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The Role of the Metabolic Acidosis in the Development of Chronic Pancreatitis

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ABSTRACT

Three main, interrelated reasons for widespread digestive disorders in the modern world might be a low exocrine pancreatic function, chronic metabolic acidosis, and intestinal dysbiosis. Chronic metabolic acidosis generally distresses two alkaline digestive glands: the liver, and pancreas, which secrete alkaline bile and pancreatic juice with a great amount of bicarbonate. The acidic shift in the pH of bile and pancreatic juice can lead to serious biochemical/biomechanical problems. The pancreatic digestive enzymes require an alkaline milieu function properly; therefore, low pH disables their activity. This may be the critical cause of indigestion. Reduction, the pH of the pancreatic juice, can initiate the premature activation of the proteolytic enzymes within the pancreas, potentially leading to pancreatitis. Acidification of the pancreatic juice diminishes its antimicrobial activity, promoting intestinal dysbiosis and makes pancreas vulnerable to infection. The acidification of bile generates bile stone formation and leads to precipitation of the aggressive bile acids, which irritate the entire biliary system. An aggressive combination of the acidic bile and the pancreatic juice can create irregular spasms of the duodenum's walls and consequent bile reflux into the stomach and the esophagus. The metabolic acidosis forces organism to withdraw calcium from bones to neutralize acidic shift in the blood. It can create calcinosis of the inner organs including pancreas.

The normal exocrine pancreatic function is the core of proper digestion. Currently, there is no efficient and safe treatment for enhancing exocrine pancreatic function. Reinstating normal acid-base homeostasis can be a pathophysiological therapeutic approach for various gastrointestinal disorders. Chronic metabolic acidosis could be a culprit for early stages of chronic pancreatitis and a range of functional gastrointestinal disorders.

INTRODUCTION

The interrelated combination of chronic metabolic acidosis, low exocrine pancreatic function, and intestinal dysbiosis can explain the widespread digestive disorders in the modern world. Altogether, these causes create a vicious circle [1]. There is not enough time for genetics to be implicated in these disorders; therefore, many scientists and doctors pay attention to environmental factors, such as food, water, stress, lifestyles, toxic chemicals, alcohol consumption, and the inner ecology.

The acid-base balance, or the acidity/alkalinity balance, is a critical factor in the health and functioning of the body. Optimal health depends on the body's ability to maintain a slightly alkaline state.

PATHOPHYSIOLOGY OF METABOLIC ACIDOSIS

Normally, blood is slightly alkaline, with a pH range of 7.35 to 7.45. The constancy of the blood pH is crucial to the body's ability to maintain a relatively stable internal environment. Its importance is revealed by the fact that a human being cannot exist if the blood's pH goes below 7.0 or above 8.0. For instance, blood with a pH of 6.95, which is only slightly acidic, can lead to coma and death.

Many body functions are designed to control the acid-base balance, including respiration, digestion, circulation, excretion, and cellular metabolism. The acid-alkaline regulation systems are interrelated and work together to prevent acute or chronic changes in the body's acid-base balance.

What causes the body to be over acidic? The main persistent factors are:

- The creation of too many acidic materials by human cells. For instance, the end products of cellular metabolism are amino acids, fatty acids, carbonic, and lactic acids.

- Intestinal dysbiosis (candidiasis and SIBO-small intestine bacterial overgrowth) causes an intensive, constant, fermentation process through the release of lactic acid, toxic alcohols, and other acidic compounds.

- Diet-induced chronic metabolic acidosis caused by the consumption of processed foods, red meat, sugars, white flour and rice, and others.

- Chronic toxicity caused by acid-forming compounds, such as alcohol, some medications, environmental chemicals, and others.

- Dysfunction of the lungs, kidneys, skin, liver and gastrointestinal organs, which are responsible for releasing acidic radicals.
- Dehydration and poor microcirculation.
- Chronic deficiency of the major electrolytes such as sodium, magnesium, potassium, and calcium.
- Low capacity of blood buffer systems, and, specifically, the low capacity of bicarbonate buffer.

The CO_2-bicarbonate buffer system (or the "bicarbonate buffer") is the main buffer system in the blood. It works as lung ↕ $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ ↕ kidney.

The pH of blood is steady, and human being struggles to maintain stable state to protect the vital organs, such as the brain, lungs, and heart, which completely stop if the pH in the blood drops even slightly. During metabolic acidosis, human beings make the intelligent choice to survive by saving the life important organs, such as the heart, lungs, and brain at the expense of peripheral "less essential" organs and tissues. The alkaline digestive glands pancreas and liver are affected most by changes in the blood pH because they manufacture pancreatic juice and bile, which are generally highly alkaline solutions.

NEGATIVE EFFECT OF METABOLIC ACIDOSIS ON PANCREATIC JUICE, BILE AND THE ENTIRE DIGESTIVE SYSTEM

Under normal conditions, the pH of liver bile is 7.5- 8.8, and the pancreatic juice has a pH of 7.1- 8.2 [2]. Consequently, the liver, gallbladder, and pancreas, are the inner organs, directly involved in the body's acid-base balance. On the other hand, metabolic acidosis alters the bile and pancreatic pH in an unhealthy way, leading to serious digestion problems.

The Importance of the Bicarbonate Ion- HCO^-_3 (Hydrogencarbonate Ion)

To maintain the alkalinity of the pancreatic juice, the bile, the liver, and, particularly, the pancreas are extracted, bicarbonates and minerals from the blood. The bicarbonate content is a key reason for the alkalinity of bile and pancreatic juice.

Table 1: Content of Bicarbonate (mEq/Liter) in human plasma, pancreatic juice and bile [3,4].

Body's Fluid	Bicarbonate
Blood (plasma)	27
Pancreatic Juice	92 -145
Bile	45

As seen in bile, and particularly in pancreatic juice, there is a lot of bicarbonate. The pancreatic bicarbonate output and duodenum pH are strongly interrelated. The interaction of digestive hormones, primarily secretin and cholecystokinin, with the autonomic nervous system regulates this very complicated mechanism [5-7].

Ductal HCO^-_3 -secretion is not only regulated by gastrointestinal hormones and cholinergic nerves but is also influenced by luminal factors: intraductal pressure, Ca^{2+} concentration, pathological activation of protease and bile reflux [4].

The researchers found that pancreas and liver extract bicarbonate ions mostly from the blood. For instance, intravenously administered bicarbonate labeled with the ^{11}C radioisotope appears rapidly in the pancreatic juice. Experiments showed "most if not all the bicarbonate of pancreatic juice must come from plasma" [5,8,9]. There is substantial evidence that in pancreatic disorders there is a decreased amount of bicarbonate in the pancreatic juice and bile [6,10,11].

Duodenal acidity primarily depends on a lesser amount of bicarbonate in the pancreatic juice and bile. In chronic pancreatitis patients with exocrine pancreatic insufficiency, the duodenal pH is persistently low [6,12].

Table 2: The Optimal pH for the Activity of Pancreatic Digestive Enzymes [13,14].

Pancreatic Digestive Enzymes	Enzyme Optimal pH
Lipase	**8.0**
Trypsin	**7.8 - 8.7**
Amylase	**6.7 - 7.0**

The pancreatic enzymes work only in the alkaline milieu. Therefore, the acidic milieu in the duodenum where general digestion occurs is a central factor of indigestion. There is also a direct connection between the bicarbonate concentration and pancreatic juice flow and the elimination of enzymes [15,16].

Stephen A. McClave, MD, believed that while healthy people have a high bicarbonate concentration in the duodenum, patients with chronic pancreatitis have low bicarbonate concentrations. In this case, the acidic fluid in the duodenum inactivates enzymes. Pancreatic lipase stops working if the duodenal pH is < 4.5 [7].

Talamini (2005) adds a new, possible risk factor for pancreatic cancer after chronic pancreatitis, namely, duodenal acidity. Patients with chronic pancreatitis frequently present with pancreatic exocrine insufficiency combined with a persistently low duodenal pH in the postprandial period. Duodenal acidity may raise the risk of pancreatic cancer in patients with chronic pancreatitis [12].

The relationship between the rate of low pancreatic HCO^-_3 secretion and high plasma H^+-ion concentration has been investigated in numerous experiments. A proportional relationship was found between HCO^-_3 secretion and plasma pH. Different relationships were discovered between pancreatic HCO^-_3 secretion and plasma HCO^-_3 concentration during metabolic acidosis. Pancreatic HCO^-_3 secretion fell to 41 ± 4% of that of the control during acidosis. The plasma H^+-ion concentration, therefore, seems to determine the rate of pancreatic HCO^-_3 secretion [17].

The importance of plasma bicarbonate is also illustrated by in vivo experiments in which

pancreatic secretion was studied under conditions of metabolic acidosis. Canine pancreatic secretion was halved when the plasma bicarbonate was lowered to 16 mEq/L [18].

Trypsinogen Activity and pH

Acidity also promotes the premature activation of trypsinogen (inactive enzyme) to trypsin (active enzyme) in the pancreatic ducts. Trypsinogen, like all other zymogens, is packaged in zymogen granules, which further retard trypsinogen activation. The high pH (an alkaline state) in the duct inhibits activation of trypsin [19,20]. The more alkaline the pancreatic juice, the higher the possibility of keeping trypsin inactive within the pancreas. Even a neutral pH of 7.0 can lead to this activation pathway [21].

Niederau C and Grendellin JH (1988) suggested that the acidification of the pancreatic juice may play a role in the progression of acute pancreatitis [22]. Bhoomagoud M et al. (2009) also suggested that metabolic acidosis may be a risk factor for developing pancreatitis. They confirmed experimentally in vivo and in vitro that decreasing pH (acidifying) increases the sensitivity of the acinar cells to zymogen activation [23].

Both experimental and clinical observations suggest that acidosis may increase the risk of developing acute pancreatitis. Peter Hegyi et al. (2011, 2013) further demonstrate that the failure of pancreatic ductal bicarbonate secretion (i.e., a decrease of the luminal pH) can increase the risk of or lead to pancreatitis [11,24].

Magnesium is an alkalized mineral. Thus, it can attenuate the intracellular activation of proteases in the pancreas and can lessen the severity of experimental pancreatitis when administered either intravenously or as a food supplement. A multicenter randomized controlled trial of magnesium sulfate in the prevention of post-ERCP pancreatitis (2013) shows the benefits of magnesium [25].

Flushing Inactive Pancreatic Enzymes Stops Their Premature Activation

Another protective mechanism to prevent the premature activation of trypsinogen to trypsin inside the pancreatic duct is rapidly sweeping out zymogens from the pancreas. Washing out and draining pancreatic juice that is full of inactive enzymes and zymogens (trypsinogen) to the duodenum as quickly as possible is an essential mechanism to prevent premature activation of digestive enzymes inside the pancreas. This flushing mechanism is significant in protecting the pancreas from premature activation of the proteases and self-digestion and thus from the development of recurrent acute and chronic pancreatitis.

The duct cells lining the pancreatic duct secrete ions, fluid, and bicarbonate. A high concentration of ions causes water to enter the lumen by osmosis. Afterward, water flushes the contents of the pancreatic duct lumen (including zymogens) out of the pancreas and into the intestine. On the other hand, a low bicarbonate output can reduce the amount of water within the pancreatic ducts. This, in turn, raises the viscosity of the pancreatic juice and slows its elimination.

Matsuno S, Sasaki Y et al. (1991) mentioned that bicarbonate plays a critical role in the viscosity of pancreatic juice. In patients with pancreatitis in which bicarbonate secretion and bicarbonate output are declined, the viscosity of the pancreatic juice was considerably increased. They also believed that concentrated pancreatic juice could cause the progression of chronic pancreatitis [6].

Bicarbonate is a central ingredient in maintaining appropriate viscosity and correct function of mucin molecules, which play a significant role in mucosal immunity and the epithelial defense system [26].

Acidification of Bile and Bile Refluxes

Bile secretion has similar regulatory and closed pathways for pancreatic juice. If the bile becomes extra acidic, it turns out to be very "aggressive". Precipitated bile acids in acidic bile corrode and irritate the bile and pancreatic ducts, the gallbladder, the Ampulla of Vater, the Sphincter of Oddi, and the duodenum.

Irritations of the duodenum's mucosa by precipitated bile acids lead to erosion, ulcers, and spasmodic, chaotic contractions, which dislocate the aggressive bile/pancreatic juice mixture. This causes spasms, bile reflux, refractory heartburn, irritation, inflammation, ulcers, and other symptoms. In a review of the refractory gastroesophageal reflux disease literature, Ronnie Fass, MD (2015) mentioned that experimental data supports a role for persistent bile acids in the reflux as a potential factor involved in refractory heartburn [27].

Aggressive, acidic bile/pancreatic juice mixtures often cause bile reflux, or backflow, into the pancreatic duct. Bile from the duodenum can flow upward, into the stomach and esophagus. Bile refluxes, which involve the duodenum, stomach, and esophagus, lead to inflammation, ulcers, and cancer [28]. Bile reflux often occurs along with stomach acid reflux, and together, they are a horrible pair, inflaming the lining of the esophagus and potentially increasing the risk of esophageal cancer [29,30].

Biliary pancreatic reflux occurs when the bile returns to the pancreatic duct. It activates proteolytic enzymes within the pancreas, and initiates acute pancreatitis and/or exacerbates chronic pancreatitis.

Rege RV and Moore EW (1986) found that the acidification of bile is a major factor in the development of gallbladder stones, which have been documented to block the bile and pancreatic ducts and cause severe damage to the liver and pancreas [31].

The Antimicrobial Activity of Pancreatic Juice is pH Dependent

When the pH of pancreatic juice falls below 7.0, the antimicrobial activity is reduced. Rubinstein E et al. (1985) found that the antibacterial activity of pancreatic juice was pH dependent [32]. Experiments on people with pancreatic fistulas showed that, under healthy conditions, pancreatic juice is practically sterile and destroys almost the entire spectrum of microorganisms.

There are remarkably few microorganisms in the small intestine because intestinal microbial homeostasis is controlled by a variety of factors. Pancreatic juice plays an essential role in limiting the number of microbes in the small intestine. There is evidence that the antibacterial action of pancreatic juice is extremely sensitive to pH, having an optimal activity at a pH of 8.5, which is an alkaline condition, and a complete cessation of activity at a pH of 7.0, which is neutral [33,34].

Acidification of the pancreatic juice and decreasing pancreatic secretion makes the pancreas more vulnerable to infection. Furthermore, the data demonstrate that the pure pancreatic juice of chronic pancreatitis patients has a markedly flawed antibacterial activity. This finding might explain the pathophysiology of this disease [35]. For that reason, the restoration of the alkalinity in the pancreatic glands is fundamental for the treatment and prevention of pancreatitis and further pancreatic cancer [36].

Calcification

If chromic metabolic acidosis occurs, calcium is leeched from the bones into the blood to neutralize acidity. The amount of calcium ions in the blood and body fluids increases, leading to the deposition of calcium in blood vessels and internal organs (calcinosis). This may explain the widespread simultaneous appearance of osteoporosis, arteriosclerosis, and calcification as calcium deposits in the inner organs. Calcification of the pancreatic gland is an important symptom of chronic pancreatitis [37].

Precipitation of calcium salts within the pancreatic duct leads to stones, which irritate or block the pancreatic duct, causing inflammation or pancreatitis. Precipitation of calcium salts inside the gallbladder induces stone manufacturing and the obstruction of the Sphincter of Oddi. This, in turn, can increase the pressure inside the pancreatic duct and activate proteases within the pancreas, causing self-digestion, damage, and pancreatitis.

DISCUSSION: CLINICAL IMPLICATIONS

The authors believe that chronic metabolic acidosis destroys the pancreas and the entire digestion process. Questions may arise from this hypothesis.

Is chronic metabolic acidosis a widespread condition in the modern human?

Does chronic metabolic acidosis have clinical significance in everyday practice?

The authors believe that subclinical, low-grade, chronic metabolic acidosis is a widespread condition that is considered to be a “disease of civilization”. Focusing on the acid-base equilibrium may be key in preventing and treating either digestive or hormonal pancreatic disorders [1].

Acidemia is the hidden menace that strikes most of the world’s population as a price for urbanization and a western lifestyle. If we consider the predominance of the acid-forming, processed foods, the consumption of alcohol and acidosis-producing medications, it can be

presumed that the prevalence of low-grade, chronic metabolic acidosis can occur in epidemic proportions [38].

Chronic metabolic acidosis is dangerous for humanity. It involves most of the global population and might cause epidemic proportions of metabolic syndrome, diabetes, osteoporosis, kidney and gallbladder stones, cardiovascular diseases, digestive disorders, cancer, intestinal dysbiosis, and many other metabolic and degenerative diseases, which have increased over the past 50 years [1,39].

It is understandably difficult to think of "metabolic acidosis" when the standard lab tests for the acid-base balance are in the range traditionally considered normal [39,40]. Ordinary tests cannot reveal the shift to acidity because humans have an enormous buffer capacity. Mild chronic metabolic acidosis can occur despite normal blood pH and bicarbonate levels [4]. In cases of metabolic acidosis, humans try to eliminate H^+ ions in body fluids. Repeated measurements of the saliva and urine pH can indirectly estimate the acid-base status. The saliva and urine pH, which are constant, lower than 6.6 can be a sign of chronic metabolic acidosis. The degree of metabolic acidosis is mild as judged by the degree of the blood acid-base imbalance, but it cannot be considered mild as judged by its negative physiological effects [39,41].

There are many reasons for chronic metabolic acidosis. Three can have major implications for the health of the current world population. They are also the predominant causes of acute and chronic pancreatitis.

- Modern food
- Alcohol consumption
- Overusing of acidosis-formed medications

Modern Food and Metabolic Acidosis

It is recognized that humans had to function at their highest physical and mental performance to survive for thousands of years. Weaker individuals or groups of people had greater chances of being eaten by predators, taken over by aggressors, succumbing to diseases and being annihilated by natural disasters. Theories are surrounding the "survival of the fittest" dictate that those who are fit well for their environment will survive. The pancreatic and liver functions and the entire digestive system of our ancestors worked perfectly well for millennia fitted for the hunter/fisher/gatherer natural diet. This diet promoted slightly an alkaline state in the human body [42-44].

The human digestive system cannot absolutely adapt to modern, chemically modified, artificial and often toxic products, which are staples of the current western diet. People cannot properly digest the foods that they are usually eating. Alkali-rich fruits and vegetables have been replaced by net acid-producing animal foods, sugars and cereal grains. One of the most prevalent and preventable results is low-grade chronic metabolic acidosis, which when left untreated poses a substantial threat to human health.

The role of nutrition in human acid-base homeostasis has received growing attention in recent years. The Second International Acid-Base Symposium, Nutrition–Health–Disease was held in Munich, Germany, September 8–9, 2006. International researchers, doctors, and scientists provided deeper understanding and updates in the scientific research of the relation between diet, acid-base homeostasis, physiology, and pathophysiological consequences. They said: "Although in healthy humans, homeostatic mechanisms and the kidneys' capacity to excrete acid equivalents can prevent strong diet-induced alterations in blood pH, even moderate increases in blood hydrogen ion levels as a result of unfavorable diet composition can have long-term consequences for the occurrence and progression of a number of diseases" [38].

Many nutrition scientists estimate the net systemic acid load supplied by the diet [net endogenous acid production (NEAP)]. The NEAP for 159 replicated pre-agricultural diets was minus 88 ± 82 mEq/d; these were net base-producing. The NEAP for the standard American diet (as recorded in the third National Health and Nutrition Examination Survey) was plus 48 mEq/d; these were net acid-producing [42].

It is clear that food is a primary cause of chronic acidity in the body. It has potential medical significance because almost all the genes and epigenetic regulatory systems humans carry today were originally selected for behaviorally modern people who appeared in Africa between 100,000 and 50,000 years ago [43].

According to Sebastian, A. and Fressetto, L. et al. (2002), "The historical shift from negative to positive NEAP was accounted for by the displacement of high-bicarbonate-yielding plant foods in the ancestral diet by cereal grains and energy-dense, nutrient-poor foods in the contemporary diet—neither of which is net base-producing" [42].

Metabolic acidosis is rampant in modern society. Mostly, this is due to the standard Western diet. [45,46]. Most of what we eat now is acidic in nature and, consequently, changes the acid-base balance toward metabolic acidosis [47]. Nutrition scientists have described the incidence of metabolic acidosis in modern man [40,45,46].

For instance, researchers from the University of California (2002) found that most health problems stem from the deficiency of bicarbonate in today's food compared to the food of our ancestors [46]. Other authors have proven that current eating habits have produced low-grade metabolic acidosis in otherwise healthy people [40,42,45,46]. Some authors found that metabolic acidosis increases with age [48,49].

Alcohol Consumption and Chronic Metabolic Acidosis

Alcohol causes inflammation to the stomach, liver, pancreas, and intestines, which impairs the digestion and assimilation of food. In addition to the direct toxic effect on the liver and pancreatic cells, alcohol is a strong acid productive agent that causes chronic metabolic acidosis and the

deterioration of the exocrine pancreatic function. Many studies show that in Western countries, alcohol is the most frequent associated factor with chronic pancreatitis (50-80% of cases) [1].

In the U.S., 10 to 20% of men and 5 to 10% of women sometime in their lives will meet the criteria for alcoholism, depending on the criteria used. These rates are similar to the rates for many countries in Western Europe [50].

Ethanol is metabolized by two pathways: the oxidative and non-oxidative pathway. Acetaldehyde and reactive oxygen species (ROS) are the main byproducts of the oxidative metabolic pathway. The non-oxidative metabolism of ethanol is characterized by its esterification with the production of fatty acid ethyl esters. All three byproducts of ethanol metabolism are believed to be acid-forming substances [51].

Medications and Metabolic Acidosis

There is no extensive research about chronic metabolic acidosis and prolonged consumption of the pharmaceutical drugs [52]. Clinical studies point to acute clear-cut cases of metabolic acidosis that is confirmed by laboratory data in the hospitals. It could be assumed that this is the only tip of the iceberg.

Several facts indicate that various over-the-counter and prescription medications can create metabolic acidosis [53].

In the article "Pharmacologically-Induced Metabolic Acidosis", Liamis, G et al. (2010) wrote a review of possible mechanism and medications that cause metabolic acidosis [54]. The acid-forming actions of common medications via metabolic acidosis can negatively affect the digestive organs and digestion. This is a large area for experimental and clinical studies.

Currently, over-acidity is frequent and can create harmful conditions that weaken all body systems. Chronic metabolic acidosis drives humans to leech alkaline minerals, including calcium, sodium, potassium, and magnesium, from inner organs, muscles, and bones to neutralize the acidity and to remove acid radicals from the body. The human being has only one way to recover from metabolic acidosis - to obtain extra minerals and bicarbonate to neutralize over-acidity. Where can the organism obtain these minerals and bicarbonate? Naturally, people can only obtain minerals and bicarbonate from food, healing mineral water and mineral supplements, such as magnesium/potassium.

If laypeople and medical practitioners in the United States know about alkaline diet and mineral supplementation, drinking healing mineral waters may sound strange. Let us look at the experience of European medical doctors, who have treated a variety of digestive disorders with healing mineral waters for hundreds of years. The European public often spends their "healthy vacations" in mineral spas, where medical doctor evaluate the patient and prescribe the quantity, frequency, and temperature of healing mineral waters. In some European countries, insurance covers balneotherapy-mineral water cures.

The small town of Karlovy Vary in the Czech Republic has enjoyed hundreds of years of popularity as a famous healing mineral spa thanks to its thermal springs. In 1522, the first scientific, medical book was published, and a regimen of drinking water from this spring was recommended for constipation. Since then, hundreds of clinical papers have been published describing the positive effects of this water on both animals and humans. Unfortunately, most of these papers are published in Czech, German and Russian; thus, they are unknown by the American medical establishment [55-57].

The demand for this water was so high that doctors in Karlovy Vary developed a vaporizing method to obtain genuine Karlovy Vary thermal spring salt 250 years ago. Dissolving this salt in the water makes it possible to use mineral water for healing at home. The water prepared from the genuine Karlovy Vary thermal spring salt has 40 essential minerals, trace elements, and bicarbonate in a proportion similar to that of human plasma. Czech doctors determined that the water manufactured from the genuine Karlovy Vary thermal spring salt had identical healing properties to the spring. European scientists and doctors have confirmed the positive effects of the Karlovy Vary healing mineral water on the pancreas and pancreatic digestive enzymes [1].

Karlovy Vary healing mineral water is a natural alkalizing compound that helps the body to restore a normal pH by neutralizing acid radicals and removing them from the body. Before the insulin era, this water was the only healing remedy for diabetes. Karlovy Vary healing mineral water helped many Europeans with environmental and professional toxicity. Scientific research shows that this water decreases gas, bloating, stomach pain, abdominal spasms, and indigestion by increasing the production of bile and pancreatic enzymes and by opening the bile and pancreatic ducts, thereby decreasing internal toxicity [55-57].

There are many complicated tests to identify over-acidity in the body. More simply, one can observe positive pH changes in his/her saliva and urine by using litmus paper at home. If the saliva and urine pH is less than 6.6 for one week, chronic metabolic acidosis and acidic pancreas and bile may be presumed.

The Prevalence of Chronic Pancreatitis may be much Higher Than Previously Estimated

If chronic metabolic acidosis destroys the pancreas, it supposes epidemic proportion of chronic pancreatitis. Considerable scientific research and practical evidence support this idea.

Ake Andren-Sandberg, Philip D Hardt (2005) in the review of the Second Giessen International Workshop on Interactions of Exocrine and Endocrine. Pancreatic Diseases gave some facts about the prevalence of chronic pancreatitis. Chronic pancreatitis is much more frequent than previously believed. 5.3% of non-diabetics had chronic pancreatitis, but 11.2% of diabetics had chronic pancreatitis. Pancreatitis or pancreatic fibrosis appear to be frequent in Western societies and might affect more than 10% in population-based studies [58].

In a study of autopsy cases, Olsen et al. [59] found that only 2 cases (0.5%) had been diagnosed with clinical chronic pancreatitis, but 13% actually had chronic pancreatitis. Hardt PD et al. (2008) "The incidence of diabetes caused by exocrine pancreatic disorders appears to be underestimated and may comprise 8% or more of the general diabetic patient population". Some physicians refer to this condition as diabetes type 3 [60].

Diabetes Mellitus secondary to Chronic Pancreatitis could be more common, which would explain the frequent finding of exocrine pancreatic deficiency in diabetics [58,60]. "Early chronic pancreatitis remains a diagnostic challenge as there is no gold standard for the diagnosis, and pancreatic biopsy is risky and impractical. Reported data on the incidence and prevalence of chronic pancreatitis are unreliable and highly variable. Chronic pancreatitis is clearly under – diagnosed" [58].

CONCLUSION

Currently, the medical standpoint on digestive disorders narrowly focuses on the "hollow" organs, such as the stomach and colon, without paying attention to the "solid" digestive glands, such as the pancreas and liver. It is known from human physiology that, without a specific quality and amount of pancreatic juice and bile, the normal digestive process in the hollow chambers could not occur. The pancreas is the main organ of the entire digestive system. Almost all of the problems of the GI tract are closely related to the proper functioning of the pancreas. Therefore, a clinical diagnosis of gastrointestinal disorders de facto presumes pancreatic disorders.

Another very important consideration is chronic pancreatitis. Descriptions of the symptoms of this disease, including pain, steatorrhea, malabsorption syndrome, and weight loss, are found in almost all medical books, textbooks, and articles. The medical literature refers to this state as "pancreatic insufficiency". It is known that these symptoms occur when only 10% of the exocrine pancreatic function is left intact. Unfortunately, this is not "pancreatic insufficiency," but instead is "pancreatic failure," for which therapeutic opportunities are very limited.

The final stage of chronic pancreatitis does not develop overnight. Typically, 8-15 years occur between the first attack of acute pancreatitis and pancreatic failure following chronic pancreatitis. Similar to disorders of other organs and systems, the initial disease stage of the pancreas does not present any structural changes. Nevertheless, after this stage, long-standing biochemical, biomechanical, neurohumoral, and inflammation responses lead to structural damage of the pancreas (chronic pancreatitis) and to a lowering of the exocrine pancreatic function while developing many accompanying digestive diseases. However, if 90% of the pancreatic functional capacity is reduced, pancreatic failure occurs with steatorrhea and malabsorption syndrome, resulting in a total crash of the digestive system and the entire human organism.

For the purpose of focusing on the early functional stages of pancreatic disorders, the authors propose the Functional Clinical Classification of Exocrine Pancreatic Disorders, which subdivides digestive disorders and diseases into three groups:

- Acidic pancreas and bile
- Pancreatic deficiency
- Pancreatic failure

1. On the daily basis of medical practice, crowds of people present with digestive symptoms that are consistent with patients in the acidic pancreas and bile stage of exocrine pancreatic disorders. Their tests are usually normal, and most of these patients receive palliative, symptomatic therapy. Restoration of the proper acid-base balance in digestive disorders may be one of the natural, pathophysiological approaches for functional dyspepsia, biliary dyskinesia, GERD, Sphincter of Oddi Dysfunction type III, IBS, and Intestinal Dysbiosis (Candida-yeast overgrowth, SIBO), among others.

Pancreatic functional disorders are terra incognita in medicine; there is low attention on the functional stage of exocrine pancreatic deficiency regardless of the pancreas being a key organ in proper digestion. H. Worning (1987) wrote in Digestion that the prevalence of pancreatic diseases as the cause of dyspepsia varies in clinical practice between 0 and 25-30%. He believed pancreatic function and pancreatic disease were closely related to various gastrointestinal diseases [41].

The connection between functional gastrointestinal disorders such as functional dyspepsia, SIBO-small intestinal bacteria overgrowth, IBS and impaired pancreatic function to a greater extent have attracted the attention of researchers and doctors for the last decade [61-63].

Goepp J et al. (2014) found low pancreatic elastase (a marker of exocrine pancreatic insufficiency) in 7.1% of the patients with irritable bowel syndrome [64]. Another point that low pancreatic function underlies dyspepsia and IBS is the beneficial effect of the pancreatic enzymes in these functional disorders [65,66].

Smith et al. (1991) described abnormal Lundh tests in 27% of patients with functional dyspepsia. They wrote, “Pancreatic disease may explain the symptoms of some patients with non-ulcer dyspepsia” [67].

It is known that dyspepsia and functional dyspepsia are common conditions globally, affecting most populations, regardless of location” [68]. Okada R et al. (2009) considered that mild functional pancreatic disorders might trigger some cases with unexplainable chronic dyspepsia [69].

Eva Lindström et al. (1990) believed that overall, 66% of the patients with abdominal pain had morphological and functional evidence of pancreatic involving [70].

Some researchers agree that differentiation between functional dyspepsia and early stage of the chronic pancreatitis is complicated [71]. Beginning of chronic pancreatitis and impaired exocrine pancreatic function are frequently misdiagnosed.

The diagnosis of the early stage of the pancreatic diseases might be missed in clinical practice because symptoms of severe exocrine pancreatic deficiency are not specific at that time. There were no malabsorption syndrome, maldigestion, and there was the absence of steatorrhea, and the pancreatic and liver enzymes levels in blood were normal. Therefore, early chronic pancreatitis is seldom suspected when pain is mild or absent, and there are unspecific symptoms of "dyspepsia".

Scientific research and clinical findings confirm that the pancreas and liver are more vulnerable to reduced functioning due to metabolic acidosis. One primary (ex juvantibus) therapy for multiple digestive and liver disorders is the mineral spa resort in Karlovy Vary and other resorts in Europe, and a great number of medical papers support the therapeutic action of the mineral/bicarbonate waters for digestive diseases.

2. Possible diseases and conditions associated with pancreatic deficiency: clinical or subclinical episodes of acute pancreatitis, chronic pancreatitis, gastric ulcers, duodenal ulcers, duodenitis, Sphincter of Oddi Dysfunction type II or III, gallbladder disorders (inflammation, stones, sludge, parasites), conditions after gallbladder removal and some surgeries on the upper GI tract, considerable intestinal dysbiosis (Candida-yeast overgrowth, Small Intestine Bacterial Overgrowth), IBD (Crohn's Disease, Ulcerative Colitis), Celiac Diseases, Cystic Fibrosis (early stage), NIDDM- noninsulin-dependent diabetes mellitus, non-alcoholic fatty pancreas, etc.

In almost all these diseases, there is a constant pancreas involvement that results in structural damage and diminished function including different severities of chronic pancreatitis.

3. Possible diseases and conditions associated with pancreatic failure: the final stage of chronic pancreatitis, Cystic Fibrosis, liver cirrhosis, cancer, etc. This final stage is just the tip of the iceberg by comparison with functional and structural pancreatic disorders.

All of the three stages: acidic pancreas and bile, pancreatic deficiency, and pancreatic failure have different diagnostic criteria and therapeutic approaches [1]. Attention to proper acid-base balance may be beneficial in all of the three stages. Nowadays, a pandemic of interrelated metabolic acidosis, low pancreatic function, and intestinal dysbiosis create a vicious circle and aggravate the clinical digestive symptoms picture.

This work is an attempt to present the fresh, holistic approach that the pancreas is a vital organ for the whole body. We feel that our work may provide food for thought to many young researchers and health practitioners.

We cannot have optimal digestion if the body's system is acidic because acidity kills the pancreas!

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