimeric peptide combining growth hormone and SST sequences	REG-O3 was able to significantly improve joint function and prevent cartilage degradation
2- Gastric microbiota Helicobacter pylori (H. pylori)				
Yang *et al* (2018)	Preclinical	Old male Wistar rats	To determine the efficacy of H. pylori Y-glutamyl-transpeptidase (GGT) in OA therapy	H. pylori GGT as a regulatory immune response alleviated osteoarthritis
Hsu *et al* (2018)	*In vitro*	Fecal samples of adult patients (age >20 yr) with gastritis	To investigate the short and long-term impacts of *H. pylori* eradication of gut microbiota	Anti-H. pylori therapy resulted in an increase in relative abundance of Proteobacteria in gut microbiota, which may contribute to development of adverse effects

Contd . table 2.

Propionibacterium acnes (P. acnes)				
Levy *et al* (2013)	*In vitro*	Joint specimens of 55 patients with arthritic shoulders	Estimation the joint presence of *P. acnes* as the etiology of OA	High incidence of *P. acnes* in joints before arthroplasty may suggest a role for *P. acnes* in arthritic joints
Trimble *et al* (1987)	*In vivo* and experimental	Rat model	The role of *P. acnes* in arthritis	Intra-articular injection of *P. acnes* caused erosive arthritis in rats
Hudek *et al* (2019)	*In vitro*	23 Consecutive, otherwise healthy patients (17/6) M/F	Detection of *P. acnes* in intra-articular specimen taken from patients having first time shoulder surgery	This study indicated *P. acnes* to be a commensal of the human shoulder joint where it persists within macrophages and stroma cells

↑= Increased; ↓=Decreased; OA= Osteoarthritis; KOA: Knee Osteoarthritis; HIF-1α=HypoxiaInducible Factor 1α; IL-6= Interleukin- 6; SAON=Steroid-associated osteonecrosis; JSN=Joint Space Narrowing; BMI= Body Mass Index. IL-1B=Interleukin-1ß; SFG=Synovial Fluid Ghrelin; SST: Somatostatin.

aggrecan, and collagen 2 (67-70). A study by Zou *et al* indicated that level of ghrelin in synovial fluid were negatively correlated with disease severity in knee OA patients (67).

Leptin is produced in significant amounts by different parts of the stomach and acts centrally to suppress appetite and increase energy consumption (71). Receptors of this peptide hormone have been identified in human cartilage, synovium, subpatellar fat pad and osteophytes (72). It seems that, in appropriate concentrations, leptin contributes to optimal homeostasis in the joint (73). Figenschau *et al*, showed that leptin-stimulated chondrocytes increase the synthesis and proliferation of ECM (proteoglycans and collagen). Their study suggested that chondrocytes have a leptin receptor (Ob-R) and that leptin may directly affect cartilage production (72). Increasing evidence shows that leptin has a potential role in the pathogenesis of OA. Accordingly, leptin levels in serum and synovial fluid of patients with severe OA are higher than subjects with mild OA and also control groups (73-76). It seems that excessive expression of leptin in the OA knee joint contributes to OA pathogenesis by stimulating the synthesis of growth factors. Physiologically, leptin may have a beneficial anti-inflammatory effect on cartilage synthesis by enhancing the anabolic activity of cartilage cells, but high concentrations can contribute to the inflammatory process of OA by reducing ECM synthesis and increasing MMP production (77). On the other hand, obesity, female gender, and reduction of cartilage volume in OA are strongly related to leptin (76,78,79). A study by Kontunen *et al* also reported that subjects with MetS have higher leptin levels compared with non-MetS subjects (80). Additionally, Ghadge and Khaire recently suggested that leptin acts as a key signaling molecule of metabolic status and is a predictor marker of MetS (81). Based on growing evidence, OA is a systemic disorder and lipid metabolism disorder is a risk factor for development of OA (82).

Gastrin is mainly secreted by G cells in the antrum of the stomach with the key role of maintaining stem cells of the stomach (83). Gastrin can increase the intestinal absorption of calcium in long bones by 30% *via* stimulating the secretion of gastric acid and regulating the homeostasis of gastric epithelial cells in physiological conditions. Moreover, gastrin can inhibit adipogenesis and inflammation pathways (84). Some of these effects are the results of changes in the expression of ECM proteins, which are responsible for regulating tissue regeneration, such as MMP, TIMMP (85). *In vivo* evidence suggests a prominent role for gastrin in the prevention and treatment of steroid-related osteonecrosis. Mechanisms include decreasing inflammation, adipogenesis, and cell apoptosis *via* reducing the expression of Hypoxia-Inducible Factor-1α (HIF-1α) (84). HIF-1α contributes to cell apoptosis and metabolic stress (86). In a study by Luo *et al*, treatment with gastrin reduced the expression of HIF-1α in all groups with osteonecrosis (84). Findings of several studies have demonstrated

that the expression of HIF-1α in the synovial fluid and articular cartilage of patients with primary OA of the knee is related to disease severity (87).

Somatostatin is synthesized by differentiated endocrine cells in the stomach and pancreas, and acts as a broad inhibitor of multiple secretory processes, including secretion of insulin and glucagon from the pancreas; and gastrin, pepsin, and gastric acid from the digestive system (16). Growth hormone (GH) and Insulin-like Growth Factor-1 (IGF-1) play a fundamental role in bone formation via a direct effect on osteocytes and osteoblasts (88). Somatostatin influences cartilage homeostasis via an inhibitory effect on the GH-IGF-1 axis. This hormone can directly modulate cartilage growth (64). In a clinical trial, intra-articular injection of somatostatin led to a significant reduction in pain and significant improvement in joint function without side effects in patients with knee OA (89). Moreover, GIT polypeptides, especially somatostatin, are important regulators of the intestinal barrier. Somatostatin protects the intestinal barrier through anti-inflammatory effects, regulation of protein tight junctions and mucin 2, as well as regulation of fluid and electrolyte transfer from the intestinal wall. A significant relationship between intestinal barrier damage and gastrointestinal and extra-gastrointestinal diseases, including OA, has been demonstrated (39). The findings of a study by Shao *et al* also demonstrated that the decrease in the expression of somatostatin following sensory denervation caused by capsaicin increases tibial subchondral bone loss, aggravates cartilage degeneration in mice, and ultimately accelerates the progression of OA, despite the fact that capsaicin is often clinically used to relieve osteoarthritis pain (90).

OA and Gastric Microbiota (Gas. M)

Due to the production of acid, the stomach was traditionally thought to be a sterile organ. Discovery of *Helicobacter pylori* (*H. pylori*) changed this understanding (91). The pH gradient of the stomach from the lumen (pH=1-2) to the mucosal surface (pH=6-7) creates different environments for the growth of microorganisms. Specifically, the mucosal surface of the stomach is more receptive to microorganisms (50). In 2006, a diverse microbial community of 128 phylotypes was identified in human gastric mucosa, and most of the sequences were assigned to Proteobacteria, Bacteroidetes, Actinobacteria, Fusobacteria and Firmicutes phyla (92). It seems that Gas. M has an important role in human health and disease that needs conducting more studies (30,93). Diet can change the entire structure of GaS. M, as well as the composition of the microbiota in the lower digestive tract (91,94). The interaction between microbiota and HFD is one of the axes of the relationship between the stomach and osteoarthritis (95). Recent studies revealed that there is a significant increase in circulating endotoxin levels, obesity and DM2 with HFD (30). Various mechanisms have been proposed for the role of the stomach in HFD-induced OA. HFD is associated with a significant reduction in *Akkermansia muciniphila* (has beneficial effects on host metabolism) and an increase in endotoxin-producing pathogenic bacteria (including Enterobacteriaceae and Desulfovibrionaceae families) in the stomach (96). The disruption in gastric mucosa and low-grade chronic inflammation lead to metabolic endotoxemia. These processes result in the production of enzymes responsible for joint destruction and thereby, increase the risk of OA (30,97,98).

Moreover, HFD causes Gas.M dysbiosis by increasing the secretion of leptin in the stomach and expression of leptin receptors, which subsequently leads to large intestine dysbiosis and its subsequent consequences (99). He *et al* demonstrated that dysbiosis of the stomach microbiota occurred after 12 weeks of HFD, while no significant changes were observed in the intestinal microbiota after 12 weeks. In addition, a significant decrease in the effect of beneficial bacteria on host metabolism, especially *Akkermansia muciniphila*, was observed after 12 weeks of HFD in the stomach and after 24 weeks of HFD in the intestine, which indicates that the dysbiosis caused by HFD in the stomach microbiota occurs before the intestines. In this study, insulin resistance and serum lipid levels were higher with a 24-week HFD compared with a 12-week HFD, which indicates a worsening of metabolic disorders with continued HFD (96). In the study by Arita and Inagaki-Ohara, the microbial diversity of the stomach did not change until 12 weeks of HFD, but it decreased sharply at

20 weeks (99). In particular, a clear increase in the proportion of *Lactobacillus reuteri* was observed in the stomach, while *Bifidobacterium pseudolongum* disappeared completely. This study showed that the stomach is more sensitive to short-term HFD feeding than the intestines (99). Moreover, the increase in the ratio of Firmicutes/Bacteroidetes in the stomach of mice with nutritional interventions is also reminiscent of the dysbiosis caused by obesity (100), which is accompanied by activation of biologically active metabolites such as SCFAs. Increasing levels of SCFAs provide a link between obesity, metabolic syndrome and OA (101).

The role of two gastric microbes, namely, *H. pylori* and *Propionibacterium acnes* (*P. acnes*) that have been found to be associated with OA are discussed in the following sections.

H. pylori

Some proteins derived from *H. pylori*, including Y-glutamyl transpeptidase (GGT), can play a therapeutic role in OA by reducing the levels of pro-inflammatory cytokines (102). In the presence of *H. pylori* Gas. M is less diverse and the dominant phyla in the stomach microbial community include Firmicutes (45.3%), Bacteroidetes (24.3%), Proteobacteria (9.9%), and Actinobacteria (5.0%) (103). Members of the Proteobacteria group, especially Betaproteobacteria, are markers of diet-induced obesity in mice and obesity in humans, both of which are strongly associated with OA (104). In a study by Hsu *et al*, eradication of *H. pylori* led to Gut. M dysbiosis with an increase in the relative frequency of proteobacteria (103). This is while some experimental evidences report a predominance of proteobacteria in the cartilage of patients suffering from OA (105). It seems that *H. pylori* has the potential to become pathological in certain conditions and plays a role in the development of OA by several mechanisms (93,106), which include 1) changes in Gas. M *via* neutralizing the acidic environment of the stomach (107), and evoking immunological responses (50,108); 2) increase in basal and stimulated secretion of gastrin and decrease in somatostatin secretion, which lead to disturbance in insulin homeostasis (98,109); 3) chronic systemic inflammation and aggravation of IR (Table 2) (98,99).

P. acnes

Cutibacterium (Propionibacterium) strains, mainly *P. acnes*, have recently been recognized as a member of the gastric mucosal microbiota (94). *P. acnes* are usually considered as pathogenic organisms, although the limited enzymatic activity of some strains isolated from the stomach of healthy adults demonstrates that some *P. acnes* species may be normal and harmless residents of the stomach environment (110). Studies by Brobeil *et al* and Hudek *et al* suggested the intracellular presence of *P. acnes* in the shoulder joint of healthy people as a normal commensal (111,112), and Pauzenberger *et al* considered it a contamination during arthroplasty (113). Although the exact role of this type of bacteria in the stomach ecosystem requires more research, it is hypothesized that it can play a role in the health and well-being of the host through immunomodulatory activities. Therefore, the study suggested that *P. acnes* be used as a probiotic to fight against harmful bacteria such as *H. pylori* (110). Some studies indicated the common presence of *P. acnes* in the shoulder joint as the initiator and promoter of arthritis (114). Trimble *et al* demonstrated that intra-articular injection of *P. acnes* in mice led to erosive arthritis (115). In a study by Levy *et al*, a possible role for *P. acnes* in the pathogenesis of osteoarthritis was suggested (116). The exact determination of the role of *P. acnes* in creating the inflammatory process related to the pathogenesis of osteoarthritis and its relationship with the stomach requires more studies.

Conclusion

The heavy burdens of OA necessitate the development of new preventive and therapeutic measures. This study presented an overview of the causal and relational links between the stomach and OA based on the organ contribution law in Avicenna' theory which is similar to the physiological pathway named Gut-Joint axis in contemporary studies. The stomach balances the metabolism of the entire digestive system and other organs, including the joints, The majority of available data indicates metabolic interactions between the stomach and the joint, which are potential therapeutic and preventive targets for OA. Thus, it seems to be beneficial to search more about the etiologic factors of arthritis (osteoarthritis) proposed by Avicenna (Table 1) in Future studies to fully elucidate the distinct role

of the stomach in OA and put new horizons in front of the eyes of researchers.

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Conflict of Interest

All the authors declared that they have no conflicts of interest.

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