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Acute Pancreatitis and Metabolic Syndrome. Literature Review

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1. SUMMARY

Both the acute pancreatitis and the metabolic syndrome are currently not only of global importance, but indeed their incidence is increasing world-wide; interestingly this development is taking place parallel for both. In addition to this the therapeutic access to both diseases turns out to be difficult due to many things we do not yet know about as to the exact pathophysiological mechanisms. However, important details have been detected about principal mechanisms running their course like the calcium dysregulation with its fatal consequence of destructing the mitochondrial power in acute pancreatitis or the dysregulation largely - but not only - concerning the three main substance classes of carbohydrates, proteins, and lipids, all this happening via abundance of food plus lack of physical exercise in metabolic syndrome. The immensely high costs for the health systems in all countries concerned with acute pancreatitis and the metabolic syndrome as well as the status of inflammation plus the role of the microbiome as important players in both diseases and furthermore the suspicion that metabolic syndrome worsens the severity of the course of the acute pancreatitis suggest the necessity to put effort into their common research. The findings then may serve as a starting point for both further research and therapeutical access.

2. KEYWORDS

Acute pancreatitis, inflammation, hypertriglyceridemia, trypsinogen, calcium, necrosis, monocytes, mitochondria, tissue damage, necrotizing pancreatitis, diabetes, prediabetes, metabolic syndrome, insulin resistance, high blood pressure, hypertriglyceridemia, HDL levels, obesity, hyperglycaemia, lipopolysaccharides.

3. INTRODUCTION

There was a time far back before Christ, when people thought that a surplus of body weight meant health. Hippocrates (460 - 370 B.C.), however, the most famous physician then, considered obese patients to have higher risk of infertility and of dying earlier. (1) In our times obesity is not only called an epidemic, but even a pandemic due to the dramatically rising numbers of obese people over the world. (2,3) Obesity obviously presents a big problem leading to more complicated diseases like the metabolic syndrome, the rates of which have been rising for decades now, too. The metabolic syndrome itself often develops into further diseases that endanger life like for example cardiovascular dysfunctions. (4) Due to certain common features connections with acute pancreatitis have been suspected. In addition to this the numbers of people suffering from acute pancreatitis are also increasing. Thus, research is taking steps to elucidate the linking parts of the metabolic

syndrome and the acute pancreatitis, in order to be able to adequately treat and cure these two diseases, for which matched therapy has not yet been found. (5)

4. LITERATURE SEARCH STRATEGY

The data sources used in this paper were mainly Google Scholar and PubMed, the latter being the most successful one for the literature achieved. To limit the search in a defined way inclusion criteria and exclusion criteria were applied: The inclusion criteria are the following: as both diseases have been rising over the past fifteen years, publications of this period fifteen years have been included: this inclusion contained articles that were reviews, meta-analyses and clinical trials. In addition, specialists´ books on medicine were consulted as to definitions. The report of the World Health Organization about obesity was not freely accessible on PubMed; therefore it was researched in the Munich State library, which is connected with the Munich- Ludwig- Maximilians University library. Two of the studies were provided by the Supervisor Teaching Assoc. Prof. Ieva Stundienė, concretely Mikolasevic et al. and Li et al.

As to the studies used first the abstracts were checked, and when they matched the subject titled, the article was considered apt for the thesis. The language was limited to English concerning the electronic articles and to English and German concerning the specialists´ books on medicine. The terms found were divided up for both realms included in the title and they are the following: Acute pancreatitis, inflammation, hypertriglyceridemia, trypsinogen, calcium, necrosis, monocytes, mitochondria, tissue damage, necrotizing pancreatitis; diabetes, prediabetes, metabolic syndrome, insulin resistance, high blood pressure, hypertriglyceridemia, HDL levels, obesity, hyperglycaemia, lipopolysaccharides.

5. BACKGROUND INFORMATION FOR ACUTE PANKREATITIS

5.1 Definition of acute Pancreatitis

Many factors seem to play a role when it comes to define the disorder called acute pancreatitis. Interestingly the authors doing research of the acute pancreatitis put their individual focus on very different key points when formulating the definition. Thus, here is the attempt of this summarizing paper to take into account the most important features met in literature: hence the acute pancreatitis represents the very state of pancreatic tissue, concretely the exocrine part of the pancreas, being inflamed to a defined, possibly - in most of the cases - self-limiting extent that due to extreme pain plus potential worst complications including vital danger, however, leads to the necessity of immediate inpatient admission. (6,7,8,9,10)

5.2 Physiology of Pancreas

The pancreas - like many other organs of our body - is a dichotomic organ, the pancreas itself bearing exocrine and endocrine function: the exocrine outstanding achievement represents the basic polyfunctions of firstly providing the digestive liquid containing bicarbonate to neutralize the acid stemming from the stomach plus secreting the enzymes ready to contribute their polycapacities for matters of digestion of carbohydrates, proteins, fats and nucleic acids of DNA and RNA. The endocrine part of the pancreas on the other hand contains the islets of Langerhans bearing important hormones for metabolic regulation of carbohydrates, namely glucose and the energy deriving from it. As this endocrinological sight is primarily not in the centre of interest in this part of the paper, it will not be focused on more unless it is necessary.

As to the exocrine function a few details seem of major importance: The pancreas releases several enzymes, with preforms guaranteeing that the impact of the enzymes only takes place in the intestine in order that the pancreas itself does not suffer from the phenomenon of self-digestion. Most essential digestive enzymes are shown in table 1, the most important role of which trypsinogen seems to play. In addition, there is a regulating instance of still higher level which rules the physiologically healthy secretion of pancreatic fluid in general, which is the so-called Protein C kinase and all its isoenzymes involved. (11)

Table 1. Overview over a selection of most important enzymes the pancreas secrets

enzymes for carbohydrates	enzymes for proteins	enzymes for lipids	enzymes for nucleid acids
amylase	trypsinogen	lipase	desoxyribonuclease
	chymotrypsinogen	pancreatic Phospholipase A 2	ribonuclease
	carboxypeptidase		
	elastase		

Pancreatic enzymes: the actual quantity amounts to about 20 enzymes (11,12)

5.3 Etiology of acute pancreatitis

A plethora of reasons is responsible for the development of acute pancreatitis like cholelithiasis, ethanol and hypertriglyceridemia. (6,9) In 2022, Szatmary et al. define cholelithiasis as the leading cause for acute pancreatitis, age and female sex being predisposing factors.

Interestingly alcoholism on its own does not per se predispose people to develop acute pancreatitis, the danger lies more within the combination of alcoholism with defined phenomena like genetics, hypertriglyceridemia and smoking, the latter representing the most effective co-driver of all.

For quite some reasons hypertriglyceridemia enjoys a special status amongst the causes responsible for acute pancreatitis, be it of primary genetic origin be it of secondary nature as an aftermath of other diseases: a 4% increase of acute pancreatitis incidence can be seen with every 100 mg/dl starting from the very specific and excessively high threshold of 1000 mg triglycerides per decilitre. Following up on that, it is of high relevance that if hypertriglyceridemia is the very cause of acute pancreatitis, the course of the disease will be exuberantly more devastating.

The knowledge that certain drugs can evoke acute pancreatitis, which happens in about 5% of the cases of this illness, however, seems of minor importance, as they need co-drivers, too; in addition, it is not possible to define any reliable specific moment in time after intake of a drug, when acute pancreatitis will turn up as a complication of it. Finally, Endoscopic retrograde cholangiopancreatography (ERCP) as a cause for acute pancreatitis is noted still more often than the drugs mentioned above, the quota being about 10%. (6) Generally spoken, external factors like alcohol and drugs, iatrogenic damage by surgical interventions and internal factors like gallstones and bile acids lead to injuries on pancreatic cell level, peripancreatic cell level and – in worse and worst cases – the cell level of even more distant tissues: indeed, the final molecular reactions of rising free acids deriving from the pancreas and from nearby could be the harbingers of death for organs. (7)

5.4 Pathophysiological mechanisms of acute pancreatitis

Looking at the beginning of acute pancreatitis at the helm there are enzymes, immune cells and their chemical messenger contents as well as adhesion molecules and reactive oxygen species. An overview is given by table 3. (7) However, in general, the researchers agree that the exact mechanisms on cell level remain untold especially where starting points are concerned. (8) It is nonetheless important to get an idea about how the reactions in the course of acute pancreatitis take place going off from a starting point via a defined cascade leading to local damages and in the worst case to necrosis and a severe course of this fulminant disease, as any functioning therapy is to be adjusted to the precise happenings on cell level. Overall, it seems of importance whether gallstones or alcohol or hypertriglyceridemia or other rarer causes are responsible for unleashing the processes of acute pancreatitis, because the respective etiologies obviously imply the triggering of special pathological mechanisms. What appears to be clear is the fact that if the first three of the reasons

named above, i.e. gallstones or alcohol or hypertriglyceridemia lead to acute pancreatitis, one can proceed from the assumption that the pathophysiological mechanisms resemble each other despite the different trigger points, so medical treatment might be adapted accordingly by the time. (6) Different theories are discussed in literature, all of which may either play together or may each separately contribute their bit to the whole process of development of acute pancreatitis

5.4.1 Pathophysiological mechanism of the Calcium signalling way

So no matter which precipitant induces the whole process leading to acute pancreatitis, at a certain point calcium channels of the pancreatic cells (the differentiation is to be discussed below still) get permeable; from both physiological calcium pools, the extracellular space and the endoplasmatic reticulum, calcium, now as a toxic agent due to its immense quantity, debouches into the cytosol of the cell, which eventually overstrains the capacity of the mitochondria, whose transmembrane potential is ruined, thus ATP production being made impossible. (6)

5.4.2 Pathophysiological mechanism on cell organelle level

In this context a special eye is kept on the level of organelle dysfunction. i.e. the lysosomes seem to play a decisive role for the development of acute pancreatitis in so far as they are the ones responsible for preterm activation of trypsinogen eventually being cell-death provoking mediators, as they lose their physiological function due to destruction of parts of their contents – enzymes – plus destruction of parts of their membranes. Thus, lysosomes cannot fulfil their physiological function anymore, on the contrary they change into destructive drivers. (13)

5.4.3 Pathophysiological mechanism on cell level

Which cells really react first is still being discussed, research mostly eyes the acinus cells and the ductus cells as to the happenings described above: their polyfunctional capacity of reactions include the production of cytokines, chemokines and adhesion molecules as reactive agents triggering for example local and spreading inflammation processes and impairing normal physiological events. (8)

5.5 Epidemiology of acute pancreatitis

Acute pancreatitis can concern anybody at any stage of life; it is, however, closely linked to geographical factors bearing multiple sources of cause (12). Even mild cases of AP can show eventual pancreatic insufficiency, affecting patients long term. Even though the mortality rate has sunk over the past 50 years, studies show a heightening of incidence in most countries, Asia remains relatively stable. (6) Thus, globally seen, the rates of acute pancreatitis at 34/100 000 inhabitants per year seem to be rising nearly all over the world with the parallel rising rates of obesity being

thought to be an essential driver. (6, 7) From the point of view of life quality, it is not only the disease itself that represents a problem exactly in that instance, but also the complications: the quota of 40% of people suffering from prediabetes or diabetes later on and the quota of 25% suffering from exocrine pancreatic insufficiency show the burden in the aftermath of acute pancreatitis.

Necrotizing pancreatitis hits up to 10% of the people with acute pancreatitis. US data says that one attack of acute pancreatitis can reattack in up to nearly 20% of the patients concerned. (7)

5.6 Diagnosis of acute pancreatitis

The fulminant orchestra of happenings makes acute pancreatitis a disease where successful therapeutical access very much depends on the ideal point of time of diagnosis. Harrison's volume of 1994 points out that „any severe acute pain in the abdomen or back should suggest acute pancreatitis." Of course the various differential diagnoses are to be taken into account, too. (12)

In general, diagnosis is based on a three- phase procedure considering firstly the symptoms the patient communicates, secondly the result of the blood sample taken and thirdly possibly detected findings on the adequate imaging:

The symptoms typical of acute pancreatitis are described as acute abdominal pain, in frequent cases spreading over the back.

As to the laboratory mainly the amounts of serum lipase and serum amylase raise the suspicion of acute pancreatitis when they reach triplex quantity above their usual level. (14) In this context Leonard-Murali et al. (2021) state that the crucial enzyme is lipase, with amylase as a marker being obsolete, because it is not reliable due to either reaching normal serum levels too early or not rising in level at all in one fifth of cases of acute pancreatitis. (9)

Eventually, if the first two terms of reference do not paint a clear picture, medical imaging hopefully provides missing information, i.e. Contrast-Enhanced Computer Tomography, Transabdominal Ultrasonography and Endoscopic Ultrasonography. (8)

There is a clear warning that during the first seven days of development of a necrosis medical imaging may fail to detect it. (14)

5.7 Assessment of acute pancreatitis

When assessing acute pancreatitis, it is of relevance to be aware of the different forms and stages of disease. Even though the complexity of events makes it difficult to firstly diagnose and secondly find an adequate therapy of acute pancreatitis, basic knowledge can help to classify at least some details carried together here, for taking necessary countermeasures:

Principally the two existing forms of acute pancreatitis show characteristic features; they are defined as the interstitial oedematous acute pancreatitis, which is the most common one (90% of patients concerned) and the necrotizing one; (14) the latter itself bears the risk of complications in two different appearances, acute necrotic collections, and walled-off necrosis.

The different types of acute pancreatitis show different forms of appearance in their pathophysiological correlate. Several methods are recommended to identify the type under consideration, i.e. magnetic resonance imaging, trans-abdominal ultrasonography and endoscopic ultrasonography. The main point as to diagnosis herein is the combination of clinical presentation of the disease and the radiographic findings at a certain point of time, being aware of the fact that experts suggest imaging only a week after breakout of symptoms. (9)

To sum it up, there are two basic pieces of information to properly assess the patient`s present state of health, which will make a prognosis possible: a thorough anamnesis plus rating of the current physical condition. Different scoring systems exist for assessment, in order to be able to estimate if the course of the acute pancreatitis might be a severe one: the Ranson Score, the Glasgow Score, which is based on the Ranson Score, the Acute Physiology and Chronic Health Evaluation II Score, the Bedside Index of Severity in Acute Pancreatitis Score, the Systemic Inflammatory Response Syndrome and the Pancreatitis Activity Scoring System. (8)

5.8 The ATLANTA-Classification

In a large cooperation team of European and American researchers of all sorts of medical disciplines an international group of experts worked out the 2012 ATLANTA-Classification for the disease of acute pancreatitis to create guidelines with reliable terms and structures. This medical committee in charge acted aware of the facts that both geographical factors play a role in the genesis of the acute pancreatitis and that the guidelines should be applicable daily. The focus of this classification was put on the three grades of acute pancreatitis, mild, moderately severe, and severe, all of which are summed up in table 1 with their most important features.

The interstitial oedematous pancreatitis is the most frequent form of acute pancreatitis, the course of which is mostly mild, 90% of cases of acute pancreatitis belong to this form. As soon as tissue necrosis occurs be it within the pancreas or in peripancreatic areas, the worse form of necrotizing pancreatitis is on the way. There is a clear definition of the localization of the necrosis in relation to the sites of pancreas and peripancreatic tissue. In comparison to the simple form of interstitial oedematous pancreatitis the necrotizing pancreatitis is divided up into sterile and infected. Contrast-enhanced computed tomography and percutaneous fine-needle aspiration will help to differ the various forms.

Before the development of this version of ATLANTA classification terms were not clearly defined. The experts placed value on practicability and based the classification on a modified form of the Marshall-Scoring System, which takes the lung, the heart and the kidneys into account when affected.

With the mild form of acute pancreatitis diagnosis can largely do without imaging, patients are no longer on ward than for one week usually. Patients with moderately severe acute pancreatitis need to stay in hospital for one or two weeks more, nonetheless local or systemic complications can lurk beneath the surface. The worst form of acute pancreatitis shows an extremely high mortality rate of 50%, which is even higher when infection turns up in the further course. (7)

Table 2. The latest version of the ATLANTA-classification

Revised ATLANTA-classification form of pancreatitis	features	and/or possible additional features
mild acute pancreatitis	➢ without local complications ➢ without organ failure	➢ without additional features
moderately severe acute pancreatitis	➢ transient organ failure over less than 48 hours	➢ with local complications ➢ worsening of additional diseases
severe acute pancreatitis	➢ organ failure lasting longer than 48 hours	➢ very often respiratory failure ➢ facultative occurrence of local complications

The ATLANTA -classification is supposed to differ the grades of severity as clearly as possible. (7)

5.9 Therapy of acute pancreatitis

Indeed, the therapeutical access to the illness of acute pancreatitis seems poorly developed, even though we have run through more than a hundred years of research already. (15, 7)

Some experts openly complain about lacking therapy options or deficient ones. The only things applied as countermeasures regularly seem to be fluid resuscitation and supportive therapies.

Nonetheless, knowledge about the molecular ongoings is bound to open new ways:

Possible etiological points for acute pancreatitis have been mentioned and described above. Among many other causes there are mechanisms concerning the cell organelles that lead to a possibly unstoppable chain reaction: in case one of the organelles fails its function, this might have a knock-

on effect on other cell organelles, the process inducing cell death. As a matter of fact, this seems to be the ideal point for intervening. (16)

Most importantly, the first 24 hours after perception of symptoms represent a temporal crossroads to pick out the patients in danger of developing a worse course of disease. (8) Thus, it is most essential to gain as much information as possible about the patient´s status; hence, according to their possibilities the doctors in charge ought to scrape the bottom of the barrel for assessment of the disease by using adequate scoring systems and applying the findings of ATLANTA 2012. There are several methods that can be helpful like fluid resuscitation, prophylactic antibiotics, enteral feeding, urgent ERCP, cholecystectomy and alcohol counselling. (17)

6. BACKGROUND INFORMATION FOR METABOLIC SYNDROME

6.1 Definition of Metabolic Syndrome

Unfortunately, there is no common consensus about a generally valid definition of the term metabolic syndrome (2, 18, 19, 20, 21, 22). The fact that the definitions of different organizations contain between four and six factors which build up the metabolic syndrome makes it a complex phenomenon.

The terms describing the metabolic syndrome used in literature show a great range, basically, five phenomena, however, are addressed by all these expressions, first the obese appearance, secondly the levels of harmful lipids, the triglycerides, then beneficial lipids, the HDL-cholesterol, thirdly insulin resistance, fourthly the glucose itself and finally, the contribution of high blood pressure, the term metabolic syndrome marking the common existence of at least three of these phenomena in one organism. (2, 18, 19, 20, 22)

6.2 Etiology and general placement

The biggest issue about the metabolic syndrome is the fact that in reality researchers have relatively little knowledge about the true mechanisms that lead to this status of the body, which is a precursor to many diseases, often vitally endangering states, as cardiovascular complications and metabolic dysfunctions of for example diabetes represent the very diseases responsible for most of the deaths in the western world. In this sense, among many other unclear items, it has not yet been understood in which way and to which percentage respectively genetics and environment trigger the evolution of the metabolic syndrome. (2) In any case, obesity is a global problem. There is a direct pathway from obesity to the development of a cardiovascular disease. (1) The metabolic syndrome is very frequently mentioned in one breath with the term of obesity. The metabolic syndrome turns into a global problem, too: to a certain extent it obviously goes hand in hand with obesity. Obesity itself

derives from factors from the immediate environment and the fundamental understanding or non-understanding of how to lead one's life as to routines and habits, especially two components of which are decisive: the quantity of calories enjoyed plus the awareness of sports and physical training. (23) There seems to be a „Damocles-trio ", made up by insulin resistance, stimulation of the neurohormonal system and development of the chronical status of inflammatory sites throughout the body; the three of them might be the very factors that finally turn the metabolic syndrome into the vital cardiovascular disease. The pathogenetic path showing highly complex mechanisms will be presented in the chapter of pathogenesis beneath. (19)

6.3 Physiological considerations as to metabolic syndrome

Insulin is a highly multifunctional hormone, as it does not only positively affect metabolic processes concerning glucose and fatty acids by triggering their metabolism in a beneficial way: its antilipolytic effect is of immense importance; however, insulin also regulates vessels by widening their lumen, moreover it affects the vegetative nerve system and has an effect on the work of the kidneys. To put it the other way round, if the metabolic role of insulin is at sixes and sevens, the body suffers from the metabolic status of a vicious circle, and especially the rising free fatty acids - set free by the insulin resistance – play a metabolic key role. (24)

6.4 Pathophysiological mechanisms

6.4.1 Starting with an overview

To put it all into a nutshell and to give an overview that adequately meets the requirements of this paper the mechanisms of the metabolic syndrome can be described in the following way:

There seem to be two starting points parallel to each other: social factors, whichever they may be, firstly lead to a surplus of nutrition and secondly to a lack of physical exercise.

From this triggering point on many fatal paths are activated over the time: first four metabolic interstages are activated, as levels of leptin rise (adipose tissue response number one), the levels of free fatty acids rise (adipose tissue response number two), the quantity of angiotensinogen increases (liver response number one), and factors of inflammatory potential show rising levels (liver response number two). This state leads to further reactions like triggering off rising levels of reactive oxygen species, promoting the renin–angiotensin–aldosterone system, and lowering, however, glucose uptake plus the quantities of insulin, a status which physiologically and pathophysiologically forces the body to parallel boost gluconeogenesis, lipogenesis and the synthesis of triglycerides. From this pathological platform three main points can be seen as the initial starting points of the metabolic

syndrome: the activation of the neurohumoral track, the initiation of inflammatory processes and the beginning of the pathway ending in what is called insulin resistance. (25)

6.4.2 Variety of pathological mechanisms

As to the pathophysiological mechanisms of the metabolic syndrome a closer look must be cast on decisive mechanisms of single components that make up the metabolic syndrome. In most of the cases the precise cascades or mechanisms of pathology are still in the dark. (20)

6.4.3 Lifestyle – Sleep and further aspects

Mealtimes ought to be compatible with our genetically programmed zeitgeber according to circadian rhythm. If not, the uptake of food rich in lipids and calories is disconnected with physiologically clocked events like the release of leptin, which bears long-time negative sequelae: people develop hyperglycaemia, insulin resistance and propensity to inflammation. Suffering from obstructive sleep apnoea means either attacks of apnoea during the night or hypopnea resulting in hypoxia which means stress to the cells, to the organs and eventually to the whole organism. This chronical burden finds expression in uncontrolled activation of metabolic pathways: metabolic dysregulations have been detected in animal testing in this context. (26) Physiologically the hypothalamic hormone, growth hormone releasing hormone (GHRH), and its messenger from the hypophysis, growth hormone (GH), are released during pre-midnight sleep, triggering important effects like the oxidation of lipid acids, bone formation and general mechanisms of cell repair. Lack of this part of sleep suppresses these natural events. Too little sleep leads to increased levels of ghrelin and decreased levels of leptin. Moreover, it impairs the physiological cerebral protein metabolism, which bears neurotoxic capacity, and results in disturbed glucose metabolism and high stress levels via noradrenalin and initiates immune activity and inflammation. (27)

6.4.4 Role of circadian rhythm

The human body shows an impressively clocked programme according to the preconditions nature imposes: light and dark are natural phenomena finding their physiological counterpart in melatonin. Regularity, predictability and reliability are features of light change and the human body works according to this natural clock, bearing dominating clocks in the hypothalamus and peripheral clocks in every single cell: one can call these the hypothalamic clock, the enteric clock, the hepatic clock etc. The two latter peripherical clocks, however, are not only controlled by the internal centre of hypothalamus, but also by external factors like timings of meals. Like this any timing uncoordinated with the described clockwork can lead to circadian dysrhythmia resulting in dysmetabolism. Studies

suggest a connection between disturbed melatonin metabolism and the development of obesity in this context due to the fact that the processes of gluconeogenesis and of pancreatic ß-cell cascades and the final state of insulin resistance are dependent upon the correct function of melatonin receptors. (28)

6.5 Epidemiology

As a matter of fact, the world` s societies are walking on destructive nutritional pathways at the time being, leading to physical status of metabolic syndrome as an epidemy. (2)

The Framingham Heart Study of 2014 states that "cardiovascular disease is the most common cause of mortality in developed countries", and clearly cite obesity, hypertension, elevated lipids and diabetes as metabolic risk factors for cardiovascular disease. Thus, the metabolic syndrome can be seen as a half-way house between single diseases which are components of the metabolic syndrome and the patient-relevant endpoint of a developed cardiovascular disease. In so far, the metabolic syndrome contributes a great deal to the prevalence and mortality of cardiovascular disease. Hence, none of the illnesses addressed should be looked at on their own. (29)

After the catch-all phrase of the metabolic syndrome had been created in the 1980s, the following years showed an increase of 35% over three following decades. (20)

Seen from our times, according to WHO obesity rates have tripled over the past half century and 34% of the grown-ups suffer from the metabolic syndrome. The whole exposition of facts underlines the development of the harmful nutritional pathways globally mentioned above.

6.6 Diagnosis

Over the time from 1998 onwards eight different health organisations have offered their own sights of which criteria are to be applied in which context to get hold of a well applicable definition of the metabolic syndrome and to couch its diagnosis on reliable reference points. To sum this all up, the criteria are obesity, glucose, triglycerides, high-density lipoprotein HDL-cholesterol (HDL-C) and blood pressure. All the organizations refer to this series of criteria and base the diagnosis of the metabolic syndrome on them with individual accents. A consensus as to this does not exist so far. (22)

6.7 Approaches of treatment

Seeing that apart from food and physical exercise many other factors play a decisive role for developing a metabolic syndrome, it is advisable to introduce a multimodal therapeutic approach. As to food there are recommendations concerning defined diets. (18)

Physical exercise as a natural gift is applied too little as a means of therapy according to Mayers et.al, 2019. Of course, restitutio ad integrum will not be possible so easily with such a complex disease as is the metabolic syndrome, but to improve the metabolic happenings of the organism will be of great advantage. Cardiovascular fitness is of utmost advantage in this context, as all the risk factors making up the metabolic syndrome are successfully fought with its improvement. (19)
Unfortunately, an explicit and unequivocal concept of this complex disease has not yet been worked out. Many researchers proceed on the assumption that the development of insulin resistance plays a major role. As plenty of external and internal factors are entangled in their interdependency it has been difficult to find a common ground of research. The fact that in very many cases obesity contributes to the metabolic syndrome and can be met with simple measures like reduction of calories and increase of physical exercise, makes this component a very good point of therapeutical origin. (19) On the other hand, the rising incidences of the metabolic syndrome and the knowledge that cardiovascular diseases can derive from the metabolic syndrome and are responsible for most of the deaths in the civilized western world underlines the urgent necessity for quick and determined interventions. (30)

7. REGARDING BOTH DISEASES TOGETHER

7.1 General synopsis of acute pancreatitis and the metabolic syndrome

Although the acute pancreatitis shows a fulminant course with possibly bad pains and the necessity of a quick diagnosis to prevent the worst, and the metabolic syndrome is an insidious process over years, perhaps decades, both diseases have lots in common at second glance. (30, 31) Acute pancreatitis itself represents a very serious disease. Its different stages, however, the mild form and two more severe forms derive from defined according pathways; concerning the more severe forms, explicitly in obese patients, toxicity of adipocytes seems to be the linchpin of events: under normal physiological circumstances lipolysis does not take place, with severer forms of acute pancreatitis and the slow destruction of pancreatic and peripancreatic tissue, i.e. adipocytes suffer from aggressive enzymes released within the pathological processes of the current happenings, in particular triglycerides are set free with their potential to destroy certain protein complexes of the internal mitochondrial membrane, necrosis of the according cells resulting from this. Via steady effects of lipase induced release of triglycerides a vicious circle starts to run its course. Within the common feature of adipocyte tissue and lipotoxicity lies one decisive meeting point of acute pancreatitis and metabolic syndrome. (32)

7.2 Synopsis of single common features and their meaning

7.2.1 Costs for the health system

The incidences of the metabolic syndrome are rising globally. In the overall sum the incidences of acute pancreatitis are rising globally, too. Both cost the health systems of the according countries a fortune. As there is some evidence that the two diseases might be interconnected, not only the individual patient will profit from further research as to this connection, but also the health-systems in charge. (13, 31)

7.2.2 Knowledge gaps

Especially the lack of knowledge as to the pathophysiological happenings of both diseases has been hindering specialists from applying an adequate therapeutical concept up to these days. Concerning the acute pancreatitis, the fulminant events developing in no time are impedimental; researchers have not yet been able to get hold of the actual starting point of the acute pancreatitis. (19)

As to the metabolic syndrome it is the insidiousness and complexity of components involved which makes research access difficult. (25)

Animal testing seems an option, of course, to get certain ideas, but the question stays, if the results can be transferred to human cells just offhand. (19)

7.2.3 Nucleus – cell axis: role of mutation and genetics

More than a quarter of a century the hypothesis has been held that the acute pancreatitis owes its initiation to mutation happenings which seems to affect both acinar cells and duct cells. The alteration concerns for example the section of DNA influencing trypsin and trypsinogen metabolism in an unphysiological way. The genetical etiology, however, is seen as a contributing factor among other contributing factors, not the one and only. (33)

A great number of genes are said to be co-responsible for the development of obesity. Although research has been going on for long and is based on a large treasure of experience genome-wide association studies (GWAS) offer with „GWAS sample sizes well beyond a million participants“, little is yet known about the real contribution of genetics to metabolic syndrome. There are clues there, however, that all the components making up the metabolic syndrome and especially the insulin resistance are linked to genetical communication in some way or other. Genome-wide association studies concretely speak of „at least 56 loci being reproducibly associated with obesity, 157 with lipids and over 90 loci associated with hypertension as well as the numerous loci associated with T2D “. (34)

The hopes for both diseases as to gaining more knowledge of genetic contribution lie within the next generation sequencing (NGS), as complete information at hand of individuals can hopefully spare time and assess risks. (35, 36)

7.2.4 Role of inflammatory substances

The fact that in both diseases immune regulation is concerned links them via all cells plus substances and reactions associated with the immune system having to do with inflammation. (37) The two phases of acute pancreatitis are characterized by immune happenings, the first phase locally, the second one systemically. (19) Concerning the metabolic syndrome inflammation plays a role which has not been cleared yet, but the capacity of adipocytes to fulfil the function of immune cells and release cytokines makes fat tissue a strong player in maintaining inflammation. (4) Relations between metabolic syndrome and its effect on acute pancreatitis are part of research. Substances like TNF-α, IL-6 and CRP are being looked at closely as well as the role of defined leucocyte cells like macrophages etc. Progress in this respect has been slow so far. (8) The common intersection of inflammatory processes will be addressed below in this paper still.

7.2.5 Role of the intestinal microbiotic diversity

The mass of bacteria colonizing our intestine is immense: About 1000 species contribute three million genes which can influence the host`s health on many levels: their expressed products are capable of modulating the immune system positively or negatively, of acting as cell protective agents or cell toxic agents and they can take the role of coenzymes or even energize the organism. Comparing the gut microbiota of healthy people with the one of obese ones showed significant difference. (38)

In addition to this hypertension seems to be connected with the phenomenon that not only the amount but also the range and quality of intestinal microbiota is largely reduced. (38)

Also, during the process of acute pancreatitis the bacterial colonization of the intestine shows significant differences as to amount and quality in comparison to individuals at good health. The events connected with spreading inflammation and mediators like IL-6 lead to the destruction of the intestinal epithelium, which is the main part of the gut barrier. Like this, harmful molecules can invade the intestine more easily and thus physiological homeostasis is disturbed. The worse the pancreatitis gets the more shifting of bacteria to more harmful species and less useful ones takes place. (39)

7.2.6 Role of hypertriglyceridemia

Although the National Cholesterol Education Program-Adult Treatment Panel III calls one of the variables of metabolic syndrome „triglycerides“ it means hypertriglyceridemia. (2) It possibly plays an important role in development of acute pancreatitis, too. Due to a dearth of studies, however, concerning the connection of hypertriglyceridemia and acute pancreatitis this is a realm that has to be worked on still. (40, 41) As to the phenomenon of hypertriglyceridemia Zeng et al. differ the three levels of mild, moderate and severe hypertriglyceridemia or type I, type II and type III hypertriglyceridemia defining them by values in mg/mL based on the national cholesterol education program (NCEP). In these values they very much differ from Habtezion et al., 2019: both groups define the mild form of hypertriglyceridemia with a plasma level of 150–200 (Zeng et al. mg/mL and Habtezion et al. mg/dL), but Zeng et al. have smaller steps between the two next levels with a plasma level of 200–500 mg/mL for moderate hypertriglyceridemia and more than 500 mg/mL for the severe form. Habtezion et al. assess the plasma level of 200–999 mg/dL for the moderate form, going beyond 1000 mg/dL for the severe form. Apart from the fact that hypertriglyceridemia ranks as the third most common reason for acute pancreatitis, all the three forms are reported to lead to more severe courses of acute pancreatitis, potentially with pancreatic necrosis, infection, shock, renal failure or if the worst comes to the worst even exitus in tow. (16, 41)

8. STUDY ANALYSIS OF CONNECTION BETWEEN ACUTE PANCREATITIS AND METABOLIC SYNDROME

Some studies try to get hold of concrete reference points as to the influences of defined parts of the metabolic syndrome on the acute pancreatitis. Research, for example, refers to the fact that obesity may have various effects, when influencing the acute pancreatitis. These influences reveal themselves through minor chronic inflammation processes. Many theories exist about their course of impact:

Firstly, researchers hypothesize that the minor latent course of inflammation of obesity is endorsed by inflammation happenings of the acute pancreatitis in the sense that the very bad and fulminant inflammation processes of acute pancreatitis exacerbate the mentioned low tier inflammation that affect obese patients. Secondly the inflammation of obesity is potentiated due to the fact that obese patients have a remarkably higher quantity of intrapancreatic and peripancreatic fat tissue that takes part in the inflammatory processes. Thirdly the secretion of inflammatory metabolites of patients hit by acute pancreatitis overstrains the hepatic capacity of obese people, as the liver of obese patients suffers from steatosis, so it cannot fulfil its physiological functions of detoxification adequately anymore. Finally, the anatomic position of the diaphragm changes in obese patients

leading to a disbalance of ventilation and perfusion of the lung, so the oxygenation of haemoglobin is not ensured any more. This effect means a vicious circle for the pancreas, as inflammatory processes there are worsened by a lack of oxygen. (40)

Obesity does not only make itself noticeable on cell level, but also on tissue level, organ level and general molecular level, where it influences whole groups of substances. To give an example for the impact on cell level, obesity can prevent endothelium and immune cells from working properly; the endothelial physiological failure plus immune cell dysfunction can concern the whole vascular system, then neighbouring tissues like adipocyte tissue and organs start suffering, too, like for example pancreas and liver. Steady minor inflammation status of tissues and organs result from this and weaken the body`s defences strengthening any nocuous event plus infectious agents. Therefore, it makes sense to keep a close eye on the happenings within the immune system of obese people:

Obesity means that the adipocytes grow in size which makes the amount of adipose tissue spread and enlargen in the body, in sum the triglycerides in the inside of the adipocytes increase in quantity. This leads to several consequences in the surrounding of the adipocyte cells: Firstly the organelles get activated in an unphysiological way, especially the endoplasmatic reticulum and their close co-operators, the mitochondria. In addition, the huge size of adipocytes oust their neighbouring cells, all of which triggers preforms of inflammatory events. In case the status does not alter metabolically, and the inflammation is kept going the adipocytes´ fatal destiny is the one of apoptosis, the dead cells spewing out substances with potential of chemotaxis: This lures immune competent cells and like this the normal average amount of about 10% of macrophages (out of all cell types) in non-hypertrophic adipose tissue can rise up to 50 % in the then hypertrophic pre-inflammatory adipose tissue. The macrophages potentiate the effect of ill adipose tissue, as both cell types generate inflammatory substances, TNF-α, IL-6 and monocyte chemoattractant protein-1. Additionally arriving leucocytes bring forth their own inflammatory chemotactic products, resistin and IL-1b. These happenings influence metabolism pushing it in the direction of insulin resistance. This effect is still promoted by the adipocytes` production of their adipokine, retinol-binding protein 4; by the time more and more triglycerides are broken up and an army of fatty acids is set free to go around in the vasculature together with triglycerides; eventually it is the organs that are overwhelmed by the surplus of fatty substances, the hepatic cells, the pancreatic cells and the striated muscle tissue being functionally lamed. At this state a blood sample would bring increased levels of C-reactive protein and proinflammatory proteins to light. These dangers not stopped, the organism slides into a vicious circle at this point. (42)

Again, one obese patient cannot be placed on the same level as another obese patient, a statement deduced from the World Health Organization`s view of obesity and the results of many studies:

When defining obesity the two parameters BMI and waist circumference play an important role. (43) The cut-off point from preobesity to obesity is a BMI of 30 kg/m^2 or more, but the World Health Organization clearly points out that the pattern of distribution of adipose tissue across the body is different in different obese people by stating: „Obesity can be defined simply as the disease in which excess body fat has accumulated to such an extent that health may be adversely affected. However, the amount of excess fat, its distribution within the body, and the associated health consequences vary considerably between obese individuals.“ (1, 44) This seems to be the case in the synopsis of acute pancreatitis and metabolic syndrome, as visceral adiposity is disadvantageous for the trajectory of acute pancreatitis, whereas lack of visceral adiposity in obese patients is advantageous. (43)

There is a discussion going on whether to use waist circumference or BMI when elucidating the role of obesity in development of acute pancreatitis. (40) There is evidence that patients with a circumference of 105 cm or more have double risk of developing acute pancreatitis, this being significant. On the other hand, literature states that the higher the BMI is the greater is the risk of higher severity of acute pancreatitis. (43)

When regarding a group of 609 patients that were diagnosed with acute pancreatitis researchers used waist circumference to define obesity in the very group that had acute pancreatitis and at the same time metabolic syndrome: thus 110 patients were classified according to ATLANTA 2012. On an average, the 110 patients with a combination of acute pancreatitis plus metabolic syndrome showed overall increase of relevant influencing factors such as age, coronary heart disease as well as the completely combined appearance of factors building up metabolic syndrome. Both the incidence of the moderately severe form and the incidence of the severe form of pancreatitis turned out to be significantly higher in this group with the corresponding values of p being $p = 0,05$ for the moderately severe form and $p = 0,01$ for the severe acute pancreatitis. Interestingly, the mild form of pancreatitis did not turn up in any of the patients of this group that in addition was diagnosed with more local complications like peripancreatic fluid collections and acute necrotic collections. The systemic complications were more numerous, too, in this group. Although the time spent in hospital was not longer for the patients suffering from acute pancreatitis plus metabolic syndrome in comparison to the patients with acute pancreatitis without the metabolic syndrome, they had to be taken care of longer in the intense care unit. Finally, not only the method of multivariable logistic regression proved the metabolic syndrome to be an independent factor for the development of moderately severe and severe acute pancreatitis, but the survival rate of the group with acute pancreatitis plus metabolic syndrome was significantly lowered. (40)

Another group of researchers examined in what way the combination of acute pancreatitis and metabolic syndrome affected the sense of well-being of the patients´. For this purpose, ten defined parameters were allowed for, which are body pain, general health, the mental component score, mental health, the physical component score, physical functioning, the emotional role, the physical role, the social function and vitality; all these parameters were lumped together to the term of health-related quality of life (HRQoL), the group of patients with acute pancreatitis was compared to a group of patients without pancreatitis. As a result, only two out of the ten parameters did not show significances, i.e. body pain and vitality, in all the other realms the patients with acute pancreatitis and metabolic syndrome had significant lower quality of life compared to the group of patients with acute pancreatitis and without the metabolic syndrome. (45)

In Hungary a research group took a closer look at the connection between the metabolic syndrome and acute pancreatitis by firstly considering the metabolic syndrome as an entity of its own being a synergical disease of many constituents and secondly focusing on each of the constituents` effects itself. For diagnosing the acute pancreatitis, the APA guidelines set the agenda, the severity code was defined by Atlanta 2012. As to the components of the metabolic syndrome obesity, hypertension, hypertriglyceridemia were clearly defined by values and diabetes mellitus was diagnosed via the American Diabetes Association Criteria 2010. Concerning obesity BMI was chosen as the decisive factor.

The three factors of obesity, hypertension and hyperlipidaemia turned out to escalate the risk of kidney failure, obesity representing an independent risk factor. Obesity and hypertension lead to more extended hospitalization and moreover, hypertension independently worsened the severity of acute pancreatitis. With a growing number of constituents, the number of bad outcome factors grew, too. (46)

9. CONCLUSION

The acute pancreatitis is a very complex and potentially life-endangering disease, the therapy of which cannot follow any clear-cut course yet: time and processes on cell level play a decisive role, a great deal of mechanisms, however, has not yet been elucidated. Further research is necessary bearing core issues to bring the therapy concept adequately and professionally into line with the pathological happenings: the core issues concern the organelle level in synopsis with time component, asking if two pathological events are to be treated at the same time, and in addition if the earliest intervention possible can prevent the unfolding and progression of acute pancreatitis. (16)

Research is still wondering which factors are to be defined as etiological factors being the starting point for the development of the metabolic syndrome; of course, some special points are always mentioned in connection with the term of the metabolic syndrome like obesity, diabetes, insulin resistance, dysfunctional fat oxidation, genetics, epigenetics, circadian deviations, inflammation processes, visceral adiposity, and hepatic adiposity. On the other hand, the literature research clearly shows that many different theories exist, where causes and effects are interchanged, which does not so much prove deficiency of research, but more the complexity of the problem presented to us, as the metabolic syndrome appears to be nothing else than the conglomeration of quite a number of diseases parallel to each other. Thus, researchers are confronted with the chicken-and egg problem struggling what to name first and what to define as a consequence. (2, 19)

There still is a paucity of studies providing reliable information about if and in which way the acute pancreatitis and metabolic syndrome are connected with one another. (37) The conspicuous thing about both certainly is the common fact of highly complex occurrences of inflammation playing a decisive role in their course. There is some significant evidence for the theory that single components of the metabolic syndrome worsen acute pancreatitis, but also that patients suffering from metabolic syndrome per se have higher risk for developing more dangerous forms of pancreatitis. (47)
Concerning both the acute pancreatitis and the metabolic syndrome the last researching word has not yet been spoken, let alone for the association of the two.

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