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Statins in Alcoholic and Non-Alcoholic Fatty Liver Disease and Chronically Elevated Liver Enzymes

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Abstract

The prevalence of alcoholic liver disease and non-alcoholic liver disease patients has nearly doubled over the past decades worldwide. Alcoholic liver disease among patients with chronic liver disease has increased with arisen due to alcohol consumption and obesity. The diagnosis plays a crucial role in treating such conditions based on the stages of liver functioning. The elevated liver enzymes are the key characterizing of identifying the alcoholic liver disease (ALD) and NAFLD. Later on, there is a progression of the disease conditions by developing fibrosis and cirrhosis, leading to liver carcinoma. The other state, steatohepatitis, is associated with an increase in liver-related and can lead to mortality. Risk factors for both diseases are growing, leading to various complications in health. There is no specific treatment up to date for these conditions, but statins play a crucial role in managing several liver disease conditions. The commonly used drug is hydroxymethylglutaryl coenzyme A (HMG Co-A) reductase inhibitors. It is also known as statins, which help normalize liver enzymes in patients with elevated plasma aminotransferases. As a result, external liver damage is considered safe for the liver as the Statin medication at low to moderate dose usage. **OBJECTIVES:** The main scope of this review is to study the various factors like pharmacological actions, adverse events, and biochemical and liver cell imaging results in patients with ALD and NAFLD. The different types of statins used in alcoholic and non-alcoholic patients' clinical data for the safety of the statin therapy were concluded in this review. Fatty liver changes of both liver disease conditions were studied using different drugs. The other liver enzymes like Alanine transaminase (ALT), Aspartate transaminase (AST), Gamma-glutamyl Transferase (GGT), and the effectiveness of Statin therapy are considered vital concepts in this review.

Keywords

Statin Therapy, Liver Enzymes, Alcohol, Steatosis, Fibrosis, Hepatocellular Carcinoma, Liver toxicity, Steatohepatitis

1. Introduction

1.1. Alcoholic Liver Disease

Regular intake of alcohol causes three stages of liver diseases: fatty liver progression, leading to alcohol hepatitis, and the final stage of cirrhosis. The fat gets accumulated in the hepatocytes; this condition is a fatty liver. This event is categorized into two types based on alcohol consumption; ALD. NAFLD is a condition that occurs without alcoholic consumption. Alcoholic fatty liver is also known as alcoholic people hepatitis, a kind of liver disease caused by excessive alcohol consumption. This condition can be treatable with abstinence. [1] [2]. It can also be treated with moderation and maintained. By managing moderation, the fat predisposing factor in patients can be controlled, which stops leading to chronic liver type disease. On progression, it causes alcohol hepatitis, which has liver inflammation where it is developing due to heavy alcohol drinking. This condition gradually leads to liver cell damage which interferes with the organ's ability to function normally.

Cirrhosis is an end-stage chronic alcohol liver disease. Cirrhosis can be characterized by replacing the normal hepatic parenchyma with fibrous tissue that looks like a thicker band. We can also absorb regenerating nodules that can progress to portal hypertension and liver damage. Alcoholic hepatitis is an alcohol-induced liver impairment that can occur at the starting stage, and this event happens after consuming a substantial amount of alcohol over a long period. In this condition, the severity may occur as symptomatic. However, one can see the liver's biochemical abnormalities, leading to death [3].

We can see that ALD occurs as the most common disease worldwide. The progression of the alcoholic fatty liver can tend to alcohol steatohepatitis (ASH). This event is a condition where hepatic inflammation can lead to fibrosis, leading to cirrhosis, and, in some cases, lead to hepatic cellular cancer (HCC) and Alcohol steatohepatitis. This condition can be seen with or without cirrhosis and can cause alcoholic hepatitis on any clinical presentation of alcohol liver disease, leading to mortality [4].

1.2. Non-Alcoholic Liver Diseases

In NALD, there is a condition where we can see fat in hepatocytes, but there is no liver damage. Non-alcoholic steatohepatitis is when the hepatocytes are filled with fat content in the liver. The characterization of NASH includes inflammation, liver cell destruction, and elevated liver enzymes. The aggressive fatty liver disease can be traced by liver inflammation, converting from non-alcoholic sim-

ple steatosis to non-alcoholic steatohepatitis. Upon progression of non-alcoholic steatohepatitis can also lead to severe liver cirrhosis. These conditions can lead to subacute liver failure and lead to a dangerous situation of hepatocellular carcinoma. This condition is similar to the harm produced by excess alcohol consumption. The induction of the inflammation in the hepatocytes tends to various diseases like NASH, Cirrhosis, fibrosis, and finally leads to hepatic carcinoma, which leads to death. This event can even link with the serious harmful events of metabolic diseases such as obesity and diabetes mellitus type 2 (DM-2). Cardiovascular disease is the most common risk factor in both ALD and NASH, where there is a chance of mortality.

In western countries, non-alcoholic liver disease drastically increases day by day [5]. In the US, CLD affects one-quarter of the population. Studies are conducted on ALD, which is the liver manifestation related to metabolic syndromes such as obesity, DM type 2, hypertension, and increased lipid levels (dyslipidemia) [6]. Here, NASH has features like liver inflammation. This item can even be seen in patients with severe scarring such as cirrhosis and liver failure [7]. Many studies, such as large-scale studies and well-conducted, randomized clinical trials, have concluded that they had evidence of the long-term use of statin. The study stated that there is significant harm to coronary diseases and vascular diseases in patients, has decreased risk when used on statins. This event can develop an average level of lipid levels in both primary prevention and secondary prevention [8]. Hence, statins are now prescribed for people with diagnostic NAFLD in several world areas.

The hepatic histology is evaluated with elevated liver enzymes before and after statin therapy for NAFLD patients. In addition, the initial and the later compassion of the historical, logical output of NAFLD patients were studied. In present studies, there was discovered that increases in the liver enzymes in hyperlipidemic individuals are not more likely joint in the development of hepatotoxicity when compared to hyperlipidemic patients with normal transaminases.

There is a study that only 24% of more alcoholic fatty liver disease patients undergoing the medication on statin move through the stage of fibrosis. Statin can promote hepatic lipogenesis, which influences the hepatic LDL receptor expression. These effects may increase hepatic fatty infiltration. The impact of statin therapy on hepatic histology in non-alcoholic fatty liver disease is unclear [9] [10] [11] [12]. Hence, the pathophysiology of NAFLD disease is still poorly elucidated [13]. The identification of NAFLD by identifying an asymptomatic increased in the frequent liver enzymes. Non-alcoholic hypertransaminasemia is used as a critical surrogate measure for NAFLD. The current label, statins, should be used with active liver disease patients and patients with increased aminotransferases. Presently, the gastric and liver specialists are consulting to refer the Physicians about Statin use in patients with increased serum transaminases. This event is due to the lack of clinical history or serum markers that would explain the liver biochemistry abnormalities. In patients with NAFLD, liver enzymes increase by up to 90% [14].

1.3. Role of Statins

The statin comes under the category of coenzyme known as HMG-CoA reductase inhibitors. This event is commonly used all over well-developed countries as a prescription drug. Statin is considered a subclass in HMG Co-A reductase classification, where the pharmacological effects will be different. The oral bioavailability and protein binding changes in the statin compared to the HMG Co-A reductase. The group of starting such as atorvastatin, Lovastatin, simvastatin, and Fluvastatin has a nature lipophilic they get metabolized with the help of cytochrome p450. The other statin, such as Pravastatin and Pitavastatin, are hydrophilic and undergo metabolism compared to the other class of drugs. The rosuvastatin has an intermediate profile in the liver metabolism. Statin is sometimes restricted as a prescription drug concerned with some side effects: muscle and liver damage. They have a chance of developing hepatotoxicity, which changes the biochemical nature of the liver enzymes; thus, it is a concern in liver disease to prescribe statins.

As the statin is causing hepatotoxicity, the Physicians are much more worried about the patient; hence it is less under-prescribed for patients with ALD and NAFLD. It is unfolding that Statin liver damage is in rare conditions. The new results on Statin prescription have potentially had a higher impact showing a positive effect in the patients. In this review, we tried to explain the statin's role in the development and how it functions during the progression of various diseases such as cirrhosis, fibrosis, and the Vaso protector efforts on portal hypertension [15]. We also concluded the Statin possibility of resolving hepatic fibrogenesis. This review concludes with the role of statins in different conditions of liver diseases, such as the development, progression, and complications.

The statin should not be administered in such patients if conditions such as active liver disease and chronic aminotransferases increase levels. The consultation of the positions such as gastroenterologist has advised that the safety of the statin has had no evidence for the abnormal liver biochemistry in the conditions of elevated serum liver enzymes. Asymptomatic liver enzymes increase due to liver impairment is a diagnostic parameter for hepatic diseases during statin therapy [16] [17].

1.4. Symptoms

Symptoms are common for both ALD and NAFLD. The symptoms depend on the severity of the disease condition. It starts with abdominal pain and tenderness, which leads to an increase in thirst and dry mouth. Next, there is an increase in liver enzymes, which leads to jaundice and yellowish discoloration of the eyes. In this condition, there is weight loss and loss of appetite. Non-alcoholic steatohepatitis is ballooning with an increase in the inflammation of lobes in the liver without fibrosis. In a state of steatohepatitis, there is an increase in fat up to 5% than normal liver, leading to insulin resistance syndrome. This condition may lead to metabolic syndromes such as obesity, diabetes mellitus, and dyslipi-

demia. There's also the condition of hypertension polycystic ovarian syndrome and the risk of cardiovascular disease in this condition.

1.5. Prevalence

The occurrence of alcoholic liver disease is due to excess alcohol intake daily. The NAFLD prevalence is the intake of mild or no alcohol intake, but it is considered a global health problem that affects 6% to 45% of the general population. In Western countries, as a daily basis it is growing up to 30% worldwide. In Asian countries, more than 40% of the population has liver disease. Hence, diabetes mellitus is considering the most critical risk factor for the progression of hepatic fibrosis. Based on the condition of ALD and NAFLD, there is a chance of occurring metabolic syndromes like obesity and DM. There is a chance of 40% cases in an advanced condition of NASH from NAFLD.

The secondary causes might include hepatic fat infiltration and other conditions like viral hepatitis and autoimmune hepatitis. There can be a cause of drug-induced liver diseases, which may cause complications with the liver condition. Alcohol abuse condition where there is >30 g/per day of alcohol for men and >20 g/day of alcohol per day for women as a diagnosis of ALD.

1.6. Pathogenesis

The pathogen causes NAFLD estriol, and the advancement of the pathogenesis of this it's still not well explained. The primary step is to store high-fat content in the liver cells, leading to inflammation. Progression of this condition can link to hepatocellular damage and cause inflammation in the fibrosis condition. There are a variety of variables that contribute to the different types of biochemical changes that occur in the hepatocytes. The changes include IR and changes in the adipose tissue Harmons. The changes in the dietary factors can also change the gut flora, which can also lead to liver Impairment. So, that is also a chance of change, and the genetic factors are the epigenetic factors that lead to liver damage.

There are different types of pathogenic factors that cause NAFLD diseases. The one with the most common factor is the genetic polymorphism that occurs in the patatin, which contains three gene proteins such as IR oxidative stress and adipokines. The adipokines are the diagnostic tool for non-alcoholic fatty liver disease, advancing participation for the endocrine disruptor. This event ultimately leads to studying the therapeutics which target NAFLD treatment.

The liver tissue captures all the excess chemicals caused by the free radicals, alcohol, and other harmful metabolites, mainly by the liver and parenchymal cells. The ROS process is due to the effect of oxygen-containing free radicals, which alter the critical signaling in the cells; hence there is a disturbance in the regulation of lipids and glucose metabolism. In addition, the ROS can directly influence the proteins and the DNA, which causes excessive oxidative stress but increases the RIS within the cells, which directly affects the proteins and DNA.

1.7. Gut Flora Leading to NAFLD

Alcohol affects the liver by increasing the chances of leakiness in the intestinal cell wall. This event causes the entry of the gram-negative bacteria as an endotoxin, which enters the blood and causes the immune response. As the process undergoes, there is an activation of the immune system leading to the activation of the immune cells known as Kupffer cells. These cells are macrophages mainly involved in removing bacteria and the foreign proteins that have entered the blood. [15] [18] [19]. The primary response is when the blood that enters the liver gets purified from the poisonous foreign particles in the liver. The activation of macrophages helps release the Kupffer cells leading to the activation of tumor necrosis factor (TNF) and different interleukins (IL). In addition, the release of the macrophages leads to the condition of inflammation in the hepatocytes.

1.8. How Does Inflammation Begin?

The National Institute of Health said Kupffer cells' role in responding to the endotoxin that enters the body results in liver disease [19] [20] [21]. The Kupffer cells and other immune cells in the parenchyma cells are being responded to, expressed in the liver; there is a pattern recognition receptor. These pattern recognition receptors combine with the toll-like receptors, which help detect the pathogen-related molecular signals and then start the process of inflammation. There is an involvement in the response of the co-receptors like CD14 and TLR4 [22]. These co-receptors help in the reaction of activating Kupffer cells in the alcoholic liver damage [23]. Later on, it starts releasing the cytokinin and activation of Kupffer cells, which leads to the activation of generating ROS in the liver. This event leads to increased oxidative stress and impairs fatty acid oxidation and cellular functioning. This event also activates hepatic macrophages leading to the inflammatory Cascade [24] [25].

There are many negative consequences of alcoholic liver disease, which is caused mainly due to inflammation, which leads to the progression of the liver cell death and regenerating nodules that also form scar tissue known as fibrosis and then leads to cirrhosis. The disturbing result in the molecular signaling pathway leads to consequences that are still unknown. The alcohol interacts with the Kupffer cells, resulting in the leaking of the endotoxin into the stomach. Here, it starts releasing inflammatory mediators like TNF-alpha and cytokinin, which leads to the production of inflammatory cytokines such as IL1, IL6, and IL8 [26] [27] [28]. Suppose there is the persistent release of the cytokinesis and the inflammatory mediators. There is an increase in inflammatory responses in the liver, leading to the progression of the disease to hepatitis, fibrosis, and cirrhosis. There is also an influence by inflammatory cytokines that lead to a process known as programmed cell death, which might be apoptosis.

The cytokines and chemokines play an essential role in the progression of inflammatory responses in ALD. In the condition of alcoholic hepatitis, there is an increase in cytokine levels like TNF alpha, IL1, and IL6. Interleukin 8 plays a vi-

tal role in neutrophil infiltration and inflammation in alcoholic liver disease. The areas of injury and inflammation and mainly attracted by the monocyte chemoattractant protein MCP1. The MCP1 attracts monocytes and macrophages, leading to the inflammatory response of alcoholic liver disease patients. The process of inflammation and fibrosis is progressing by the presence of chemokines like MCP1 and RANTES1. This event helped boost the stellate cell activity. This activation of stellate cells leads to severe fibrosis conditions in the liver [29].

1.9. Stellate Cells in Liver Diseases

Stellate cells in the liver placed a crucial role in forming fibrosis; this also helps heal the liver injury tissue. This event involves the activation of IL8 and MCP-1, where their activity leads to many therapeutic implications. Stellate cells can respond to the injury and help heal certain types of damage in the liver. That is also a recent study about the impacts of the sterlet cells, which can inhibit certain kinds of chemokines [30] [31].

2. Risk Factors for NAFLD and ALD

2.1. Age

The prevalence of ALD and NAFLD increases with an increase in age [32] [33] [34]. NAFLD prevalence related to non-alcoholic fatty liver fibrosis increases with age. A study was made by Frith and colleagues on 351 patients who had undergone biopsy-proven NAFLD. The patients, based on their age, were categorized into three groups. The oldest group is greater than 60 years, the middle-aged people are between 50 and 60 years old, and the younger group is less than 50 years old [35]. They have identified a connection between age and the frequency of non-alcoholic liver diseases linked with fibrosis conditions. The older group has considered at a higher risk and NAFLD such as increased hypertension, diabetes, and increased lipid levels that are hyperlipidemia and diseases like obesity are Common.

Another study on NAFLD incidence in hospitalized geriatric patients is studied. A prevalence rate of 46% is found, which is high compared to the general population study [36]. In the study, there is no link between NAFLD and metabolic syndrome. Therefore, there is no cardiovascular risk in this category.

The pathophysiology of NAFLD may vary in different age groups. The prevalence of NAFLD is related to the age correlation where older people have a higher risk of disease progression, which sometimes leads to death [37] [38] [39] [40].

The progression of the disease conditions such as hepatic fibrosis eventually leads to hepatocellular cancer, which leads to comorbid conditions like diabetes mellitus, which increases with age [41] [42]. A study on liver donors found an age-independent risk for severe hepatic steatohepatitis. Elderly diabetic individuals have a higher risk of cirrhosis, known as burnt-out non-alcoholic hepatitis. Still, the condition here is that the patient is obese presently or in the past [43].

As per the research conducted by Frithet, the older patient has a greater risk of hepatic fibrosis and cirrhosis. Age plays a crucial role in the condition of cirrhotic patients. Younger people were affected by increased ALT activity. There was no clear explanation for the liver enzyme increase with the hepatic steatosis condition [44]. In the research conducted by Hui and his colleagues, they did not find a significant variation between the age groups and the progression of the disease NAFLD. There is no link between the age groups getting NAFLD and fibrosis yet. It is essential to know the association between age and the incidence of non-alcoholic and alcoholic liver diseases, which helps to see the progression of the disease like fibrosis and cirrhosis.

2.2. Race and Ethnicity

During the condition of liver biopsy, it is hard to find the frequency of NAFLD. According to a study conducted by Wagenknecht and his colleagues on the liver disease condition, the visceral any positive virus in different ethnic groups. In Hispanics, they are different types of coordination such as age, triglycerides, and PAI1 in the conditions of liver diseases. On the other hand, serum adiponectin levels in African Americans due to the influence that genetic and environmental factors cannot explain [43] [44] [45]. There is research on the genotype in data relating to the epidemiology of liver disease with genomic medicine in this present world.

The family clustering shows the genetic variations studied as extensive family-based coherent studies that have the heritability in the disease to the condition such as hepatic steatosis, which is about 0.27% [46] [47]. A gene such as PNPLA3 produces adiponectin, a significant genetic contribution to the ALD and NAFLD [50] [51]. In Caucasians, it is at 0.23%. Assuming the same genes promote the increase of liver enzymes by 28% in non-steatosis individuals. The homozygote, I148M, is the more common condition of non-alcoholic steatohepatitis [48] [49].

The regression analysis has taken the sequence of two genes contributing to 72% of hepatic fat changes observed in different ethnic groups. The gene PNPLA3 losses its functions and leads to the condition of hepatic steatosis. In a study of 592 participants, the biopsy-proven underground with the condition hepatic steatosis did Sean the result of having polymorphisms in fat accumulation in the liver, which is due to PNPLA3. Many other genres, such as NCAN, GCKR, and LYPLAL1 when they undergo genetic variation, they play a significant role in the contribution of the ALD and NAFLD. For example, a gene known as 70 GCKR is associated with identifying ALD and NAFLD diseases in Chinese patients.

2.3. Gender

Liver impairment is assumed to be more frequent in females, but this research has been proven false [52] [53] [54] [55]. A study was fibrosis conducted by 527

Asian people who had done medical health checks have liver disease prevalence with 31% in males and 16% in women [56] [57]. In India, a study mentioned the clinicopathological characteristics where men can have a high majority of liver failure. There is also a link in the increase in liver enzymes, and historical findings of non-alcoholic steatohepatitis and hepatic fibrosis in men are prevalent. This event can lead to mortality in the NAFLD.

There is only a little research regarding the female link between NAFLD and fibrosis. One of the research projects mentioned a high risk for females to have NASH in individuals with metabolic syndrome. Based on these results, the ALD and NAFLD act differently in men and women. According to the physicians, the upper and the lower limit of the liver enzyme ALT activity in the woman show up like ULN£30 UL AND ULN£ 19 UL, respectively [58] [59]. Kunde and colleagues had explained the old and new aminotransferases thresholds. Prevalence of liver disease in women increases in liver enzymes with obesity is up to 28%, and at the unique point, the percentage has increased up to 63%. Analogous studies which relate to the aminotransferase threshold in men have been declining.

2.4. Metabolic Conditions

NAFLD is commonly seen in patients already having metabolic syndromes in the general world. Diabetes mellitus with this condition having a liver impairment is most prevalent. There is a prevalence rate of 69%, and the patients have diabetes mellitus type 2 with changes in the ultrasonographic report. In conditions such as obesity and hypertriglyceridemia, there is a condition of ALD and NAFLD with increased liver enzymes. There is no link between diabetic degenerative sequence and the prevalence of ultrasonic changes in liver disease [60].

A recent study shows a high frequency of liver impairment in people with Diabetic Type 2, progressing to liver diseases. The ultrasonography changes in 127 in 204 people with diabetic people have a fatty liver. A study says that 87% who had been accepted for the liver biopsy and exhibited heavy liver changes in Ultrasonography have been diagnosed with alcoholic fatty liver disease [61]. The study findings can confirm an increased incident rate of non-alcoholic steatohepatitis, which tends to be a metabolic syndrome. The non-alcoholic steatohepatitis with severe fibrosis has a condition of the report diabetic with no symptoms indicated in abnormal liver enzymes.

A polycystic ovarian syndrome is an ovarian manifestation of metabolic syndrome in a study with the polycystic ovarian syndrome in women with hepatic steatosis up to 55% [62] [63]. Another study said that 41% of women with polycystic ovarian syndrome have NAFLD with the symptoms of hepatic steatosis and elevated ALT levels with an incident rate of 19%. Individuals with obese PCOS have a higher risk of NASH and NAFLD [64] [65].

2.5. Chronic Infections Associated with Fatty Liver

Hepatitis virus C (HCV) can lead to metabolic dysfunction that can increase in-

sulin resistance (IR), increase blood glucose levels, and lead to diabetes mellitus type 2. NAFLD consists of cases with hepatitis C virus (HCV). The steatohepatitis condition occurs in almost all patients suffering from hepatitis C virus-infected individuals. Patient with HCV has a high frequency of HIV positive [66] [67] [68]. There is a high incidence of fatty liver in patients with chronic HCV and HIV infection [69] [70] [71].

3. Search Methods

The review has been concluded based on several searches on databases such as MEDLINE and PUBMED. Review of clinical trials related to the liver enzymes elevated in conditions of alcoholic and non-alcoholic liver diseases such as ALT, GGT, and AST in response to the Statin therapy. The literature on the topic and a comprehensive evaluation are the considerations to identify the effect of statin use in ALD and NAFLD. The keywords are chosen based on the subject we searched the articles in PubMed; the last search date is on February 10th), 2022. The keywords in the investigation include "statin treatment, fibrosis, hepatic histology, steatosis, inflammation, oxidative stress, liver enzymes, hepatocellular cancer, liver toxicity, dyslipidemia, alcoholic liver disease".

3.1. Electronic Searches

The literature is collected using different online search engines Like Medline PubMed databases. All the review articles related to the liver enzymes like ALT and AST, elevating commonly in Alcohol and NAFLD. In this search, the response of statin in both conditions is considered. In the research evaluating the effect of statin in the use of alcoholic and non-alcoholic diseases, a comprehensive evaluation of the literature is collected. The data literature is searched in the online search engine PubMed based on keywords. The last search date is February 10th, 2022.

3.2. Data Collection and Analysis

Study Selection

After evaluating the abstracts and titles of the publications that I found in the database searches to identify research that could be acceptable for further evaluation, later, we assessed the study, which is compatible with our topic based on suitability and completeness. We have divided the study selection into different parts. First, we selected the case and searched the electronic databases based on the chosen set of keywords. Then based on the inclusion and exclusion criteria, the data was selected. Finally, all the data was gathered, and the reports were studied.

A final study of the complete papers decided on the report's title, relevant to the topic. The evaluation of the article for the relevance of the title and the abstract will bring evaluated. The two review orders had given eligibility criteria review without any limitations on the paper.

3.3. Selection Criteria

3.3.1. Inclusion

We considered most clinical studies submitted on liver enzymes before and after statin therapy.

This review includes case-control studies that reported liver transaminase levels in both the case and control groups.

We only selected English-language articles having full-text access.

We included case reports from ALD and NAFLD patients who responded to various statins.

In this review, Statin alone groups are selected.

3.3.2. Exclusion

Studies with fewer patients that are fewer than 15 patients were, excluding.

Dual and multidrug therapy has been banned, except only statin treatment.

The other language studies except English are not in this review.

This review did not include the editorials and comments; we also stopped the letters and animal experiment studies.

3.4. Criteria for This Review

3.4.1. Types of Study

There is no specific module, so the randomized clinical studies compared different types of people taking different kinds of lipid-lowering medications and the other with the control. The randomly assigned participants were considered regardless of the count or the publishing status, such as the publication's year and language. The reports were being evaluated for the non-randomized studies, and the Adverse Events of each study were concluded.

3.4.2. Types of Interventions

Different statins include Lovastatin, atorvastatin, simvastatin, pravastatin, and rosuvastatin. Fluvastatin was given to the patients for three months and, at a minimal dose, was considered an experimental intervention study. The participants in this exploratory study were compared with the placebo patients. They were not given any medications in the other group as those receiving another type of lipid-lowering medication. The route of administration in these patients is only the oral route. Finally, the data report was included as per the result obtained by the different groups.

3.5. Outcomes Measures

3.5.1. Primary Outcomes

The primary outcomes considered the mortality that might occur due to any cause and the adverse effects. And that caused hepatitis is regarded in the mortality condition as an adverse event, including the number and the kind of adverse effects and the severity of the event's damaging effects. In addition, the International Conference on harmonization (ICH-GCP 1997) is an additional con-

sideration.

3.5.2. Secondary Outcomes

The secondary outcomes include the logical history response, which consists of the biochemical and Imaging reactions in the disease patients. The number of people who had significant changes in their history reports related to the fatty liver infiltration or the inflammation in the hepatocytes. There is also a condition of fibrosis. In the biochemical response, the subjects are testing serum liver enzymes such as AST and ALT levels. Where has a fantastic response, including Ultrasonography and CT scan or MRI, which are high in usage in the current diagnosis. This response clearly states the condition of the liver damage based on the Imaging report showing the fatty liver infiltration, fat accumulation, inflammation conditions, and fibrosis. This event is advantageous in differentiating various stages of liver disease, mild-moderate or severe, as per the classification.

4. Diagnosis and Classification

The diagnosis of ALD and NAFLD includes two types of tests. The first is the blood test. The rest is the Imaging tests such as an ultrasound, CT scan, and MRI scan. The blood test helps detect liver function by showing the results of elevated liver enzymes [72]. In addition, the lipid profile measuring the cholesterol levels, blood triglycerides, and LDL levels allows the detection of NAFLD.

4.1. Mechanism of Action of Statins

Statins improve alcoholic and non-alcoholic liver diseases by different types of mechanisms. They improve hepatic steatosis hepatitis by reducing LDL levels. They also act by the proteins known as activating sterol regulating element-binding proteins (SREBPs), which help improve transcription and maintain lipid homeostasis [73]. The peroxisome proliferator-activated receptor alpha (PPAR) plays an essential role in reducing inflammatory responses of NAFLD.

4.2. Anti-Inflammatory and Anti-Fibrotic Effects

Statins act as an anti-inflammatory by inhibiting the small GTPase prenylation, decreasing the downstream signaling [74]. In the initial stages of fibrosis, the stains can work by reducing the bile acids by activating the pregnane X receptor and PPAR-α. Anti-fibrotic effect of statin can be seen by paracrine signaling of the liver cells on the hepatic stellate cells, which then block the hepatic stellate cell's activation. Hence the fibrogenesis is blocked [75]. The hepatic stellate cell pathway is activated by the Rho kinase [76]. The fibrosis gets improved by inhibiting the RhoA.

The role of statin in portal hypertension works by the following mechanism: an increase in the intrahepatic resistance imbalance, which affects the regulation of RhoA and nitric oxide signaling pathway, leading to vasoconstriction.

5. Treatment

5.1. Liver Toxicity Caused by Statin

There is a rare chance of liver damage by statin therapy, but they can be dangerous Adverse Events using statins. An asymptomatic increase in serum ALT has been prevented in statin-treated people here. There is a risk of observation in liver damage in a few cases. Asymptomatic raises in ALT during statin treatment are not considered evidence of ongoing liver disease or injury [77].

The word "transaminitis" is characterized by hepatic enzyme leaking that does not result in hepatotoxicity that may explain many types of blood ALT increases in statin-treated patients [78]. There is a widespread agreement that ALT is More effective than AST in detecting the potential hepatotoxicity because AST levels can arise either in muscle or liver damage. Hence, ALT level increase is a successive test because a single ALT increase is more similar to transaminitis than liver injury. The treatment of the different types of statins has clearly stated the uses and dosage in **Table 1**.

In the previous case report, there is a condition where statin use caused autoimmune hepatitis [79] [80] [81] [82]. There is a study about three cases of autoimmune hepatitis. There is induction of hepatitis after treatment with Fluvastatin in two cases. The third case is atorvastatin-induced autoimmune hepatitis. Lovastatin use, particularly at high doses of 80 mg per day, has a modest increase in the liver enzyme up to 5% of patients [83] [84] [85] [86]. There is a chance of developing centrilobular necrosis, fulminant liver failure, and cholestasis [87]. Simvastatin can lead to liver damage due to drug-drug interactions with the self-drug [88].

5.2. Role of Statin in Abnormal Liver Test Patients

The primary issue in clinical practice is an increase in the serum liver enzyme, which is usually caused by concomitant comorbid diseases like obesity, pre-diabetic, and diabetic conditions, as well as dyslipidemia, which has the typical characteristics of NAFLD. Statin therapy decreases the cardiovascular risk in people with low to moderate levels of abnormal liver tests. Hence, statin therapy is considered safe and can even improve the liver test.

The liver blood tests should be repeated as soon as possible to declare an increase in the levels. Before starting the Statin treatment, the diagnosis part plays a crucial role. The quality of evidence is less Baseline liver enzyme testing is adjusted before starting the Statin therapy. Before beginning the statin therapy, a low grade of strength was observed.

5.3. Statin Treatment in Dislipidemia

Hyperlipidemia is considered atherogenic dyslipidemia and can be characterized by an increase in the serum triglycerides and low HDL cholesterol, which is regarded as good cholesterol, and the presence of small LDL particles. In addition, atherogenic dyslipidemia is symptomized by insulin resistance and metabolic syndrome, including obesity, diabetes mellitus, and hypertension.

Table 1. Details of various stains usage in different liver disease conditions based on severity along with their doses [89] [90] [91].

STATIN	TREATMENT	DOSE
CERIVASTATIN	Decreases elevated liver enzymes.	10 - 80 mg/day
ATORVASTATIN	Increased serum transaminases. Autoimmune hepatitis.	10 - 80 mg/day
LOVASTATIN	Resolving hepatic fibrogenesis. Increased serum transaminases.	80 mg/day
SIMVASTATIN	Cirrhosis	20 mg/day
PRAVASTATIN	Steatosis	20 - 80 mg/day
FLUVASTATIN	Fibrosis of liver	80 mg/day
ROSUVASTATIN	Hyperlipidemic liver diseases.	10 - 80 mg/day

It can be safely treated with a statin, which treats hyperlipidemia. Furthermore, statin hepatotoxicity is very low in these patients; hence, NAFLD and NASH can be clinically treated with statins.

Statins play a crucial role in managing increased lipid levels in NAFLD patients by decreasing the lipid levels. The statins successfully reduce cholesterol levels in people with non-alcoholic liver disease. But one statin that helps reduce the incidence rate of cardiovascular events is atorvastatin [92].

Many studies consider the safety of Statin therapy for this lipidemia in patients with NAFLD. It is regarded as a safe and well-tolerated treatment with pravastatin at 80 mg/day with reduced LDL, TC, and TGs in Hypercholesterolemic Patients with NAFLD. However, there is an increase in serum ALT levels in patients with NAFLD and NASH when treated with a statin. Consequently, under treatment with a statin patient with NAFLD has frequently been a source of worry [93].

5.4. Role of Statin in Non-Alcoholic Liver Disdisease

Statin is an antithrombotic, anti-inflammatory, and antioxidant independent of lipid-lowering activity [94] [95]. The statin treatment plays a significant role in NAFLD and NASH as both the conditions have inflammation and oxidative stress [96]. There is an increase in NOX2-related oxidative stress in patients with NAFLD associated with severe liver steatosis [96].

Up to date, there is no data showing medication for NAFLD. As of now, there is less evidence relating to the effects of statins in NAFLD [97] [98]. The GTPase plays a significant role and non-alcoholic steatohepatitis through signal transmission, protein synthesis, cell differentiation, and intracellular vesicle movement. Statin helps by preventing non-alcoholic steatohepatitis by decreasing GTPases. The PPARs play a significant role in inflammation, metabolic pathways, and non-alcoholic steatohepatitis Statin acts on The PPAR receptors and helps degrade fatty acids. Paraoxonase 1(PON1) is present in the liver and acts

as an antioxidant enzyme with anti-inflammatory and Antiatherogenic properties [99]. The Statin therapy improves PON1, decreasing due to lipid peroxidation [100].

Simvastatin improved the progression of non-alcoholic steatohepatitis-related fibrosis in animal models (rats). Endothelial and inducible nitric oxide synthase production can restrict the stellate cell activation. After four years of therapy with Atorvastatin 20 mg, 71% of patients with NAFLD had improved and reduced their risk [101].

6. Newer Studies with Various Targets

The Statin metabolism involves several cotransporters and enzymes, affecting the effectiveness and tolerance of the statin administration in these patients. In addition, the hepatic action can also be affected by the cotransporters and enzymes by administering the statins.

In chronic liver disease, as the patients have a poor liver function, the safety of the individuals is more concern; hence, statins are subsequently being as potential therapeutic options in both ALD and NAFLD are still under examination. Some polymorphisms affect the gene, which impacts the statin pharmacodynamics and pharmacokinetic properties and changes the course of fatty liver disease and the lipid metabolism of NAFLD [102]. As the patients with NAFLD have a high level of P450-2E1, this issue leaves the polymorphism in PPAR Alpha and Gamma 2, leading to an increase in the risk for the patients.

Since recent research indicates that patients with elevated baseline liver enzyme levels can benefit from statins, optimism has increased that these medications can reduce cholesterol and decrease NAFLD-related liver damage [103] [104].

7. Conclusions

Statins are prescribed to people with high liver enzymes due to ALD and NAFLD. Observational studies revealed no impact, suggesting that statins are safe for ALD and NAFLD patients' livers. What're more stains work effectively in all conditions of liver problems, from the stage of Fatty liver to cirrhosis and portal hypertension.

The review mainly discusses the summarization of the role of statins and ALD and NAFLD. They primarily focused aspects of this review paper on a statin role in endothelial dysfunction in chronic liver disease caused by alcohol and non-alcoholic. The other aspects as modulating hepatic fibrogenesis and the Vaso protective effects in portal hypertension were discussed. In this review, we mainly focused on the data representing the role of statins in the various conditions of ALD and NALD. The progression of the disease conditions and the complications of cirrhosis are critically assessed in this review paper.

Liver failure worldwide is considered very rare, with an occurrence rate of 2 in 1 million treated patients. The most helpful treatment in the present day for

ALD and NAFLD is statin therapy, as it is well-tolerated and safe for the patients. Statin therapy shows minor side effects such as myalgia in a few patients and Rhabdomyolysis in other patients, significantly less commonly seen. The adverse impact seen is an increase in the liver enzymes like aminotransferases, which might be harmful to the patient. The increase in temporary asymptomatic aminotransferases is commonly seen in a tiny percentage of patients, nearly 0.1 - 3. Statin tends to change the ultrasound readings. The patients having the adverse symptoms of 1.8% to 12% have a significantly elevated risk of cardiovascular problems.

8. Discussion

There is no specific efficacious treatment for NAFLD, even though NAFLD is an emerging disease condition worldwide. Hence, pharmacological medication must be considered for this condition as soon as possible to improve the health care system. The use of statins and NAFLD and alcoholic liver disease has been commonly prescribed worldwide. This treatment has been used to reduce the comorbid conditions eventuality as the cardiovascular risk associated with non-alcoholic steatohepatitis.

The statin treatment also improves the conditions of alcoholic liver disease with the comorbid conditions of metabolic syndrome and type 2 diabetic Mellitus. Many factors like liver-related mortality, liver histology, plasma liver enzyme activity, and ultrasonographic abnormalities were investigated when taken by the statin treatment. We can see many changes in the patient's liver with the NAFLD and ALD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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The Role of Recruitment and Retention in Clinical Trials

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Abstract

It is evident that both recruitment and retention play critical roles in clinical trials. Recruitment and retention models are beginning to be analyzed worldwide in an effort to assess how to conduct studies more efficiently, all the while, allowing researchers to provide sound and ethical data to help advance medicine through clinical studies. Sponsors and sites have recognized that clinical trial enrollment must become more diverse and inclusive. In this review, we address the important topics of recruitment and retention in clinical trials. Specifically, the obstacles in regard to recruiting vulnerable populations. Methodologies to improve both the understanding of the study population and community engagement are outlined. In particular, newer strategies such as use of social media and more reliable strategies such as trust and relationship building are described in detail. A strong focus on recruitment is becoming widely recognized as being of such importance that consideration is given to this key component even during initial protocol development. Attention to recruitment and retention in the strategic planning process of clinical trials can mitigate enrollment issues that clinical researchers are experiencing.

Keywords

Recruitment, Retention, Clinical Trials, Enrollment, Study Population, Inclusivity, Diversity, Social Media

1. Background

Researchers are realizing that traditional recruitment and retention processes are no longer the most effective way to enroll clinical trial subjects, particularly in regard to diversity and inclusivity. Recruitment and retention are topics that need continued attention to help us better understand the populations needed

for each study. It is an area of focus that still requires much research to be done and a focus on utilizing the ever-changing technology that is available to us. In considering the future of clinical trial recruitment, researchers have identified that the internet and social media will play a vital role in the future of subject and site interactions.

1.1. Human Subject Research

It is necessary to understand how human subjects are defined and how far clinical trials have come over the years. The history of human research reveals that there have been a number of unfortunate scandals. Due to this history, there have been several safeguards put into place to protect and advocate for human subjects. Today, all credible agencies in the field of *clinical research* use the definition of a human subject, created by the U.S. Department of Health and Human Services:

(e)(1) Human subject means a living individual about whom an investigator (whether professional or student) conducting research: 1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or 2) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens (§46.102 e.1.) [1].

This classification helps researchers categorize a human subject to better protect them from mistreatment. It also helps essential agencies such as the Food and Drug Administration (FDA), National Institutes of Health (NIH), and Institutional Review Boards (IRB) to remain consistent in their definition of human subjects [1].

Institutional Review Board (IRB) for Recruitment

Institutional Review Boards (IRB) are responsible for reviewing patient-facing study information to protect study participants' human rights and welfare. They ensure that ethical standards are met and followed. IRBs were introduced and became a requirement in 1975 after unethical clinical trials negatively impacted many lives. Now, IRBs help to ensure human subjects are treated ethically and are appropriately informed of all study details [2].

1.2. Clinical Trial Recruitment and Retention

Recruitment and retention of human subjects in clinical research is a multifaceted topic. It is a topic that is potentially one of the most crucial aspects of the clinical trials process. Trial recruitment is as essential for the clinical trial process as the subjects themselves. Not only are human subjects a requirement, but there is usually a defined number of subjects required for each clinical trial. Subject retention is also a critical factor because, once they have completed a trial, they often choose to participate in subsequent trials that are available to them. From what I have encountered in clinical trial recruitment and retention, most strategies can apply to both recruitment and retention. However, it is evident that it is harder to build a relationship than it is to maintain one.

2. Methodology

2.1. Recruiting Vulnerable Populations for Clinical Trials

Recruiting youth can be a difficult feat. You not only have to receive the assent of the minor, but you are also required to obtain the consent of one or both parents, or the child's guardian. To reach multiple generations, the trial must have aspects that catch the eye of these two vastly different age groups which can be quite challenging. Enrollment success depends on perceived benefits from participating in the study, whether that is relief from their condition, health monitoring, or other benefits that may result from study participation. A majority of common struggles are time demands, unstable living conditions, comprehension, and communication issues such as language barriers. However, data shows that the most successful components of recruiting minors are establishing trust, creative advertising, and monetary incentives [3].

Numerous sites have turned to recruitment strategies that focus on offering monetary incentives due to the success seen with school-based sites. Another key incentive in recruiting adolescents is when studies offer free comprehensive health screenings followed up with a detailed explanation of the results from a health care provider. Technology-based incentives and online advertising primarily on social media platforms have also proven to be effective. Trust building is interesting when concerning pediatric and adolescent recruitment because the site staff not only has to gain the trust of the potential subject, but also the trust and confidence of the parents or guardians [3].

Active strategies tend to be the most effective when recruiting children. Active strategies include physician referrals and targeted mailings. Physician referrals usually result in an enrollment rate of just over 50%. Referring physicians reflect more successful enrollment numbers when they are familiar with the inclusion and exclusion criteria. In addition, these referrals typically require consistent communication with providers and their staff to ensure that the studies remain a priority to the patient. Targeted mailings, however, usually have a hefty cost attached and result in roughly a 30% enrollment rate [4].

Passive recruitment strategies include advertisements such as having an internet presence, word of mouth, and newspaper, bus, and television advertisements. Surprisingly, of all the active recruitment strategies, newspaper advertisements are the most valuable and unfortunately, the most expensive. The enrollment rate is at about 5%, so you can see that active strategies yield much better results in regard to enrollment numbers [4].

Social media is becoming more embedded into our everyday lives as time progresses, and sites are beginning to take advantage of this tool in recruiting for clinical trials. A study was conducted in 2017 to try to mitigate the additional burden that recruiting minors presents in trying to gain assent and consent [5]. They detailed the use of Facebook ads and traditional mailings in recruiting adolescent females for a drug prevention trial. The results suggested that Facebook did prove to be useful as an initial point of contact, and it is a cost-effective

recruitment tool. This tool can be helpful if used properly, however it does require vigilant monitoring of campaigns, and it has risks [5].

When it comes to recruiting elderly patients, there are often obstacles that arise. Older adult recruitment takes research staff more time to recruit than with the general population. Based on data collected in regard to the recruitment of older adults, the majority of these elderly patients were more inclined to participate when they had cultivated relationships with community-based organizations and recruiters that met the candidates face to face prior to signing the informed consent. They also had greater success when the study sites offered to provide services such as blood pressure checks to assess the eligibility of participants [6].

2.2. Diversity in Clinical Trial Recruitment

In the field of clinical research, it is a known fact that there is not a whole lot of diversity in study participants. It is also a fact that many are now making this issue a priority. Part of this lack of diversity stems from unethical trials of the past. The dark history of clinical trials unfortunately sticks with people to this day. Getting past this barrier requires a little historical context. If looking only at African Americans, historically, there is an extensive list of unethical human experimentations. The Tuskegee experiment is one of the most well-known human research events that a number of people associate with clinical research even today [7].

Research by Dennis and Neese (2000) suggests that minorities continue to be less insured than their white counterparts [7]. The inequality and lack of inclusivity can hinder minorities from participating in clinical trials and should be taken into consideration when recruiting for clinical trials. Another issue to consider is research bias. Research bias is another barrier that holds us back regarding diversity in clinical trial enrollment. Research is supposed to be based on sound scientific rationale; however, research protocols can be biased toward specific populations. The inclusion and exclusion criteria should be clearly stated and in great detail, leaving no room for confusion or doubt. Larson (1994) found that out of 754 protocols from her institution, about half of them had age exclusions and a majority of them did not have clear justifications [8]. The race of the participant was least likely to be an exclusion criterion; it was, however, along with age and socioeconomic status, linked to unexplained exclusionary criteria for studies [8].

Dennis and Neese (2000) outline six concepts that have developed as fundamental to research involving diverse groups:

1) historical cognizance; 2) sanctioning; 3) trust-building; 4) recognition of group heterogeneity; 5) mutuality; and 6) researcher self-reflection and introspection.

These concepts, if implemented along with planned strategies, can prove to be quite successful in working with diverse populations [7].

3. Recruitment Challenges

Recruitment does not often receive support or praise throughout the study process. When it comes to the study budget, recruitment is often an afterthought. This oversight results in sites being unable to meet their enrollment goals. Common causes for such shortcomings are that 1) sites do not create a recruitment strategy early in the process, 2) community members are not engaged, resulting in a lack of knowledge, and 3) lack of trust in the research team and clinical trials in general, which can sometimes be due to cultural differences.

Though there are various limitations that can hinder study enrollment, distrust is one of the most significant barriers for research sites all over the world. Study design, inconvenient locations, visit times, low compensation, education, lack of transportation, and a participant's general lack of interest in the study are also factors. All of these challenges make it difficult to recruit subjects. Still, thanks to research, there is data that shows us what effective strategies look like and how we can overcome these barriers to increase volunteer patient enrollment in studies.

4. Effective Recruitment Strategies

Combinations of recruitment techniques are used in clinical research every day. These techniques include clinic and hospital outpatient and inpatient referrals, patient database searches, community provider referrals, distributing flyers, newspaper advertisements, field-based recruitment and more. Field-based recruitment methods such as community outreach can include patient education events and campaigns. Recently, researchers have taken notice that community outreach is a crucial piece of the recruitment puzzle. Community outreach, field-based recruitment, and referrals are methods that are becoming strongholds in recruitment practices [9].

4.1. Knowing the Target Population for Clinical Trial Recruitment

In the past, recruitment was being given a one size fits all model; however, researchers have discovered that this theory is not sustainable in this day and age. Better knowing the populations that are being recruited will help to increase overall recruitment success. Recruitment specialists must now cater their recruitment strategy to the target population based on each protocol for more effective results [10]. Even so, the protocol procurement phase should involve thorough consideration of recruitment. It should also be completed with a clear idea as to who the population is in regard to the study that is being developed. One way to achieve this is to include the expertise of a recruitment specialist in the protocol development process.

4.2. Community Engagement

Community engagement is a crucial aspect of not only knowing your target population but also building trust with community members. Anastasi, Capili,

Kim, & Chung, (2005) noted that having a relationship with community servants in the field of study can help researchers gain the information they would not have otherwise [10]. A New York City research team had built a relationship with the Healthy Life Choices Project (HLCP). HLCP was able to inform the research team that a great deal of participants struggled with transportation costs, so the research team will begin to accommodate these costs in the future by adding travel reimbursements to their study budgets [10].

Being involved in the community can provide feedback such as transportation needs, appointment time flexibility, study materials not being easy to understand, and insights into what the community members value. When you engage the community's target populations, it can help you build trust and, in turn, improve enrollment [11].

4.3. Trust Building

Trust is something that is not only built but also maintained [12]. Based on a multitude of evidence, establishing trust between researchers and participants is crucial in human subject recruitment and enrollment. Building trust can be done by openness, providing a sense of security and comfort, and even expressing genuine gratitude [6]. It is necessary to increase trust and transparency throughout the research process because it is associated with participants' willingness to participate in studies [13]. Trust is more vulnerable during transitions. Usually, these transitions occur from care providers to research staff [12].

Swift Trust

Swift trust begins when a patient is referred to a site, during the recruitment process, and even during treatment phases of a study. It develops in temporary systems with patients, their loved ones, community providers, and with research staff interactions. It focuses on expectations and assumptions that people are dependable and capable. Recruitment is stressful as it is and there is added pressure due to time constraints that force the study team to make quick decisions with the information that is available to them. These time constraints sometimes also require the participants to make quick decisions and judgment calls with the lack of a relationship to support such decisions [12].

Within swift trust, there are five types of trust. *Ex-ante* refers to a referring physician that initiates trust between the participant and the research team. *Role-based* trust is trust that is solely based on an assumption of trustworthiness due to the researcher's position. *Rule-based* trust focuses on the hierarchy within the research team members in which they frequently interact. *Dispositional* trust refers to an individual's disposition, typically based on what they believe or how they carry themselves. *Category-based* trust focuses on one's identity or stereotypes [12].

Traditional Trust

Traditional trust usually comes following swift trust because it gradually develops over time. This form of trust can be considered knowledge based. It con-

siders a person's behavior and grows based on familiarity experience [12].

Within *traditional* trust, there are four stages of trust. *Calculus-based* trust is a simple form of trust as it is task-oriented. *Knowledge-based* trust is developed through deeper familiarity and interaction. *Affect-based* trust is formed based on reciprocated care and concern. *Identification-based* trust is built by understanding desires and intentions. It is usually socially driven and develops over time [12].

5. Discussion

Recruitment and retention for clinical trials is a multifaceted beast that has its difficulties along with its benefits. Underenrollment in clinical trials wastes resources and delays the discovery or development of new treatments [14]. After the review of data and statistics regarding recruitment and retention, it is clear that trust is a significant barrier. That being said, it is also one of the most popular strategies used to enroll minors, older adults, and underrepresented participants.

Recruitment and retention practices and their impact on clinical trials is complex. Many are using a limited number of tactics that considered to be traditional. Despite the wide variety of novel solutions available to sites, traditional approaches including use of physician referrals, radio and television advertising are most prevalent, whereas social media is just now beginning to be used on a global scale. Centralized recruitment is another nontraditional tactic that has proved to be an effective tool in recruiting clinical trial participants. More sites are beginning to incorporate solutions to recruitment issues that do not follow the traditional strategies but are effective and supported by increased enrollment numbers [15].

6. Conclusion

My hope is that all of the new research will put a spotlight on recruitment and retention in clinical trials, giving it the attention it deserves, in the world of research. Tracking metrics and specific organized recruitment methods should be commonplace, and models should be provided to the study staff at the site level. Despite the additional attention placed on recruitment and retention in clinical trials, there is still much to accomplish. The extra attention has opened countless doors in the field, though the industry would advance even further if those doors led to new recruitment and patient management platforms that could track studies, their recruitment metrics, and regulatory documents. Improvements like this would significantly impact the advancement of effectively recruiting and running clinical trials.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Minimal Vasovagal Dysautonomia in Patients with Rare or Unique Syncope

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Abstract

Introduction: It is common to find people sent to perform a Head Up Tilt Test (HUT) who suffered a single syncope, or syncopes that occur during certain periods and never appear again. We wonder how these people are different from those who have never had syncope. Methods: We found 300 patients who suffered only one (unique) or a maximum of 5 vasovagal syncopes during their life. And their HUT was positive for vasovagal dysautonomia. We compared them, with 120 healthy volunteers who have never had syncope. We try to explain how some constitutional predisposing factors act in these patients, and are associated with environmental triggers to precipitate the syncope. Results: We found differences between cases and controls in predisposing factors such as: heredity, joint hypermobility, baroreflex failure, venous compliance and some neurological diseases. Then an environmental factor acts as a trigger for syncope: prolonged standing, stress, pain and emotions, dehydration, use of certain drugs, abundant food. Conclusions: There are people with minimally expressed vasovagal dysautonomia who have an organic predisposition to present vasovagal syncopes (heredity, joint hypermobility, baroreflex failure, venous compliance, some neurological diseases, etc.). But this predisposition is not enough by itself to produce syncopes. One or more environmental factors must be added, acting as a trigger that would be the reason why these episodes are so infrequent.

Keywords

Dysautonomia, Unique Vasovagal Syncope, Head Up Tilt Test

1. Introduction

In our clinical practice performing Head Up Tilt Test (HUT) we found 300 patients, suffering only a single syncope or short periods with syncope that later disappear.

Our objective is to describe predisposing factors that we find in these persons that probably suffer from minimal dysautonomia.

1.1. Definition of the Group to Study

Between 2006 through 2021 we found 300 patients who consulted after having suffered a single syncope or a maximum of 5 episodes in their lifetime, in whom the positive HUT suggests that there was a hidden predisposing vasovagal dysautonomia.

Also shown are 120 healthy volunteers, who have not suffered from syncope, with an age and sex comparable to the patients

1.2. Ethical Clearance

Our study has been approved by the Militar Hospital's Ethics Committee, and has been carried out in accordance with the ethical standards established in the Declaration of Helsinki 1964. Patients and controls gave their informed consent before inclusion. Anova and logistic regression are used for statistical comparison and, depending on the sample size, a non-parametric test is used.

2. Material and Methods

2.1. Previous Study to Head Up Tilt Test and Inclusion Criteria

Our investigation included a retrospective data analysis of 1034 patients studied with HUT (60% women), carried out between 2006 and 2021. The average age of these patients was 30.5 years (range: 6 - 89 years).

In this persons we found 300 cases (29% of the patients examined in that period), which fulfilled the definition of the group to be studied

To rule out a cardiac or other cause, prior to the HUT, a careful medical history is taken, physical examination, evaluation by a cardiologist and some tests: electrocardiogram (12 leads), echocardiogram, heart rate 24 hours holter, and sometimes an electrophysiological study. If this previous study is negative, the patient is referred for our neurological evaluation and HUT.

One hundred and twenty volunteers of the same age and sex served as controls.

Subjects and controls were recruited from patients at the Santiago's Militar Hospital.

2.2. Exclusion Criteria

If a cardiac cause was found, the patient was not included. The same if the patients suffer from epilepsy or pseudosyncopes.

Patients whose HUT was negative were excluded, in order to study only those

patients with a higher probability of vasovagal dysautonomia.

3. Head Up Tilt Test Exam Conditions

Fasting patient (between 8 and 12 hours). Quiet room, with dim light at a temperature between 20˚C - 22˚C.

Exam is supervised by a neurologist, a cardiologist and a medical technologist. Cardiology staff install continuous ECG and HR monitoring.

A hemoglucotest is done before the exam.

Electrocardiographic monitoring and continuous measurement of blood pressure and heart rate is performed. In case of an emergency, medications, venous line, defibrillator and equipment for cardiopulmonary resuscitation are available.

4. Head Up Tilt Test Protocol

A record of heart rate (HR) and blood pressure (BP) and of symptoms reported by the patient is kept every 5 minutes. Any important incident is noted and recorded at any time. The sublingual nitroglycerin protocol is based on Del Rosso [1].

Time line: Initial questioning (15 minutes)/Monitoring installation (digital cuff to measure BP and continuous electrocardiogram) (10 minutes)/Basal HUT (horizontal) for 10 minutes/Passive HUT (standing at 70˚) 45 minutes/active HUT with 0.3 mg of sublingual trinitrin (without laying the patient down) for 10 minutes/Final recovery lying down (6 minutes) Total HUT: 55 minutes. Approximate total time: 90 minutes.

Carotid massage is performed on all patients over 60 years of age. Previous discard of murmur or carotid stenosis or stroke in the last 6 months. Five minutes on each side [2] [3] [4].

Tilt Test ends, if a "positive HUT" is obtained: This is if syncope (loss of consciousness) or presyncope occurs (dizziness, nausea, paleness, etc., announcing that syncope is imminent). Associated with low blood pressure (systolic BP < 70 mmHg) or low blood pressure plus bradycardia, or if intolerable patient discomfort occurs.

If there are no symptoms, HUT is terminated due to the end of the protocol.

In addition, sympathetic and parasympathetic function tests (Valsalva maneuver and deep breathing test) are performed in order to support or rule out failure in the baroreflexes.

The equipment consists of: Digital monitor (Ohmeda 2300 Finapres BP Monitor USA). Digital cuff placed on the index or middle finger to measure BP and HR continuously. Electric tilting table (Magnetic Manumed USA) and electrocardiogram monitor (Quinton Q4500 USA). The patient is fastened to the table with two velcro straps (knees and chest).

For the statistical comparison, Anova and logistic regression are used, and depending on the sample size, a non-parametric test is used.

5. Results

The age (at the moment of HUT) and sex of cases and controls can be seen in Table 1.

In Table 2 we can see the number of patients, number of syncopes and the time between the episodes.

Table 3 shows the result of the Tilt test in 300 cases.

All volunteers presented a negative HUT.

We found some factors that are linked to syncope in these patients. These are: heredity, joint hypermobility, venous congestion during HUT, food intake, drug use, emotional stress, and pain.

Joint hypermobility ("ligamentous hypermobility")

We found a very important prevalence (192/300) (64%) of joint hypermobility in our patients (score 5 or ≥ on the "Beighton Scale") [5] [6] [7].

113 (37.5%) of our patients had a family history of syncopes in first degree relatives, of whom 70% have joint hypermobility.

Forty-three percent (83 cases) of our hypermobile patients reported that syncope occurred or increased during a period of strong emotional stress, and then at the end of this period the syncope eased.

Of the healthy volunteers, only 2.5% ($p < 0.02$) had a joint hypermobility score 5 or ≥ on the "Beighton Scale".

Table 1. Average age and sex of cases and controls.

	Cases			Controls		
	Male	Female	Total	Male	Female	Total
% patients	44% (n = 132)	56% (n = 168)	300	45% (n = 54)	55% (n = 66)	120
Average age (years)	33.7	33.6	33.4	37.6	36.5	37.0

Table 2. Patients with syncope. Number of patients, number of syncopes and time between episodes.

N° of Syncopes	1	2	3	4	5	Total
N° of cases	102	72	57	49	20	300
Range of time	Unique	2 months to 20 years	3 months to 10 years	2 months to 30 years	6 months to 15 years	2 months to 30 years
Average years between episodes	-	5.3 years	4.7 years	5.4 years	6.6 years	5.5 years

Table 3. Tilt table test results in 300 cases.

HUT Results	N	%
Vasodepresor syncope	144	48%
Orthostatic hypotension	72	24%
Mixed syncope	66	22%
Cardioinhibitory	18	6%
Total	300	100%

Orthostatic intolerance due to prolonged standing

22% of patients (66 cases) reported that their symptoms were precipitated by 20 to 30 minutes of standing, thus they avoided prolonged standing such as queuing or ceremonies of any kind.

In 80% of these 66 patients prolonged standing during HUT induced syncope or severe orthostatic hypotension. This forced us to return the patient in recumbent position.

In these patients we found associated factors such as heredity (72%), joint hypermobility (76%) and increased venous pooling in standing position (82%).

In healthy controls, prolonged standing causes discomfort in the legs and sometimes plantar pain. But dizziness or syncope did not occur.

Fear, emotional stress and pain

It is common for patients examined after one or several syncopes to indicate that fear, pain or emotional stress coincide with the period of their syncope or lipothymia. And without the presence of these factors, syncope does not occur. [8] [9] [10] [11]. The frequency of these associated emotional factors is in our cases (185/300) = 61.5%. After the stress period is over, the syncopes disappear.

Of these patients, 43% were hypermobile, 25% had a family history of syncope, and 47% had large venous pooling in the lower extremities.

Of the healthy volunteers, 22 (18%) recalled having gone through intense periods of emotional stress during the last year. This period manifests in insomnia, headache, irritability or discouragement but not with the presence of syncopes or lipothymia ($p < 0.02$).

Regarding emotion or pain as syncope triggers, we found different types of patients: Some of them with sudden pain or emotions (for example, a hit, getting vaccinated or fear), and others with subacute emotions installed for several weeks (for example work or academic stress) and others with both conditions (n: 22 cases).

1) Sudden emotion or pain: 119 cases

a) Acute pain; b) Bleeding; c) Acute fear; d) Taking a blood sample or injections.

2) Subacute distress, emotion or stress overload: 44 cases

a) Concerns (financial or family stress); b) Work or study overload; c) Loss of a relative or divorce; d) Personal diseases.

In **Table 4** we see types of stressful or emotional factors acute and subacute associated with syncope.

Heredity

A family history of syncopes in first degree relatives of syncope is frequent [12] [13] [14] [15].

In 113 of our patients we found a history of syncope in first degree relatives (37.5% frequency).

In these patients, we found an association between heredity with emotional factors (pain, fear or stress) as a trigger for syncope (29/113): 26%.

Table 4. Types of stressful or emotional factors acute and subacute associated with syncope.

Acute event (n: 119)	Female (n)	Male (n)	Age of onset	Total (n)
Sudden fear	11	4	15 - 18	15
Hit or Pain	13	22	12 - 20	35
Blood sample or Injection	45	24	12 - 18	69
Subacute event (n: 44)	**Female (n)**	**Male (n)**	**Age of onset**	**Total (n)**
Work/Study overload	28	7	17 - 22	35
Loss of a relative or divorce	2	5	35 - 51	7
Personal illnesses	0	2	48 - 52	2

Of the healthy volunteers, only 0.8% ($p < 0.02$) recalled having had a family member with syncope.

Venous congestion ("pooling") in the lower extremities due to prolonged standing

We observed a relationship between the accumulation of "venous pool" in the passive phase of HUT and syncope. Venous congestion was measured by visual observation of the color and congestion in lower extremities and feet with a score ranging from 1 to 5.

1 = nothing (little or no change in color of feet), 2 = mild (pinkish feet), 3 = moderate (reddish feet), 4 = severe (dark reddish feet) and 5 = very severe (acrocyanosis and purple feet).

216 of 300 patients (72%), had, severe or very severe (score 4 or 5) venous congestion during passive HUT. From these 140 patients (65%) presented syncope or lipothymia during HUT. In contrast, only 28 patients with no venous congestion or only in a mild degree (score 1 or 2), had a positive HUT (9%) ($p \leq 0.02$).

Venous pooling found in our patients was closely linked to orthostatic intolerance (76%), prolonged standing (83%), ligamentous hypermobility (68%), postprandial syncope (78%) and a hereditary history of syncope (58%).

In the 120 healthy controls we found only 18 patients (15%) with significant venous congestion (score 4 or 5) ($p < 0.02$). In the rest (85%) the venous congestion was moderate or little.

Syncope during military standing formation

Thirty-three of our patients (11%) consulted for syncope during prolonged standing in a military formation (45 - 60 minutes). All were under 25 years of age (x: 22.5). 70% were hypermobile (≥5 Beighton scale), 66% had a family history of syncope and 69% had severe or very severe venous congestion in the lower extremities during the passive HUT.

None of the healthy controls, had syncopes during military standing formation ($p < 0.02$).

Post-prandial syncope, heavy food, or gastric discomfort

Twenty-six patients suffered from postprandial syncope (8.6%). Their syncopes were not related to hypermobility, heredity or emotional stress. Their age was on average older than most of the other patients (age X: 64 years). Their venous congestion score was 4 - 5 on our visual scale.

These patients suffered from diseases such as: supine hypertension in 84%, orthostatic hypotension in 70%, diabetes in 38%, hypercholesterolemia in 27%, obstructive apnea in 11.5%, autonomic cardiovascular neuropathy in 19%, Parkinson's Disease in 6%, and multiple systemic atrophy in 1%.

Three patients started with post-prandial syncope after bariatric surgery and abdominal distension. Phenomenon that is known, but not yet be well explained [16].

None of the healthy controls suffered from postprandial syncopes ($p < 0.02$).

Use of prescription drug

In 10% of our cases (30/300), the effect of drugs was considered essential for the occurrence of syncope. These were mostly medications introduced before syncope started, or recently increased doses. Its subsequent removal or reduction resulted in relief of fainting.

The drugs alone or in combination, most associated with syncope due to orthostatic hypotension were: atenolol, carvedilol, valsartan, losartan, enalapril. Also some antidepressants with action in the CNS: venlafaxine, trazodone, sertraline or amitriptyline combined with each other or with hypotensive drugs.

The associated factors that we found linked with the drugs mentioned above in patients with syncope were: venous pooling in prolonged standing 85%, age ≥ 60 years 80%, orthostatic hypotension 50%, cardiovascular autonomic neuropathy 10% and postprandial syncope 6%. There were no cases associated to: heredity, joint hypermobility or emotional stress.

Twelve of the healthy controls (10%), consumed hypotensive drugs, but none suffered from syncopes ($p < 0.02$).

Dehydration and fasting

This combination occurred in 29 patients (9.6%) during a military campaign, with great environmental heat, under fasting conditions, without drinking fluids for 12 hours. It was the only syncope in their life. All cases had ≥5 in Beighton's scale of hypermobility. Twenty of them had a family history of vasovagal syncope.

Four of the healthy (militar staff) controls (3.3%) campaigned, fasted, without drinking fluids for 12 hours, but none fainted ($p < 0.02$).

Central and peripheral nervous system diseases

Four patients were type 2 diabetic with more of 35 years of evolution with severe autonomic and distal diabetic neuropathy. All four are consulted after one single syncope (age X: 79 years).

Other 3 patients had Parkinson's disease and orthostatic intolerance. They consulted after having four or five syncopal episodes (age X: 77 years).

In these 7 patients, syncope in HUT was preceded by severe orthostatic hypo-

tension.

None of these 7 patients was hypermobile, nor did they have relatives with syncope.

In 3 of them certain hypotensive agents were suspected as adjuvants of syncope: enalapril alone or in combination with diuretics, trazodone or amlodipine, losartan alone or in combination with amlodipine or atenolol or with diuretics.

None of the healthy controls suffered from central or peripheral neurological diseases.

A summary of the predisposing factors to present syncope can be seen in **Table 5**.

6. Discussion

Heredity

Family history of syncope is described in 19% - 90% of first-degree relatives of patients with syncope [12] [13] [14] [15]. In our sample, this relationship was 37.5%.

The existence of vasovagal syncope shows a much higher concordance in monozygotic twins than in dizygotic twins [15]. So heredity is clearly an organic predisposition to syncope. [12] [13] [14]. The association between heredity and syncope in our sample is remarkably clear. So for us having first degree relatives with vasovagal syncope is an important risk factor for fainting when an environmental cause is added.

Hypermobility and venous pooling in lower extremities

Hypermobile people have a higher proportion of type III collagen, which is more elastic. Their veins accumulate more venous pooling when standing up [17] [18]. Giving the conditions to trigger a syncope by systemic hypotension and cerebral circulatory deficit [5] [17] [18].

Table 5. Frequency of factors predisposing to syncope in patients versus controls.

Predisposing factors	Patients		Controls	
Heredity	n: 113	37.5%	n: 1	0.8%
Joint hypermobility	n: 192	64%	n: 3	2.5%
Severe venous pooling	n: 216	64%	n: 18	15%
Emotional stress and pain	n: 185	61.5%	n: 22	18%
Drug treatment	n: 30	10%	n: 12	10%
Postprandial syncope	n: 26	8.6%	n: 0	0%
Fasting/ Dehydration	n: 29	9.6%	n: 4	3.3%
Neurological diseases	n: 7	2.3%	n: 0	0%
Prolonged standing	n: 18	6.0%	n: 0	0%
Military standing formation	n: 33	11%	n: 0	0%

We observed an increased venous pooling linked to orthostatic intolerance, prolonged standing, joint hypermobility, postprandial syncope and a hereditary history of syncope. Of our patients with severe or very severe venous congestion (grade 4 or 5), 63% had an intense degree of joint hypermobility ≥ 5 ($p \leq 0.02$).

The presence of joint hypermobility and the occurrence of lipothymia or vasovagal syncope is clearly linked [5] [6] [7], and even with POTS (postural orthostatic tachycardia syndrome) [5] [19] [20] [21].

Prolonged standing

Standing for long time causes blood retention in the veins of the abdomen, pelvis and lower extremities thus producing a decrease in venous return and orthostatic intolerance [16] and this is worse in hypermobile people.

Venous pooling was very clear in our patients during prolonged military standing formation or those who participate in standing ceremonies or queuing. [16].

Some articles support the use of compression stockings to reduce or eliminate venous congestion of the lower extremities [17] [18].

Emotional Stress, pain and fear

Fear, pain, stress and emotion have always been associated with vagal syncope [9] [11].

A higher frequency of recurrent vagal syncope has been found in depression, panic attacks, emotional stress, generalized anxiety and somatization disorders [8] [9] [10] [11].

Syncope improves, as the emotional state improves, or worsens when the opposite occurs [8].

The presence of pain, emotion, or fear as a trigger for syncope in our patients was associated with factors such as joint hyperlaxity, a family history of syncope and severe venous pooling in the lower extremities.

Post-prandial syncope, heavy food, or gastric discomfort

Failure of the baroreflexes is capable of producing hypotension and postprandial syncope. This is most commonly seen in older adults, parkinsonians, diabetics, hypertensive, and dialysis patients [22] [23] [24] [25].

In our experience these patients were not related to hypermobility, heredity or emotional stress. Their age was older than 60 years old and their venous standing congestion score was high (4 - 5 on our visual scale).

Syncope in them was mainly associated with orthostatic hypotension (87% late hypotension vs 13% early) and of course associated to prolonged standing (82%).

These patients suffered from infrequent diseases in other syncopal patients: Supine hypertension, orthostatic hypotension, Diabetes mellitus, hypercholesterolemia, obstructive apnea, autonomic cardiovascular neuropathy, Parkinson's Disease, and multiple systemic atrophy [23] [24] [25] [26].

Postprandial orthostatic hypotension occurs even in patients being treated for arterial supine hypertension [27] [28].

Syncope during military standing formation and **excessive venous pooling in the lower extremities**

Patients that consulted for syncope during prolonged standing military formation were mainly hypermobile, had a family history of syncope and had severe or very severe venous congestion in the lower extremities during the passive HUT.

Excessive venous pooling in prolonged standing is closely linked to orthostatic intolerance, joint hypermobility, and hereditary history of syncope [29] [30].

Use of prescription medications

Medications such as antihypertensive, diuretics, nitrates, beta-blockers, antidepressants, antipsychotics can predispose to the appearance of syncopes. This is worse in older adults, this group present more frequently alterations in the baroreflexes [31] [32].

We observe that the hypotensive action of these drugs in our study is aggravated by factors such as: venous pooling in long standing position, age ≥ 60 years, SNC diseases (ex. Parkinson), peripheral neuropathy, cardiovascular or diabetic autonomic neuropathy, cardiovascular diseases, postprandial hypotension and patients with polypharmacy [24] [32].

Fasting and dehydration

In certain persons fasting and hypoglycemia can be added to hypotension in the production of vagal syncope [33] [34].

In young women, a greater sensitivity to insulin has been seen. Their fasting glycemia tends to be lower than in controls, and they more frequently have a positive vasovagal reaction and even a positive HUT if they are fasting. [33] [34].

All these patients (n: 29) were hypermobile and 20 of them had a family history of vasovagal syncope.

Chronic diseases of CNS o PNS

Chronic diseases that affect circulatory regulation in the central and/or peripheral nervous system such as Parkinson's, Multiple Systemic Atrophy (MSA) and Diabetes mellitus, damage severely the autonomic baroreflexes and it is very likely that these patients will present many syncopes and falls during their life [35] [36] [37] [38].

In these patients, during HUT syncope was preceded by severe orthostatic hypotension (early or late hypotension). They were not hypermobile patients, nor did they have a family history of syncope. In them, the frequent use of hypotensive drugs is observed, as adjuvants of the syncopal picture (43%).

7. Study Limitations

First: It is difficult to obtain statistically valid conclusions due to the small number of patients studied in our sample. We understand that a greater sample is necessary in the future.

Second: We depend on the good memory of the patients or their relatives to recall their first syncopal episode or the total number of syncopes. In some cases,

the patient, after a second interrogation, remembers having suffered episodes during childhood or adolescence.

Third: Altough an exhaustive interrogation and pre-HUT exams, it is not always possible to completely rule out causes other than vagal syncope, such as drowsiness, vertigo, orthostatic dizziness or accidental falls.

Fourth: Despite follow-up and complementary examinations, there were 4 patients (1.3%), in whom we find only one factor that made them prone to syncope. In these four cases, syncope occurred only once. Therefore, it is difficult for us to attribute their case to a minimal dysautonomia or perhaps it was just a casual and unique syncope, unrelated to a dysautonomic propensity.

Fifth: Our visual scale, used to assess venous congestion of the lower extremities, is not yet internationally validated. It was our creation, documented with photos and statistically closely related [29] [30] to prolonged standing and joint hypermobility, but not yet validated.

8. Summary

People who suffer a single or very occasionally syncope during their life have a constitutional/organic predisposition to have a vagal syncope.

But syncopes do not occur unless an environmental factor appears (potentially manageable) unbalancing the circulatory balance. So these patients lead a normal life for many years, and their syncope occurs very infrequently (minimal dysautonomia).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Bicuspid Aortic Valve Disease in Turner Syndrome: A Meta-Analysis of Prevalence

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Abstract

Turner syndrome patients partially or completely lack the X chromosome. 1 - 2500 female live births are affected. Clinical features include webbed neck, short stature, broad chest etc. Bicuspid aortic valve disease (BAV) occurs in more than 30% of Turner syndrome patients causing significant morbidity and mortality. We aimed to establish a more reliable estimate of the prevalence of BAV in Turner syndrome. PubMed, Embase and PsycINFO databases were searched until 2022. Review Manager (RevMan 5.4.1) and the JASP software (0.16.00) were used for meta-analysis. 15 studies with a total of 3189 patients were combined. The pooled prevalence of BAV in Turner syndrome was 22.0% (95% CI: 15.0% - 29.0%). Sub group analysis by 45, X0 karyotype and age had prevalence of 24.0% and 8% respectively. The studies had high heterogeneity and possible publication biases. In summary, the study established that the prevalence of BAV in Turner syndrome patients diagnosed by echocardiogram, CT and MRI scans, is 22.0%, and 24% in patients with true monosomy 45, X0 karyotypes. Routine BAV exam should pay particular attention to monosomy 45, X0 karyotype patients, and where possible, CT and MRI should always accompany echocardiography for BAV screening, especially for pediatrics.

Keywords

Bicuspid Aortic Valve, Turner Syndrome, Meta-Analysis, Prevalence

1. Introduction

Turner syndrome is a genetic anomaly in which an individual partially or completely lacks the X chromosome [1]. It occurs in about 1 - 2500 female live births [2], and physically presents with clinical features such as a webbed neck, short

stature, cubitus valgus, a broad chest, gonadal dysgenesis, and late puberty [3]. Close to 50% of Turner syndrome patients develop congenitally or acquired cardiovascular complications causing significant morbidity and mortality [4], among them are aortic coarctation, elongated transverse aorta, partial anomalous pulmonary venous return, and bicuspid aortic valves [5].

Bicuspid aortic valve disease (BAV) is a congenital heart defect in which the aorta has only two instead of the usual three valve leaflets [6]. BAV is a clinical feature of more than 30% of Turner syndrome patients [7]. It's often asymptomatic in the general population and only discovered on routine medical check-ups [8]. However, in Turner syndrome, the co-occurrence of other heart defects such as aortic coarctation exacerbates the condition resulting in aortic dilation and dissection of the aorta which is fatal [9].

The close association between Turner syndrome and BAV warrants a regular cardiovascular assessment of all Turner syndrome patients to ensure early and prompt interventions, and so, knowing the prevalence of BAV in Turner syndrome patients facilitates planning this assessment process. Various studies have reported the prevalence of BAV in Turner syndrome, and one meta-analysis provided a summarized estimate, albeit with few studies combined and small sample size [10]. In this meta-analysis, we provide a more comprehensive and reliable pooled prevalence estimate of BAV in Turner syndrome and attempt to establish prevalence in sub populations of Turner syndrome such as the pure monosomy 45, X0 karyotypes and pediatric patients.

2. Materials and Methods

2.1. Search Strategies

Three reviewers independently searched PubMed, Embase, and PsycINFO databases for relevant studies on the prevalence of BAV in Turner syndrome patients. The customized search strategies for PubMed were #1. ("Prevalence" [MeSH Terms]) OR ("Occurrence" [All Fields]) OR ("Prevalence" [Title/ Abstract]) OR ("Presence of" [All Fields]), #2. ("Bicuspid aortic valve" [MeSH Terms]) OR ("Bicuspid aortic valve disease" [Title/Abstract]) OR ("BAV" [All Fields]) OR ("Bicuspid valve" [Title/Abstract]) OR ("Bicuspid aorta valve" [Title/Abstract]), #3. ("Turner syndrome patients" [MeSH Terms]) OR ("Turner syndrome" [Title/Abstract]) OR ("Turner disease" [Title/Abstract]) OR ("TS" [Title/Abstract]), #4. #1 and #2 and # 3, while those for Embase and PsycINFO were: #1. (Prevalence/exp) OR (Occurrence .ab,ti.) OR (prevalence.af.) OR (presence of .ab,ti.), #2. (Bicuspid aortic valve/exp) or ("Bicuspid aortic valve disease" .ab,ti.) OR ("Bicuspid aorta" .ab,ti.), #3. (Turner syndrome/exp) OR (Turner syndrome disorder .ab,ti.), #4. #1 and #2 and # 3.

The databases were searched in July 2021, then updated in December 2021 and February 2022. The studies were then exported into Endnote software (version 9) for cleaning, and duplicates removed. Studies from the initial search were rejected immediately if the title or abstract did not report prevalence or inci-

dence of bicuspid aortic valve disease in Turner syndrome patients. Full texts were then extracted for the remaining articles and analyzed. Manual search of all the references of the full text articles were done. Disagreements that arose during the search were all settled by consensus. Extraction of information was carried out according to the Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [11].

2.2. Inclusion and Exclusion Criteria

Relevant studies that were selected for inclusion had to meet the following criteria: 1) Assessed the prevalence of bicuspid aortic valve disease in patients with Turner syndrome; 2) BAV diagnosis was conducted using TTE or TEE or CT or MRI; 3) Had enough raw data to calculate prevalence of BAV in Turner syndrome if not already reported. Studies were excluded from the analysis if they were: case reports or case series, reviews or meta-analyses, conference abstracts or papers, did not assess the prevalence of bicuspid aortic valve disease in Turner syndrome patients, and was not published in a peer review journal.

2.3. Quality Assessment of the Studies

Three authors independently evaluated the methodological qualities of the selected studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross sectional studies [12]. Interrater reliability above 80% were considered acceptable, and all disagreements were resolved by consensus. The filled checklist is provided as supplementary materials 1. The JBI checklist assesses studies on nine critical areas that include: sample frame appropriateness, sampling technique, and sample size among others.

2.4. Data Extraction

A data extraction questionnaire was created and relevant data extracted from the included studies. Data extracted included: Name of first author, year of publication, country of the study, diagnostic tool for bicuspid aortic valve disease, summary of participants' age, number of events (BAV), total number of participants, prevalence of BAV and its calculated standard error and Turner syndrome karyotypes.

2.5. Statistical Analysis

The prevalence of BAV disease was determined as number of BAV cases over total number of Turner syndrome patents x100. Standard Error (SE) was calculated for studies that did not report them, using the prevalence data and the formula: SE = Sqrt of $p\,(1 - p)/n$, while the 95% confidence interval (CI) = $p \pm 1.96 \times \mathrm{SE}$; where, p = Prevalence. The data were combined using Review Manger (RevMan 5.4.1) and the JASP software (0.16.00). Heterogeneity was assessed using Chi-square test, and the I^2 test. Random effect model was used to pool the results. Possible publication bias was assessed by visual inspection of a funnel

plot and the Egger's test.

3. Result

Preliminary searches yielded 901 records altogether. No additional records were found from other sources. 812 of the studies were from PubMed, 83 from Embase and 6 from PsycINFO databases. Following removal of duplicates, 778 studies were left and their titles and abstracts screened for eligibility. 749 studies were then excluded and eventually 29 qualified for full text screening. Here, 14 studies were omitted; 5 did not report prevalence of BAV in Turner syndrome patients and didn't have the required raw data to manually do so, 7 were abstracts only or conference presentations and 2 were letters to the editor. Altogether, 15 studies [13]-[27] ranging from 2010 to 2020 and containing 3189 Turner syndrome patients were enrolled for meta-analysis (Table 1). The study selection and eligibility flowchart is presented in Figure 1. Among them 4 were conducted in the US, 2 from Turkey, 2 from the Netherlands, 2 from Poland and 1 each from France, Ukraine, France, Canada and Taiwan.

Table 1. Characteristics of included studies.

Author ID	Area of study	Diagnostic tool	Mean/median age of patients (Years)	Number of events (BAV)	Total number of participants (N)	Prevalence of BAV (%)	SE
Chou *et al.* 2019	Taiwan	Echo, CT, MRI	22.5 ± 5.7	6	88	6.8	0.0268
Donadille *et al.* 2012	France	Echo, MRI	25.6 (19.6 - 34.2)[1]	49	233	21.03	0.0353
Olivieri *et al.* 2013	USA	Echo, MRI	32.9 ± 15.5	47	208	22.6	0.0289
Yesilkaya *et al.* 2015	Turkey	Echo	0 - 18[3]	61	719	8.5	0.01
Bondy *et al.* 2013	USA	MRI	18.1 ± 1	57	185	31.0	0.034
Klaskova *et al.* 2017	Poland	MRI	14.0 (6.6 - 32.5)[2]	19	67	28.3	0.055
Mondal *et al.* 2020	India	Echo	14.8 ± 3.97	6	103	5.8	0.023
Yetman *et al.* 2018	USA	Echo	31.7 ± 12.6	226	569	39.7	0.02
Kim *et al.* 2010	USA	MRI	18.4 ± 6.9	20	51	39.2	0.068
Zelinska *et al.* 2018	Ukraine	Echo	9.33 ± 4.93	11	538	2.04	0.0061
Yigit *et al.* 2017	Turkey	MRI	14.3 ± 3.5	9	47	19.1	0.0573
Obara-Moszynska *et al.* 2018	Poland	MRI, Echo	13.9 ± 2.2	16	39	41.0	0.076
Duijnhouwer *et al.* 2018	Netherlands	MRI, CT	28.7 (21.3 - 39.7)[1]	59	268	22.0	0.0253
Bons *et al.* 2018	Netherlands	CT	35 ± 13	12	50	24.0	0.06
Somerville *et al.* 2016	Canada	MRI	13.3 (9.0 - 17.9)[2]	9	24	37.5	0.0988

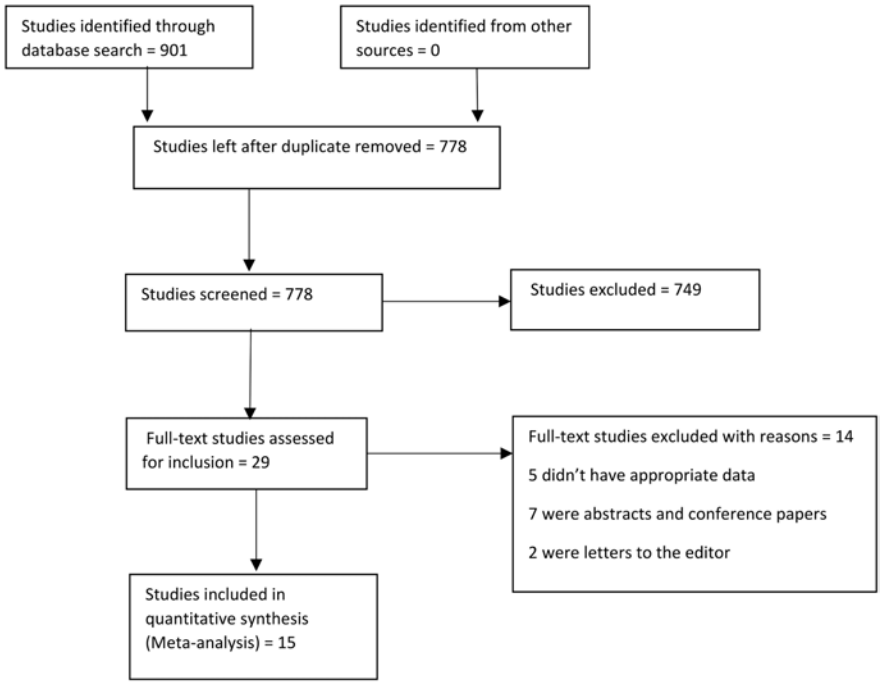

Figure 1. Study selection flowchart.

From among the included studies, the prevalence of Bicuspid Aortic Valve disease (BAV) among Turner syndrome patients was between 2.04% to 41.0%. The pooled prevalence after meta-analysis was 22.0% [95% CI: 15.0% - 29.0%], (**Figure 2**). Studies varied widely as indicated by the high level of heterogeneity, I^2 = 97% (P < 0.00001). Possible publication bias was determined by visual inspection of a funnel plot (**Figure 3**), and an Egger's test conducted (**Table 2**). Four studies determined the prevalence of BAV by Turner syndrome karyotype. Monosomy 45x karyotype had the most frequent cases of BAV compared to others. A subgroup analysis of the four studies conducted by Turner syndrome karyotype showed a pooled prevalence of 24.0% [95% CI: 9.0% - 39.0%] among the Monosomy 45x patients (**Figure 4**). Similarly, three studies explicitly studied BAV among children with Turner syndrome aged 0 to 18 years. Pooled prevalence in these studies was 8.0% [95% CI: 2% - 15%] (**Figure 5**).

4. Discussion

In this study, we have provided a summary estimate of the prevalence of Bicuspid aortic valve disease (BAV) in Turner syndrome patients. We have pooled published studies up to 2022, without any time constraints, as a result, our study had a combined total of 3189 patients, adequately powering the study. This is a comprehensive assessment of studies conducted on BAV in Turner syndrome patients, hence giving a more robust and reliable estimate of the prevalence of BAV in Turner syndrome. In addition, we were able to conduct subgroup analyses for age and Turner syndrome karyotypes to account for the heterogeneity that existed among the individual studies. Our pooled prevalence indicates that

close to a quarter of Turner syndrome patients (22%) develop BAV, while the prevalence were 24.0% and 8% for 45, X0 karyotype, and pediatrics respectively.

This result is comparable to a similar study conducted by Li *et al.* [10], who found a prevalence of 23.7%. Unlike their study however, ours is more comprehensive and highly powered; with a sample size three times theirs. This makes our study more robust and reliable. Furthermore, unlike theirs, our study evaluated prevalence of BAV in Tuner syndrome patients with 45, X0 karyotype (being the most common karyotype), and among pediatrics, since BAV is a congenital disease.

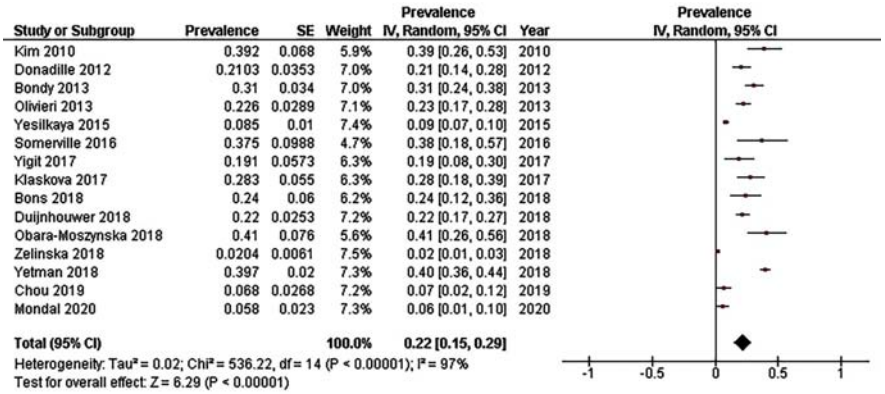

Figure 2. Forest plot of the pooled prevalence of BAV in Turner syndrome patients.

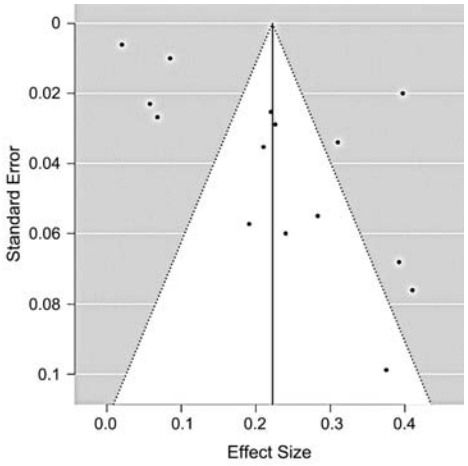

Figure 3. Funnel plot indicting possible publication bias shown by the lack of symmetry.

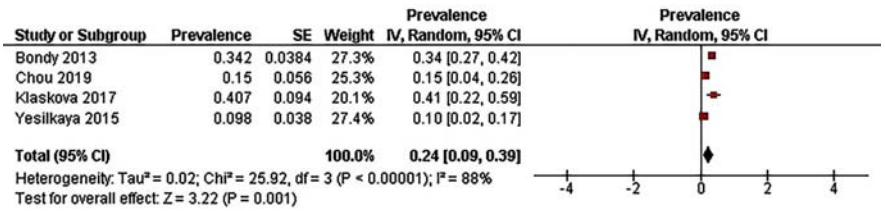

Figure 4. Forest plot showing prevalence of BAV in true monosomy 45, X0 Turner syndrome patients.

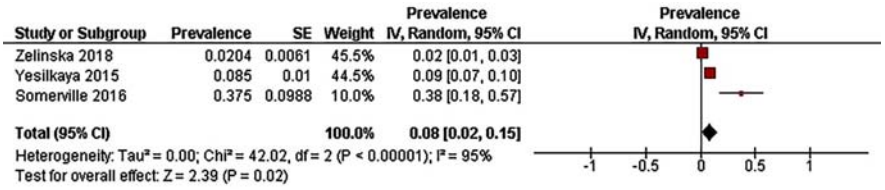

Figure 5. Forest plot of prevalence of BAV in pediatric Turner syndrome patient.

Table 2. Regression test for Funnel plot asymmetry ("Egger's test").

	z	p
sei	2.926	0.003

The possible association between Turner syndrome and cardiovascular defects including BAV has been demonstrated by a number of studies [13]-[28], as a result, vasculopathy is often seen as one of the defining features of Turner syndrome [29]. Cardiovascular complications are of particular concern to Turner syndrome patients because factors that promote cardiovascular diseases such as obesity, hyperlipidemias, atherosclerosis etc. are also quite common among Turner syndrome patients [30]. Malformation of the aortic valve is manifested in changes to the way blood flows in the ascending aorta, and is one of the causes of aortic dilation and dissection [31]. Our findings—showing that close to 1 in 4 Turner syndrome patients had BAV—reinforces the 2016 recommendation by Gravholt *et al.* [28], that all Turner syndrome patients should be routinely examined for BAV. However, in the course of this routine examination, emphasis should be put on 45, X0 karyotype patients, since by our results, they seem to have a higher prevalence of BAV than the other karyotypes. Other cardiovascular defects associated with BAV and Turner syndrome that should be equally checked include; aortic coarctation, elongated transverse aorta, and partial anomalous pulmonary venous connection [21].

Despite the frequent presence of mosaicism among Turner syndrome karyotypes, true monosomy X having the 45, X0 still accounts for an estimated 40% - 50% of all cases [32]. In our analysis, the pooled prevalence of BAV among the 45X, X0 karyotype (24%) was just slightly above that of the general Turner syndrome population. This however, was an estimate from only four of the studies that had data for the association. We therefore think the true estimate could be much higher if more studies had data on this association. BAV is a congenital heart defect that is often asymptomatic in the general population, sometimes until adulthood [8]. This is not the case with Turner syndrome where the risk developing symptomatic BAV right from childhood is exacerbated by other associated cardiovascular complications. Our pooled prevalence of BAV in pediatric Turner syndrome patients was 8% from three studies. Much as echocardiography is the diagnostic tool of choice in BAV, it is not entirely sensitive enough and may miss cases especially in children. Bondy *et al.* and the Turner syndrome study group advised that Cardiac Magnetic Resonance Imaging (CMR) be done

for all pediatric patients who can be imaged without sedation whose Echocardiogram results are negative [33]. Similar remarks form a study conducted specifically in pediatric subjects by Somerville *et al.*, reaffirmed this suggestion as CMR was able to detect BAV cases that were missed by Echocardiogram [27].

Limitations

Being mostly retrospective cross sectional studies, we could not rule out potential biases among the individual studies. In fact both the funnel plot and Egger's test conducted showed possible publication biases. Secondly, the studies were quite heterogeneous hence somehow affecting generalization of the result. Lastly, most of the studies did not evaluate BAV prevalence by Turner syndrome karyotype, and so the sub group analysis by karyotype should be interpreted with caution.

5. Conclusion

In summary, this study found that the prevalence of BAV in patients with Turner syndrome is 22% and that by karyotype, 24% of true monosomy 45, X0 develop BAV, while 8% of pediatric patients develop the complication. With a sample size of 3189, this is a more reliable estimate of the prevalence of BAV in Turner syndrome patients. Given that 1 in 4 Turner syndrome patient is likely to have BAV according to this result, and that true monosomy 45, X0 karyotypes seem to have a higher prevalence than the rest, particular attention should be put on patients with true monosomy 45, X0 karyotypes in the course of routine screening for BAV and other cardiovascular diseases in Turner syndrome patients. Lastly, where possible, CT and MRI should always accompany echocardiography for BAV screening, especially in pediatric patients.

Author Contributions

"Conceptualization: Erick Thokerunga; methodology: Erick Thokerunga; software: Erick Thokerunga; validation: Erick Thokerunga; formal analysis: Erick Thokerunga and Yahya-Abdullahi Ali; data curation: Yahya-Abdullahi Ali and Erick Thokerunga; writing-original draft preparation: Erick Thokerunga; writing-review and editing: Yahya-Abdullahi Ali and Christopher Ntege; supervision: Christopher Ntege; funding acquisition: Christopher Ntege. All authors have read and agreed to the published version of the manuscript".

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supportive and Palliative Care in Cancer Therapies—Path from Tumor-Driven Therapies to Patient-Driven Ones

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Abstract

Cancer patients frequently report a set of symptoms including fatigue, pain, and physiological and social distress. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices. Medical professionals have a responsibility to clear this field and concentrate on patients' well-being and personal needs. According to our approach, the integration of supportive and palliative care with conventional therapies needs a change of paradigm from tumour-driven to patient-driven treatment actions. Supportive/palliative care includes a broad spectrum of applied methods, including medications, nourishments, electrical effects, and psycho and social supports. Our goal is to discuss the possibilities for combining conventional oncotherapies with additional supportive/palliative care and to give suggestions on a professional basis.

Keywords

Cancer, Vitamins, Minerals, Fungi, Immune, Phytomedicine, Complexity, Electric-Stimuli, Hyperthermia, mEHT

1. Background

Cancer patients frequently report a complex syndrome of the disease, a set of symptoms including fatigue, pain, and physiological and social distresses. Families and other personal lay relations give proposals to take supportive drugs and supplemental nutrients, without professional knowledge about their actions. Internet search engines and social networks serve up most of the treatment proposals, opening wide possibilities for quackeries and predatory money-making practices.

The application of supportive and supplemental drugs for cancer patients is a hot topic not only in the relevant professional literature, but also in patients' self-help groups and traditionally formed societies, and among patients' family members who would like to help their ill relatives. Supportive care (SC) is a general category of attention regarding the patient throughout the complete course of cancer treatment, involving self-help support, information exchange, physiological and psychological support, symptom control, social support, rehabilitation, complementary therapies, spiritual support, palliative care, and end-of-life care too [1]. SC could be provided at all stages and on all pathways of cancer treatment from the established diagnosis and therapy process onward. SC is a necessary condition for accurate cancer treatment, and, of course, SC is very personalized. Due to the absence of a standard protocol of SC it has a risk of non-reproducibility, so even the best supportive care (BSC) cannot be simply adopted as a reference for any clinical trial [2]. SC is focused on the well-being of the patient, improving the quality of life (QoL) and decreasing adverse effects of ongoing treatments or preparing conditions for planned therapy.

The growing incidence of malignancies drives the cancer therapy market. Cooperation in academic research, mergers in the pharmaceutical industry, and the gradual harmonization of the activities of various organizations make the field of supportive therapies massively influential in the global market [3]. An estimated 16.9 million cancer survivors were registered in the United States on the 1st of January 2019 [4]. Due to increasing survival rates a huge number, 22.1 million patients, are estimated for the 1st of January 2030 [4]. Two thirds of cancer survivors (67%) have 5+ years of overall survival, and 18% were diagnosed 20+ years ago, and also nearly 2/3 of cancer patients are 65+ years old [4], so the demand for SC is massively growing with these numbers. Consequently, many uncontrolled patient's practices of SC (pSC) grow rapidly, supported by massive advertising and "mouth propaganda".

The hopes and beliefs in traditional healing practices and pSC are supported by information reported about various spontaneous regressions. As early as the beginning of the last century, 185 spontaneous regressions were collected [5] and another collection of cases was published in the early 1960s: 202 cases were collected within four years [6], while 98 cases were also shown in the middle of that decade [7]. Many surprising spontaneous remissions were described in a monograph [8]. The literature on the spontaneous remission of cancer is impressive

[9] [10] [11] [12]. A large number of clinical cases have been collected to study the topic: 176 cases between 1900 and 1960 [13] [14]; 489 cases described from 1900 to 1987 [15], and a large meta-analysis was applied to about 1000 cases [16]. The topic was brought into focus again a few years ago by the "Armstrong effect" [17]. These published data give special (sometimes illusionary) hope to cancer patients and also to professionals. However, statistical evaluation is not possible on the sporadic facts, and pieces of weak evidence may give false hopes, supporting the belief that the patient often self-heals with the help of unprofessional healers.

The main realistic expectation of SC is the improving of the QoL, and by this progress the establishing of a condition of well-tolerated and elongated overall survival time too. Health professionals must pay more attention to patients' fear and complaints during therapy. Professionals have to offer appropriate SC, explaining the disadvantages of the uncontrolled intake of drugs in pSC, and clarifying the possible advantages of the regulation of diet and supplements by experts.

Nevertheless, the uncontrolled pSC became common in the self-care of cancer sufferers. Statistics show that a vast number of cancer patients use various herbal products without questioning the physician or nurse in connection with conventional cancer therapies [18]. Unfortunately, many of these intakes of additional drugs are not reported to the oncologist, though their interactions with chemotherapy could limit the benefit of the full therapy. The numbers are high: 81.7% of patients use herbs uncontrolledly during the various chemotherapies, and 94.3% of patients take herbs/vitamins before their surgery. The influence to use herbs intended to help with complaints concerning the conventional therapies came 39.8% from the media and 20% from internet searches, the patients' own physicians recommending of the applications in only about 1% of cases [16]. The results of another survey [19] also showed that patients having chemotherapy frequently use pSCs believing in their advantages. Some supplements are harmless, but many have interactions with the actual conventional therapy and could have significant disadvantages too. Almost one third (28%) of the patients were at risk due to the harmful interactions of pSC intake with the chemotherapy they received [20]. The vast use of pSC is based on various hopes and beliefs. The use of supplementary herbs or vitamins is rarely documented; frequently patients rely on their friends and naturopathic providers who are many times not in complete knowledge about the actual status of the patient his/her basic therapy. Despite the weak documentation and the small number of pieces of evidence, patients and their families massively request pSC, creating a not negligible demand for the doctors. This "grey zone" of treatment has to be investigated and a definite evidence-based approach established to put pSC in its place among the cancer therapies.

The patients in this way become easy targets of the misconceptions of unprofessional laypersons or, in more serious cases, they become the victims of quackeries, fake information, and harmful cheats. Frequently the leading causes of

imbalance in patient's decision-making are:

- a massive fear of the side-effects of conventional therapies;
- suffering from declining quality of life;
- the vast number of irresponsible advertisings by various information resources in society, including via modern information technology.

The high-level demand for supportive care of cancer patients in physiological and psychological help and in getting information about appropriate changes to make to their lifestyle is massively under-satisfied [21] [22]. The absence of an appropriate understanding of supportive care for cancer patients results in its under-utilisation in medical applications. The non-appropriate pSC accompanied with a lack of knowledge among healthcare professionals. Consequently, the sometimes inappropriate evaluations of physicians significantly limit the development of the cancer-supporting therapeutic industry and sometimes push disoriented patients to unproven, uncontrolled courses of treatment. Another unrecognised and uncontrolled source of herbs and supplemental drugs are the local historical diets and traditional habits which may interact with drugs [23]. The disease and its therapy may drive patients to seek a change to their regular every-day lifestyle, including a change to their traditional diet, which could be culturally inherited according to national character or individual family lore. Psychosocial distress could be an additional factor in the lifestyle change of the patient [24]. Due to this complexity, SC varies by country due to cultural differences and available resources [25]. The change in diet could involve not only an alteration to the set of nutrients consumed but in fact a complete rearrangement of the usual daily life of the patient, forming a new lifestyle and preferences.

The need for effective supportive cancer care increases with the longer survival times and with the transformation of previously fatal cancers to chronic disease [26]. The further development of the field requires a reliable and valid evaluation of global needs for supportive care with standardized guidelines [27], which could differ according to specific challenges in various countries [28].

The increase in the number of patients affected by various anti-cancer therapies, or by those therapies having become ineffective, pumps-up the global market for palliative and supportive care, which is a clear market for home-care too [29]. pSC is a special and considerable part of the SC market, pumping up the need for herbs, supplementary drugs, and vitamins by mass marketing and the extreme attention of social media. The time is ripe for a change of paradigm.

The meaning of SC by clinicians drastically narrows in everyday patient practices, becoming limited to the simple addition of dietary supplements, diet-protocols, herbs, vitamins, teas, decoctions, and other "home-made" practices, without the assistance of medical professionals. Proper SC is based on cooperation between the patient and the doctor, the therapist, who knows well the applied protocol, the possible adverse effects, and the actual support needs. The objective of our article shows for professionals the complexity and great potential in the SC.

2. Change of Paradigm

The patient demands for SC met with the medical needs of the broad range completing the curative therapies. A high number of patients strongly request such complementary pSC services despite these mostly having mere shreds of evidence. The Guideline of the National Health Service (NHS, UK) [1] focuses on the needs of patients, expressing the importance of providing reliable information for proper decision-making, and taking care that patients can access these therapies safely when they insist on a therapy. Interestingly, end-of-life care does not increase the survival when the therapy directly includes the patients (or "the family members") preferences [30].

SC has to consider the complexity of cancer and its embedded value in the family and society. However, its proper application needs a change of paradigm from cancer-driven to patient-driven therapy. This refocused attention becomes strong only when the conventional cancer-driven approach is limited or has failed, and then palliative treatment (PT) will be at the centre of considerations, with concentration on the QoL and the easing of the suffering of the patient. The PT is this phase the only help, and in the meaning of the patient support this phase is an intensive and medically controlled SC. Unfortunately, PT has no unified definition [31], but the common meaning generally reached is that it does not follow a curative approach but concentrates on the elimination of symptoms. It is the active holistic care of patients with advanced, progressive illness, managing the pain and other symptoms, predominating in end-of-life care [32]. More detailed definitions have been elaborated by the NHS (UK) [1], listing the needs for SC and PT for medical professionals. The key idea of SC is not a distinct specialty but is the responsibility of all health and social care professionals delivering care. It requires a spectrum of skills, extending from basic skills to highly specific expertise and experience. PT is described thus [31]: "Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families". The importance of SC/PT is widely recognized and is provided not only by medical experts, but the family, the social environment, and other care-providers have a part in the complex process.

The WHO defines PT more widely [33]: "Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness and is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life."

Despite the above definitions, some confusions between palliative and supportive care exist in medical practice. The main attempts to distinguish SC from PT point to apparent contradictions between them, listing that PT is passive care, is relatively cheap, and is applied for a short time during the end-of-life care; while SC is an active intervention, chronical, and expensive [34]. In this approach, it looks as if SC and PT are complementary, but in the complex pa-

tient-oriented therapy these are not distinguishable into disjunct groups, so we cannot formulate these independently from each other. In general however, supportive care is rather oriented towards helping the patient to achieve remission as long as it is feasible by the "holistic" combination of therapeutic and supportive interventions.

2.1. Challenging Present Conventional Consensus

The actual challenge of SC/PT is the inherent complexity of the human being and in consequence the complexity of human medicine. The rigid conventional consensus in oncology, which is oriented towards the tumour, somehow forgot that the lesion belongs to an individual patient. This conceptualisation has led to overly simplistic therapeutic protocols. There is a slogan sometimes quoted by doctors to patients who are suffering from the side effects of the actual medication: "The drug which has no side effect has no effect either". This opinion mirrors the missing complexity of the therapy; the drug which is administered focuses on one effect, ignoring its embedded interconnections to the complex system. SC/PT has to complete the therapy, compensating for the missing apprehension of complexity in the approach of the primary treatment.

SC and PT focus on the patient, who is the host of the malignancy, while oncology concentrates on the tumorous lesion, ignoring the complexity of the disease. The missing complexity has to be found again, answering the question as to "where medicine went wrong" [35]. The medical paradigm of oncology has to focus on the complexity of the malignant situation and evaluate and treat the patient as a whole.

The aim of this article is to summarize the recent achievements of pSC applicable in the PT process and to firmly embed the importance of general SC in everyday oncological practice. We want to point to the responsibility of those health professionals showing the optimal way to use pSC, giving stable support for disoriented patients, preventing them from becoming victims of quackeries or simply of their own beliefs.

The SC of individuals could start with the prevention of malignant diseases by advising on lifestyle and diet, as well as by proposals for checks depending on the individual's various life-conditions, habits, and environmental circumstances, including the actual daily risk factors and the ages of the subjects. In diagnosed, established malignant disease, supportive care focuses on the treatment of cancer-related diseases, comorbidities, and side effects of the active therapy [36]. Palliative care usually follows supportive care, when the support is not enough, and in many cases when the active curative approach has failed [37]. The goal of both is to keep the QoL as high as possible. This is the final turning point from the tumour-oriented to the patient-oriented concept. We have to have a certain change of paradigm. Interestingly, artificial intelligence and robotic technologies started to enter this field too [38].

To meet patients' demands, there are three major categories of pSC to be applied in the frame of the general SC:

1) Increase the efficacy of conventional cancer therapies, maximizing their curative effect.

2) Decrease the adverse effects of conventional therapies, increasing the quality of life of the patient.

3) Regarding the newest developments of immuno-oncology, the support of the immune system, and the revitalizing of the toxic degradation of immune effects is a new goal.

All of these categories are focused on the patient-guided treatment plan instead of the tumour-guided methodology (Figure 1). The curative effect must consider the patient's personality and individual factors (like comorbidities, allergies, disease history, environmental factors, dietary factors, life-style). Local treatment has to be effective systemically too.

Anyway, the change from tumour-focused to patient-focused therapies is inherently included in the definition of malignancy. Cancer is a systemic disease from its early beginnings in the body. By the conventional view the PT period of the treatment starts only in advanced cases, when the metastases limit curative interventions. Patients suffering extensively by the intensified illness need extended support. Hope and sometimes false advertisements and unprofessional bits of "helpful" advice make the patient vulnerable and could orient the patient towards uncontrolled pSC and PT. It is the task of healthcare professionals to keep the patient on a safe course of treatment together with providing patient satisfaction. The satisfactory condition is mostly related to the QoL and, of course, the elongation of the life-span with acceptable living conditions.

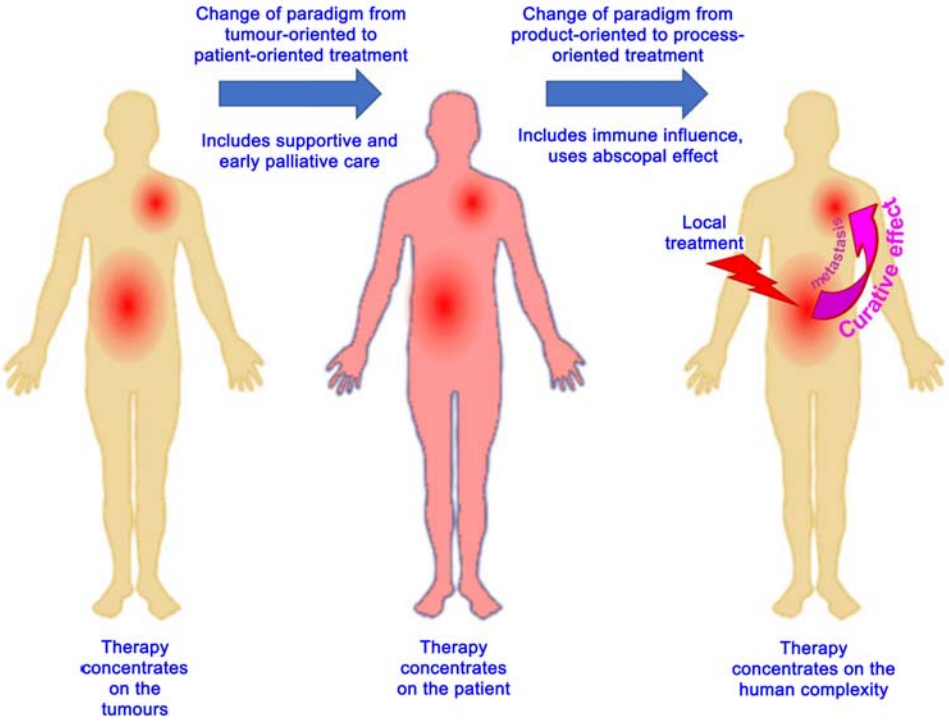

Figure 1. It is time to change the paradigm of cancer therapies, and take the patient as whole in the centre of actions.

The patient-oriented attitude of the therapy concept re-establishes the complexity in the mind of therapist and offers for the patient the possibility of a better prognosis, longer survival, and higher quality of life. The integration of SC/PT into oncology relies on specific knowledge and skills [32]. The two existing models of SC and PT have to be integrated, challenging a certain "dualistic perspective" [32]. The classical cancer treatments are tumour-oriented, focusing their attention on eliminating the malignant tissues. These intensive processes can cause extensive side effects and may cause irreversible comorbidities too. The growing number of serious adverse effects and the lack of effective approaches to managing them raises new challenges [39]. Such new, high-hope treatments as targeted therapies have serious side effects [40] and can decrease the QoL of the patient [41]. Immunotherapy may even worsen cancer development, causing hyper-progression [42], well showing a double-edged sword effect of immuno-therapeutics in cancer treatment [43].

The conventional therapies, led by chemo and hormonal remedies, have lost their overall primacy. According to a WHO consultation publication [44], the classical chemo and hormonal therapies can be grouped into five categories by their effectiveness: 1) potentially curative, 2) adjuvant with benefit for local disease, 3) palliative in metastatic stages, 4) local control enhanced, and 5) chemotherapy is ineffective. The ten most frequent cancers (lung, stomach, breast, colorectal, cervix, head and neck, lymphoma, hepatobiliary, oesophagus, and prostate) are all in category 3, which well supports the importance of the PT processes. Most of the essential high priority drugs are developed for the top ten cancers [44], and despite the mostly improving overall survivals, the results are not satisfactory yet. It is obvious that in most of the disease manifestations PT/SC is not an alternative treatment to the curative conventional chemotherapies but it is a part of the therapy.

Expectations of a simple situation in a system which has multiple regulatory feedbacks and interactions which request a harmonic coexistence of the regulatory actions is unrealistic. Chronic inflammation often promotes tumour development, including the dissemination and formation of metastases too. Acute inflammation, however, could act oppositely, causing a dilemma [45]. The accompanying pain, depression, psychosocial stress, fatigue, and other bad conditions of patients combine to accelerate their loss of QoL and shorten their survival. It could be a matter of slowing the acceleration of symptoms when PT/SC care starts at the first diagnosis of a fatal malignancy [46]. Even sophisticated PT/SC is not able to be superior over combined SC and conventional therapy. This is statistically proven, for example, in advanced metastatic colorectal tumours [47].

As an actual example of the need for complexity-oriented approaches in both CT and PT, one is directed to e.g. the presently extended discussions about the "miraculous" effect of medical cannabis [48], treating the symptoms, relieving the pain, decreasing nausea and vomiting, and so increasing the QoL. Currently

there is no scientific evidence for these results, but in any case it is unlikely that one single herb could solve the complex problem of PT/SC.

Cancer presents a massive challenge for patients, their families, and their social environment. The medical challenge for professionals is complex, and they have to consider the involvement of SC/PT actions too. A natural consequence of such consideration is to apply it much earlier than the conventional palliative phase. Many aspects of PT are also applicable in conjunction with other treatments from the discovery of the malignant transition [30]. It could be given equal priority alongside diagnosis and treatment [49].

While traditional PT starts when symptom management massively demands it, in the new paradigm early palliative treatment (ePT) starts at diagnosis, in the very early stages [50], and increases its dominance with the expansion of the disease [33]. The integration of ePT into therapy has three levels: linkage, coordination, and full integration [51]. Presently ePT integrated into oncology is in its infancy, while a few clinical trials reveal that ePT may have beneficial effects on QoL [52]. The integration of ePT into the treatment of cancer patients is recommended [53] [54] [55], but presently it is limited mostly to inpatient services [54] [56] [57]. Due to the complexity of cancerous diseases and the growing number of high-line treatment applications, ePT is having a gradually stronger effect on treatment protocols [58]. Due to this trend, general SC is receiving a growing emphasis and is making the complete process integrative, taking care of patients in its complex unity. At this point supportive and palliative care are united, the ePT component being adequate within the SC, unifying the care domains in physical, psychological, social, spiritual, cultural, end-of-life, and ethical aspects [59]. This integrated treatment approach, one which includes the oncotherapy being integrated with the SC and ePT, is the complex treatment approach (CTA). Cancer causes a complex local and systemic change which needs a complex answer to reestablish the healthy homeostatic control.

Meta-analysis shows that ePT improves the QoL significantly compared to standard cancer-care alone, and no extra adverse effects appeared [52]. ePT delivered in parallel alongside the conventional standard treatments increases the survival time [60], which together with better QoL is a great support for patients and their families [61]. The American Society of Clinical Oncology (ASCO) gives special attention to ePT too [62], and has expressed the opinion that the optimal care needs to include palliation [63]. There are further efforts requesting the integration of oncology and PT [64]. It is shown that ePT could even start at home. The meta-analysis of palliative home-care shows the benefits, but general attention and the partnership of family and medical professionals have to be improved for its success [29]. The standardizing of PT and the improvement of its quality are general wishes for the new concept of oncology care [65], including for the psychosocial aspects of this activity [66]. More attention to PT practice in rural areas is necessary [67], and in poor countries as well, fitting the actions to the actual availability.

Clinical decision-making requires prognosis estimates, which must include the PT too [68]. Some models for clinical prognosis including PT have been developed, such as the Palliative Prognostic Score [69], the Palliative Prognostic Index [70], and the Glasgow Prognostic score [71].

The harm is relative: "no action" is harmless compared to intervention, but its consequence could be harmful, leaving a disease uncontrolled. The "action" of treatment, however, could cause harm, but compared to the benefit this harm could be evaluated as low. Tumor-oriented "action" in oncology could cause patient-oriented harm, measurable by the quality of life or by acute discomforts, pain, etc., and the clinical evaluation hinges on the harm/benefit (H/B) ratio. The complete process could have a good H/B on average, but with fluctuations the risk of causing a high H/B value could be unacceptable, and thus the "action" not be approved. The decisional fact from a medical point of view is the direction of the changes caused by "action", that is, the results: at the end of the day the patient has to have stable homeostatic control, as near to the usual healthy state as possible. The Hippocratic phrase "nil nocere" ("do no harm") also has to be understood only within this tendency towards dynamism, otherwise the meaning would be "do nothing". The goal of the "action" always has to be patient-oriented as a tendency, or else it is a medical irresponsibility. This evaluation has become central to SC/PT "actions", which have to be integrative parts of the complete therapy. Logically, when this integration of therapies is involved, the ePT concept opens the opportunity to fulfil the need for a complexity of treatment that may lower H/B values. The first line oncotherapies (like surgery and chemo- and radio-therapy) could fail without ePT. The treatment of pain syndrome by ePT is standard of course, but other factors of this complex approach are frequently absent. Indeed, presently most CTA interventions are missing in first line treatments, which can drastically decrease QoL, and this contradicts the patient-oriented dynamical expectations for H/B too.

As well as the use of ePT in seeking to implement the CTA process, the direct optimization of H/B requires natural additions to the active medical intervention. It is general nourishment that insures the basis of the complex treatment approach's potential.

2.2. The Challenge of Nutrition

Life is not in a state of static equilibrium, it is permanently undergoing dynamical changes, an everlasting transformation of energy intake maintaining the equilibrium. We have to quote Albert Einstein who formulated it very simply: "Life is like riding a bicycle: to keep your balance, you must keep moving" [72]. The energy intake comes from the environment and is focused on nourishment. As another Nobelist (another Albert), Szentgyorgyi, formulated the situation: with life-energy it is unimportant that the monkey goes through the jungle; the important thing is that the jungle goes through the monkey, in the form of nutrition, water, and oxygen [73]. The jungle becomes a part of the monkey and in

this manner all the living objects there are interconnected; we cannot discuss the energy-cycle of a species without considering the energy-cycle of the other lives in its environment. To maintain all the energy cycling functions of a healthy organism, well optimized, enzyme catalysed biochemical reaction cycles are a must. Nutritionally available micro- and trace elements (Se, B, Ni) or mesoelements (Zn, Cu, Mg) are important cofactors in the catalytic centres of these proteins. In this regard, inconclusive evidence points to the beneficial effect of Zn and Se supplementation in treatment settings for some cancers, especially for an increased quality of life [74] [75].

The culinary and medicinal use of spices and herbs has long been a part of human culture. Presently one major focus regarding diets is weight-loss, variants of which entail extreme selections of foods (like the Atkin's diet, for example). The direction of diets can be in another direction too, to keep the healthy state permanent (like the ketogenic diet), and a third direction is that of special diets to prevent and/or cure various diseases. Comparison of the various diets shows well that the extrema are not helpful in any situation [76], emphasizing the popular knowledge that "the difference between medicament and poison is only the dose". The uncontrolled take of pSC drugs causes adverse effects at incorrect dosing. For example, the extra high dose of fat-soluble vitamins (like Vit. D and E) could cause severe adverse effects, or the high dose of ion-support could produce severe alkaline-acid imbalance.

Due to the complexity of the reactions in living objects we expect well defined negative feedback mechanisms with promoter and suppressor components balancing to a dynamical equilibrium. Over- or under-dosing hurts this balance, favouring one or other of the regulatory sides, destroying the equilibrium and so acting against the homeostatic control. However, it is not only the dosing that causes dietary challenges, but also the complex variety of the nutrients needed [77], healthy homeostasis requiring a diverse nourishment containing all the supporting components in the necessary amounts for the complex processes of living.

The compounds in plants have boosted research interest towards the protection and maintenance of human health and the treatment of some previously untreatable diseases [78]. Phytochemicals in plant materials have attracted interest among scientists, producers, and consumers and have given rise to a new scientific approach, phytochemical research, and on this basis a new industry has arisen. A discipline of phytomedicine has appeared, emphasizing the therapeutic value of herbal medicine [79].

The development of the nutraceuticals field drives phytomedicine's emergence, with even the reactivation of ancient culinary cultures [80]. It makes use of the traditional values of the omnivorous feeding of hunter-gatherer humans along with modern pharma-productions and with public reference to healthy nutraceuticals too. The research in this field stimulates the industry and is also actively incorporated into human healthcare and the pursuit by individuals of

healthy lifestyles. A harmony is sought as historic medical experience (famously represented by the Far-Eastern herbal culture) and up-to-date medicine are amalgamated, in the realization that not only the target (*i.e.*, the human homeostasis [81]) but also natural medicines and the products derived from them are complex; phyto-products cannot be regarded as simple, single chemical compounds.

Traditional medicine in the Far-East, including China, India, Korea, and Japan, is traditionally popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. The natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active substances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their simple standardized production is impossible. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phytochemical products, but also in human individuals too, who show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. From the metabolic point of view the herb-derived products can be categorized into defined groups: carotenoids, alkaloids, polyphenols, organo-sulphur, and nitrogen compounds [83].

An increasing body of scientific literature suggests that dietary components may exert cancer preventive effects [84]. Tea, soy, cruciferous vegetables, and other foods have been investigated for their cancer preventive potential. Diets rich in polyphenols could help as prophylactics [85] [86]. However, the overdosed consumption of polyphenols could induce possible harm too [87]. The potential harm of some polyphenols leads to international regulations recommending safe levels for polyphenol consumption [88], but the appropriate dosing limit is debated [89].

Prevention-related nutritionally available mediator and hormone-like molecules such as the long-chain omega-3 polyunsaturated fatty acids (O-3s), such as EPA Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) must be accounted for. Humans need O-3s for optimal functioning at every stage of life [90], as well as their anticancer effects are also being investigated [91] [92]. Another formerly neglected, but recently rediscovered hormone-like substance, Vitamin D3 also belongs to supportive nutritional mediators of the immune system. In a recent meta-analysis of 52 trials with more than 75,000 cases, Vitamin D3 supplementation reduced the risk of cancer death by 16% [93] [94] Hypovitaminosis D is associated with a worse prognosis in breast [95] [96] [97], lung [98], colon and thyroid cancer [93] [94]. There is a significant linear dose relationship between the active metabolite 25OH-D-vitamin levels in blood and overall survival in breast cancer patients.

Like all other actions, balance is needed for the maintenance of homeostatic

equilibrium [99] [100].

The human body lives in symbioses with a large number of bacteria. The number of these single-cell organisms is greater than the overall number of the cells in tissues of the human organism [101]. A major part of these are gut-bacteria (microbiome) which make a contribution to healthy balance as well as to diseases and immune-disorders [102] too. Intestinal homeostasis is an integrative part of the whole body's well-being [103]. Many nutrients are "pre-digested" before their further digestion for human use, as well as the symbiosis making a contribution to general metabolic processes too [104]. There is an emerging research interest in the interaction of polyphenols with microbiota [85], but the present knowledge is insufficient to decide upon the optimal polyphenol intake for maximal health benefit [103]. Despite the field demanding intensive research in recent years, the prospects are great, and the modulation of the microbiota by polyphenols is one greatly focused upon [105].

Other important factors in phytomedicine are the soy phytoestrogen isoflavones Genistein and Daidzein, expected to be potent anticancer ingredients of the daily diet of eastern countries [106]. Traditional Chinese medicine favours the medical plant Astragalus too, due to its antiviral [107], anti-inflammatory [108], and antioxidant [109] properties. These properties, with an immuno-stimulative effect, make it useful for anticancer application too [110].

The traditional medicine of the Far-East, including China, India, Korea, and Japan, is historically popular, and its application reaches approximately one half of the human population. The dosing, however, could be a challenging point for its production and application. From the metabolic point of view, herbally derived products can be categorized into defined groups: the carotenoids, alkaloids, polyphenols, and organo-sulphur and nitrogen compounds [83]. As previously stated, the natural products derived from the roots, leaves, fruits, or whole plants have a large variance in the concentration of their active substances, depending on such environmental conditions as the sunshine, weather, soil components, and bacteria involved during plant growth, so their standardized production is far from simple. Complicated, modern investigations are necessary to create feasible products [82]. However, it is the large variations not only in the natural herbs which are challenging in the application of phytochemical products, but also in human individuals, who show large personal variability in their gut microbiota, which has an essential role in most of the actions of the remedies. Despite the underlying mechanisms of the effects of gut microbiota on personal homeostasis in humans being largely unknown, some hints on the regulation of metabolism have recently been published [111].

One important step ahead to accept the achievements of the traditional Chinese medicine (TCM) was the awarding of the Nobel Prize to three co-recipients in 2015 for the medicament named Artemisinin (isolated from the plant Artemisia annua, sweet wormwood) which treats malaria [112]. The history of this discovery shows well the general challenge of the complexity of phytochemical

products: the basic discovery was made by the Chinese scientist Tu Youyou, using an herb from the vast range in TCM. It was helpful for malaria, but it was quickly recognized that the malaria parasites soon develop resistance to it, so the WHO terminated its certificate [113], asking producers to halt sales. Subsequent research later developed a Nobel-winning combination therapy, based on Artemisinin. Presently the therapy is a world-wide routine treatment for malaria. Some other herbs originated from the TCM and their Japanese versions (Kampo) are widely used in active cancer therapy [114]. The most accepted member of these is the active ingredient group of Shikonin. Shikonin suppresses the oncogenic pyruvate kinase-M2 (PKM2) [115], reducing the cell proliferation in this aggressive disease, and induces cell death by inhibition of glycolysis [116]. The blocking of ATP supply for PKM2 by Sikonin allows the cytotoxic Ca^{2+} overload and promotes apoptotic cell death, proven by treating the ductal pancreatic adenocarcinoma [117], and could induce mitochondria mediated apoptosis even in cisplatin refractory ovarian cancer [118].

Polyphenols are involved in a large category of antioxidants. The polyphenol-rich foods, principally fruits and vegetables, are beneficial to healthy life. Most vegetables are rich in flavonoids, which are a branch of polyphenolic compounds and make up a significant part of the human diet, having anti-inflammatory activity together with related polyphenolic compounds [119]. Many flavonoids (anthocyanins, flavanols, flavanones, flavones, isoflavones, catechins) could suppress the effect of free radicals and arrest the proliferation activity in tumours [120].

Clinical evidence has been collected on the beneficial effects of polyphenols in colon, prostate, epithelial, endometrial, and breast cancer [121] [122]. The early research on polyphenols focused on their antioxidant activity. We will shortly review ramifications of the antioxidant effects of polyphenols here

The effect of the application in SC of various antioxidants in combination with chemotherapy has been reviewed in a comprehensive analysis [123] showing that antioxidants reduced the side effects and so that these remedies have an exceptional ability to reduce the chemotherapeutic induced toxicity, and to increase the QoL and survival time of patients.

Polyphenols can induce mitochondrial adaptation to actual ROS attack [124]. The high antioxidant capacity of vitamins and polyphenols has no overall benefit regarding mortality rate. However, the benefit of these antioxidants in sustaining health is not questioned. The apparent contradiction could be resolved by the assumption that polyphenols are mitochondrial adaptogens, defending the mitochondria from oxidative stress; however it is not a simple reduction of this kind attack, but complexly regulates the mitochondrial biogenesis [124]. Due to the well-known fact that mitochondrial dysfunction has a pivotal role in many diseases, such as neurodegenerative or cardiovascular diseases, and actually having functions in ageing, repairing mitochondrial functioning or at least improving its normal activity could have substantial health benefits.

Certain differences in the metabolic processes of malignant and healthy cells have been observed [125] and it is one of the hallmarks of cancer development; in a malignancy a primitive, simple, but fast acting, "old fashioned" metabolism is promoted that produces ATP by a fermentative process instead of by mitochondrial Krebs-cycle, so in this context the most important aspect in the origin of malignancy is a metabolic (mitochondrial) dysfunction [126]. The revolutionary discovery was honoured by a Nobel Prize for Otto Warburg. His idea has been revised [127] [128], and it is enjoying a renaissance nowadays [129], the Warburg effect returning "in a New Theory of Cancer" [130], and new hypotheses being born on this basis [131] [132]. A malignancy is usually hypoxic because of the intensive fermentative metabolism. This hypoxic environment is a possible selective factor for medical targeting [133].

The response of mitochondria to hypoxic stress is a changing of their sub-cellular localization. The hypoxia ignites mitochondrial fragmentation, forming perinuclear clustering [134] [135] around the nuclei [136]. The hypoxia-induced nuclear relocation of mitochondria is associated with increased nuclear ROS, which can suppress the electron flux and so further increase mitochondrial ROS production [137], and it may allow the ROS signal to directly affect the nucleus. Furthermore, the "wasted" energy of the low efficacy anaerobic ATP production heats the lesion. The increased local temperature helps diffusion processes, as well as inducing higher blood flow and supporting the permeability of the vessel walls. The diffusion coefficient depends linearly on the temperature [138], so the diffusion of intra- and extracellular electrolytes is likely to be higher than in healthy counterparts. The development of ROS has again a complex balance, showing that the way bactericide antibiotics act is possibly connected to ROS [139]. The regular use of antibiotics could be a risk-factor for cancer [140], and in general has a risk of shortening survival [141]. The main disadvantage of antibiotics is that they do not differentiate between pathogenic and beneficial (gut) bacteria [142]. The homeostatic balance of gut microbiota is essential for antitumour responses, and could directly impact tumour outcomes [142]. Again, a complex balance has to be considered; pathogens can cause cancer, but the gut microbiota could impact the immune-system and so the cancer's progression [143].

Another large and extensively studied category of phytomedicine is that of the mushrooms used for culinary and medical purposes. It has been used in the treatment of infections for centuries, and is very popular in Far Eastern medicine. In recent decades medical mushrooms have been a part of the regular treatment of cancer in China and Japan [144]. Presently medical mushrooms are in use in more than 100 medical applications [145]. Two of the crucial ingredients of these are Polysaccharide Krestin (PSK) and polysaccharo-peptide (PSP), also used recently in Western medicine too [144]. PSP is a protein-bound polysaccharide extracted from the edible mushroom Coriolus versicolor [146]. Hundreds of studies have been conducted on the immuno-stimulating and anti-

tumour effects of mushroom polysaccharides [138].

The active ingredient of the mushroom Grifola frondosa (Maitake) is a protein-bound polysaccharide, a bioactive extract (proteoglucan) [147]. The purified soluble b-glucan has immunomodulatory and anticancer activity [148] [149] and could inhibit metastases [150]. It stimulates immune activity in experimental models [151]. It has synergetic effects with vitamins, especially when it is intravenously applied [152], as well as increasing bone marrow colony formation, reducing the toxicity of doxorubicin [153].

The mushroom Lentinula edodes (Shiitake) improves gut-immunity and well reduces inflammatory symptoms [154]. A clinically approved intravenous pharmaceutical for third stage gastric cancer with the active ingredient branching polysaccharide, beta-1,3-1,6-D-glucan. Lentinan has been on the Japanese market between 1984 and 2004, manufactured by Ajinomoto and then Taiho Pharmaceuticals. It was successfully applied for inoperable gastric cancer treatment in combination with some chemotherapies [155], but later was withdrawn due to skin-related side effects. L. edodes also showed antiviral activity [156] and immune support [157], as well as improvement of quality of life being observed when it was applied complementarily to other cancer immunotherapies [158].

The mushroom Ganoderma lucidum (Reishi) helps prolong cancer survival [159] in adjunct to conventional treatment to potentiate conventional therapies, enhancing tumour response and stimulating host immunity. Reishi shows immunomodulation in cancer [160] and enhances the response of the tumour [159]. However, its toxicity is also measured on leukocytes [161], as well as hepatotoxicity also being detected [162] [163]. There are some other commonly consumed medical mushrooms, such as Agaricus bisporus (button mushroom) [164] [165], Agaricus blazei (almond mushroom) [166], and Pleurotus ostreatus (oyster mushroom) [167], which are nowadays studied intensively [168] [169].

Various forms of mistletoe extract (Helixor®, Iscador®, Lektinol™, Cefalektin®, Eurixor®, etc.) are extensively applied in various cancer treatments [170] [171]. Its immune-stimulating effect probably plays a pivotal role in its anticancer applications [172], which is probably combined with a tumour-inhibitive action as well [173]. Again complex in its action, balancing the dose for proper homeostasis is of great importance in mistletoe administration too: it could be found to be anti- or pro-proliferative, depending on the dose [174].

A relatively cheap and effective drug of natural origin is the Metformin, which is a long time accepted first line standard clinical drug to treat type 2 diabetes. It was developed from a natural product, Galega officinalis as the natural source of galegine, used for natural medicine [175]. Metformin is a guanidine analog, product in the synthesis of N,N-dimethylguanidine [176]. It was recently observed that application of Metformin in cancer treatment lowers the incidence of tumor development and the risk of mortality [177]. Studies proved the direct antitumor effect of Metformin, by inducing apoptosis and suppressing the malignant. It was tried for various cancers like breast [178], lung [179] and leukemia

[180]. Metformin limits the mitochondrial respiration [181] and it works like the energetic stress on the cell.

The largest and most popular, broadly applied pSC group of remedies are the antioxidants. Antioxidants in their simple chemical meaning are reducing agents, taking up electrons in their reactions. Blocking oxidation is a negative when we consider that this is the fuel of energy in life, ATP being produced by oxidative phosphorylation in mitochondria in most eukaryotes. This energy-production is highly efficient, but can produce a natural by-product, the reactive oxidation species (ROS), which has an important role in homeostasis [182]. The ROS is formed as a by-product of the normal respiration process in mitochondria, as well as being produced by inflammatory processes and the myeloperoxidase action in defence mechanisms. A great many adverse reactions of conventional therapies produce ROS extensively, causing oxidative stress. The ROS, highly reactive compounds definitely being toxic in some cases, can cause significant oxidative damage of cellular structures. Antioxidants could be used as a precious tool in blocking the toxic effects of ROS. The control of ROS could have great potential in complementing chemotherapies to increase their therapeutic efficacy and decrease their toxicity [183], regulating the redox balance between oxidants and antioxidants.

Antioxidants naturally exist as vitamins, minerals, and other compounds (like polyphenols) in foods. Vitamins are natural antioxidants, too, being essential for health. Vitamin therapies are most frequently applied in the antioxidant role in general use for SC/pSC in oncology practice. The vitamins are used in the broad area of diseases in the complete range of medical activities: prevention, curative treatment, palliative application, and rehabilitation too. Most of the vitamins are taken in connection with nutrition and via the microbiome, because they are not produced naturally in the human body [184]. These can be fat soluble (like A, D, E, K vitamins) or water soluble (like ascorbic acid, pantothenic acid, folic acid, niacin, riboflavin, cobalamin, pyridoxine, thiamine, biotin). The early recognition of the importance of vitamins occurred at the beginning of the last century [185] and is currently subject to critical evaluation [186].

The application of antioxidants in cancer prevention and cure is widespread among laypersons, and a significant percentage of cancer patients use antioxidants to prevent malignancy or, very often, apply them during active cancer treatment [187]. Fruits and vegetables are good sources of antioxidants, and it is known that diets high in these sources are healthy in general; antioxidant rich diets are followed for prevention, and presently intensive research is governmentally funded [188].

Antioxidant compounds could prevent or delay the oxidation of compounds in life-processes. The discovery of ascorbic acid (vitamin C) was a great step forwards towards understanding the importance of antioxidative action and the redox balance in living systems [189]. Intensive research has identified more vitamins among which are the most known antioxidants among the general popu-

lation. The proposed mechanisms of vitamins in cancer-prevention and cancer-cure have been discussed and the ratio of the observation and expectations (O/E) of effects of vitamins collected from 102 cancers [190], measuring the plasma-concentration of the A, C, and E vitamins, which have significantly higher observed values than expected in low concentrations of the compounds.

Special attention on the antioxidative effect of vitamin C in cancer treatment has been proposed in a new concept of L. Pauling, a double Nobel Laureate. Pauling proposed using vitamin C to prevent and cure cancer [191]. The proofs of his concept were presented in retrospective clinical trials [192] [193] [194]; however, a placebo-controlled study could not find a similar effect [195] [196], and the method was not approved. Extended and sometimes emotionally heated debates on the antioxidants have appeared in recent research, inducing parallel discussions about general nourishments in which old ideas have been reborn. The application of vitamin C for malignant diseases has recently had a renaissance [197], its effect in cancer therapy being revisited [198]. Phase I clinical trials show its safety and high tolerability [199] [200] [201] and relief from the side-effects of chemotherapy [202]. Clinical trials indicated the efficacy of intravenous vitamin C (IVC) acting as a potential anticancer therapy and reducing toxic side effects when administered complementarily to chemotherapy [203] [204] [205]. Its dose escalation did not show side effects [206]. Its synergy with chemotherapy improves the QoL [207] [208]. It is also useful for the prevention of malignant diseases [209], as well as suppressing inflammation [210].

Despite the positive results the intensive debate about vitamin C continues [211] [212]. Misconceptions block a clear picture from being formed regarding the situation [213]. These deeply set beliefs have to be understood for progress to be made. All the challenges originate from the clear complexity of the topic. The action of antioxidants has to help in the balancing of the redox status of normal living processes. But inappropriate applications could cause harm, even vitamin C being potentially toxic when applied improperly [214]. It has also been shown, however, that antioxidative supplements confer no prevention of malignancy [215], while other research shows the opposite [216]. Also debate has arisen regarding preventive applications of antioxidants. The role of defensive mechanisms has been discussed in detail [217], a triple step defence activity being composed: 1) preventing the formation of new radicals; 2) capturing free radicals to prevent oxidative chain reactions; and 3) repairing the damage caused by the free radicals.

A significant shake-up in the debate around antioxidants was made by another Nobel laureate, J. Watson (the explorer of DNA). Watson published his opinion that antioxidants are harmful, may cause more harm than good, and, contrary to widespread belief, promote cancer [218] [219] [220]. This new turn was an attack not only against the application of vitamin C, but in general against antioxidant treatments in oncology. Extended systemic analyses of the clinical data show increased mortality with treatment using beta carotene, vitamin A,

and vitamin E, while vitamin C and selenium had no significant impact on survival [221] [222]. Some evidence has been collected supporting the increased mortality of patients treated with antioxidative therapies [223] [224] [225].

The heated debate was cooled down by opinions that the topic is a double-edged sword [226] [227], and that depending on the cellular concentration and micro-environmental conditions the antioxidant could have both pro- and anti-cancer potential [228]. Unfortunately, the interaction of antioxidants with anticancer drugs is not understood completely [133], which increases the challenge.

The balance of oxidative stress defines the action of the antioxidants. Many anticancer therapies, including radiotherapy and most chemotherapies, act therapeutically with massive oxidative stress [229]. Supporting the effect of these conventional therapies the naturally present antioxidant defence mechanisms in cancer cells [230] have to be controlled too. This therapeutic approach tries to maximize the oxidative stress in tumour-cells, and the out-balanced redox situation kills them. This approach emphasizes again the extreme complexity (embedded interconnections and self-regulation [231] [232]) of the living substances, where the main goal is the selectivity of cancer cells with oxidative stress, while the heathy cells have to maintain their normal redox balance. The oxidative and antioxidative impacts depend on the concentration of the natural antioxidants, acting like a "double-edges sword" in cancer, in dependence of the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) as one of the transcription factors [109].

The selective factor of electron transfer, a definite clue of oxidative actions [233], could be the hypoxic environment of the cancer-cells [133]. The debate on vitamins in cancer prevention, cure, and palliation is not over yet. Results are promising, but not conclusive [234]. Intensive research and further facts are necessary to harmonize the pro and con opinions. According to our opinion, the doubtfulness is inherent, well showing again the essential complexity of the living structures and their homeostatic balance. As recognized early, the actual homeostasis is personalized [235] and also depends on the mood, and on the actual physiological and psychological condition, as well as on the stresses of the individual [236] [237]. Homeostasis depends on the gut microbiota of the human subject too [238], showing the interdependence of the parts in the symbiosis of human life [239]. To this theoretical consideration, one should add the network-based metagenomic and systems-ecology observations made recently [240]. Clinical analyses show a dependence of cancer [241], especially mucosal cancers [242] [243], on microbiomial composition. These recent reports also clearly support decreasing cancer risks with different preemptive and supportive nutritional manipulations on the microbiome, even in lung cancer [241] [244].

This extreme complexity demands new theoretical consideration, attempting to describe the adaptive dynamics of the phenomenon by cell-population calculations with emphasis on the heterogeneity of cancer cell populations [245]. Sys-

temic-Evolutionary Theory, a new interpretative model of cancer complexity, has evolved [246], as well as the fractal-physiology approach being summarized to explain cancer evolution in connection with metabolism and immunity [247], with the demand of a new paradigm, a new strategy, to win the war against malignant diseases.

Healthy homeostasis struggles to control the malignancy. The first few attempts to block the proliferation start intracellularly by controlling the DNA replication. It fails for various reasons, including genetic aberration [248], mitochondrial dysfunction [249], or other intracellular hallmarks of the cancer [250]. An additional challenge is the extracellular factors such as permanent uncontrolled stress (chemical, mechanical, etc.) [251], unhealed wounds [252], inflammation [253], and the extracellular hallmarks of malignancy [254]. The permanent proliferation could be stopped by natural apoptosis, but this mechanism is missing too [255]. Cancerous proliferations and bacteria have a lot in common [256]. The tumour itself has something like an atavism [257], in the sense that the malignant cells act like self-ruled unicellular organisms. The atavism-like process is general, not only with the loss of cellular connections, but also with the intracellular genetic structures being altered. The unicellular individualism develops great potential for adaptability to environmental changes, and in fact makes these cells more vigorous than those in the multicellular network. Disorganizing the multicellular structure is the modified genetic activity at the active boundary between unicellular and multicellular areas, promoting primitive transcriptional programs [258]. The malignancy in this general meaning is a distortion of the healthy cellular network, the rules of multicellular organization being broken. The breaking of cellular networks is a general behaviour of all the tumorous cancers independent of their locations in the body (**Figure 2**). In this sense, the cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism, individualism prevailing [259]. The change, however, is not free from new organizing processes, because this unicellular autonomy brings its own requirements regarding environmental conditions for survival [260]; the cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality, strengthening with angiogenesis, injury current, and numerous other supports.

It is interesting to note that the widely applied traditional cancer chemotherapies (anthracyclines) are in fact antibiotics derived from some species of fungi. They are topoisomerase inhibitors and act in the S-phase of the cell-cycle (disturbing the DNA synthesis). Such broadly known and intensively applied antitumour chemotherapies as Mitomycin-C, Doxorubicin, Epirubicin, Daunorubicin, etc. are all connected to the soil fungi family Streptomyces. In this regard cancer is treated like a bacterial infection, which somehow favours the supporters of atavistic ideas. In fact, a simple atavistic model cannot work in a limited environmental condition; the early unicellular organisms at the beginning of evolution had in fact unlimited nutrients from the environment. However, there

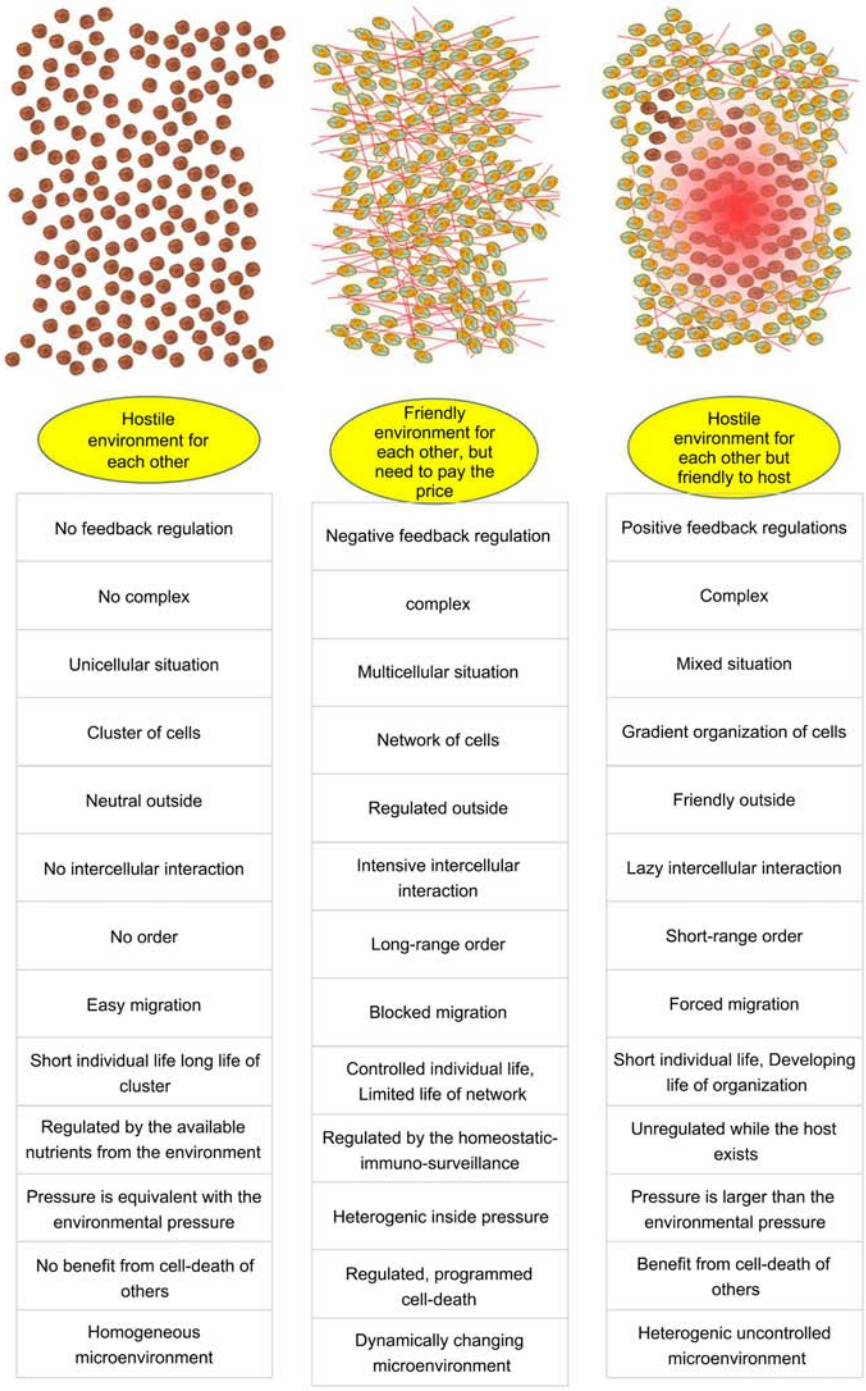

Figure 2. The differences between (a) unicellular living clusters, (b) healthy organized clusters, and (c) malignant clusters of cells. It is clear that the atavistic approach is only formal; the interactions and the organizing of the systems are different.

is knowledge to be gleaned from the atavistic idea: the unicellular organisms were not capable of adapting themselves to broad environmental challenges, their innate adaptive facility was not enough to keep up with environmental developments, and networking started to help their overall survival by work-division, practical networks of cells having a higher survival probability than individuals.

The main development was the adaptive immune system which learned and memorized threats and the protections against them. The atavistic model could be used as a starting point, but this model does not consider all the crucial details (hallmarks) which keep the unicellular units of the cancerous development alive [261]. Both the multicellular networked and the unicellular autonomic states of cells maintain a balance which is probably realized by an electromagnetic route [262]. The FDA-approved TTF also uses this kind of interaction to arrest malignant cell-division [263]. The method of mEHT uses an electrical field to modify the polymerization process [264] with fractal noise modulation for a complex effect. The applied noise is an active harmonizing factor [265], which has an emerging application in physiology [266]. The monitoring of the noise as fluctuations in the complex system could be a factor in its surveillance [267].

The well-structured polymer cytoskeleton is missing in cancer-cells due to their permanent division. The sluggish polymerization of the cytoskeleton [268] [269] promotes huge deformability in cancerous cases [270], cell proliferation being gained with the softer consistency of the cells, which is combined with robustly increased cellular motility [271]. The higher extracellular pressure [272] promotes this higher motility of cancer cells, stimulating the spread of metastases.

The healthy networks are formed mainly by adherent connections in a chain of transmembrane proteins connecting the structure of the cytoskeleton [273] [274]. The protein-chain in the cytoskeleton is a polymerization-like networking [275], where the microfilament structure drastically changes with the electric field [276]. The protein-based networking in the intra and extra cellular milieu is extended with a high-speed network of proton (hydrogen ion) transport. The proton is mostly transported by hydrogen bridges, which allows low energy-dissipation in the transport propagation accompanied by speedy exchange (Grotthuss-mechanism [277]). The proton in this procedure tunnels (jumps) from one water cluster to another through the bridged hydrogen bonds [278]. The lifetime of the H_3O+ (hydronium ion) which is involved in this mechanism is rather short ($\sim 3 \times 10^{-12}$ s) so the speed of proton transport is approximately ten times higher than that by diffusion.

To re-establish multicellular networking we have to increase the cooperative driving force, and present a better efficacy of energy-consumption in the network than without it. The division of cells themselves does not act against the cooperative networking when it is also regulated by natural controls like apoptosis and differentiation, as in the natural healthy development of organized tissues. The structures and the functionality are interconnected [279] and define the dynamisms of the interactions which are always in a critical state [280]. The maintenance of homeostatic equilibrium defines a certain range of parameters of heathy life. The analysing of the huge set of interconnected data has opened a new scientific approach, network medicine, which tries to discover the network-

ing properties of life and of the development of cancer by big-data analysis [281]. The chemical complexity of the human diet is extremely important in regard of living processes with their environmental facilities, and the manner in which life transfers nutrients to its own building-blocks. The huge scale of the chemical diversity of food ingredients and its interactions with the broad spectrum of life remains poorly understood, characterizing a "dark matter of nutrition" [282].

The dynamic interactions in life are complex, but the chemical reactions and the transport of various species as well as the broad spectrum of signal transductions are rather unified in all the living tissues, forming scale-free networks [283]. The living complexity has a self-organized critical state (SOC) limited by the environmental interactions [284]. The dynamical fingerprint of SOC is the well-organized distribution of fluctuations (pink or 1/f noise) [231] [285]. Applied, this fractal noise could be one of the driving forces of reorganization, at least at the interface of the multi and unicellular regions [286] [287]. Usage of this special frequency distribution as a constraint for dynamism could improve success as mEHT does [288]. The electrical current of the modulated radiofrequency delivers the information through charge redistribution [289].

A quotation borrowed by Bjelakovic, Nikolova, *et al.* [247] from the Chinese military strategist and philosopher Sun Tzu states that "just as flowing water avoids the heights and hastens to the lowlands, so an army avoids strength and strikes weakness". This philosophical intention, a "target the weakness strategy", was adopted by Paul Davies and his colleagues [290], showing that one of the weakest sides of cancer's development is to the immune system. This could be a perfect target instead of the cancer's main strength, its proliferation. The lack of adaptive immunity to tumours can be revised, and the malignancy is attackable by the host system itself.

The main arrangement of the body remains networked and organized on the homeostatic complexity around the smaller tumours. Multiple robust effects, such as apoptosis and the innate and adaptive immune actions, could be naturally activated to rebuild the overall normal structure. The first step in the regular division of a healthy cell is formally similar to the beginnings of a malignancy: the cell breaks the healthy networking around it and expresses its individual demands for higher energy-intake to perform the delivery of the daughter cells, building up new constituents, creatively doubling the original structure. Its environment during this division is free from the normal networking limitations, and diffusion and osmotic activities are increased, facilitating the necessary transport of nourishments for the development. The electromagnetic properties change in the transition from the networked to the individual state [291]. However, when tumour-cells are clustered, adaptive abilities to the changed conditions are quickly developed. The tumour lesion is associated to an inflammation [292], as was first hypothesized by Virchow in 1863. The inflammatory phenomenon is a critical hallmark of many cancers [253] [293] [294] [295]. The situation is similar to that of a wound which has never healed [252], turning into a

chronic injury [296]. After a long period of silence, the inflammatory wound theory is emerging again [297]. The malignant tumour mimics a wound, stimulating the host tissue to support its "healing" [298], avoiding by this "trick" attack by the host's immune surveillance [299]. Contrary to numerous inflammatory immune cells being presented, no immune attack destroys the developing tumour [300]. The malignant cells may hide their individual behaviour from the immune surveillance. The malignant cells develop robust adaptability even to aggressive environmental conditions and also to the attack of natural immune actions. In the case of a developed malignancy even strong natural immune procedures alone are ineffectual. The definite difficulty is that the malignant character of the tumour-cells is hidden and that the immune-cells are not able to recognize these cells as a "disease"; the innate immune-attack and the adaptive immune reaction are absent.

The standard opinion in healthcare at present is that the immune system does not protect against malignant development. However, the absence of any expectation of immune action does not mean that the natural defence mechanisms are beyond consideration. The CTA constitutes a complex treatment, and a variety of antimutagenic factors could be used to prevent the malignant development in its early form or to block the development of new daughter cells in the wide periphery. There are vitamins and micronutrients (often antioxidants), such as vitamins A (in the form of b-carotene), C, D, E, D-glucaric acid, selenium, and uric acid, as well as essential oils [301], that may have roles in cancer prevention, blocking or at least limiting carcinogenesis by interfering with the malignant actions of carcinogens and mutagens as well as of other promoters of cancer development [302]. In this way the inhibitors of malignant initialization and progression become involved in a complex process within the homeostatic dynamism, preventing critical carcinogens in the metabolic processes, detoxifying the tumour-promoting factors, and limiting the possibility of cancer. Or to formulate it in other words, a properly balanced diet could maintain a healthy homeostatic dynamism, avoiding any malignant actions. The effect of course involves a complex synergy of diet with lifestyle and environmental conditions, including the avoiding of damaging habits (like smoking, consuming alcohol, etc.) which could negatively interfere with the homeostatic regulation. It has been proven that interferon-gamma with lymphocytes blocks carcinogenesis [303], which in vivo experiment was later evaluated as a "Pillars Article" by Nature [304]. The same group of researchers has published further results on immunosurveillance and cancer immunoediting [305] [306]. The research, clarifying the role of natural killer-cell (NK-cell) in cancerous processes [307] and the character of regulatory T-cells (Treg) in control of NK-cell activity [308], targets the topic of how the immune-system may prevent the development of malignant processes.

An important topic is the role of gut microbiota in immune reactions, due to a symbiotic complexity of the gut bacteria with the host system in which the transfer of ingredients of nourishment for systemic use is manipulated, which

could be used for medical targeting as well [301]. The role of gut microbiota is essential in the actions of the host immune system, working in a complex feedback frame to ensure the dynamic equilibrium of the homeostasis [309] The biota acts on the initialization of the immune effects, supporting the fight against "intruders" into the system, and has a role in the maturation of the dendritic cells to prepare the defence [310] [311].

There is currently intense research activity focusing on immuno-oncology [312]. This promising research and its medical application has a long history, starting in 1868, observing the protective effects on cancer of intentional inflammation [313], and continuing with various Nobel Prize awarded works in the field of immunology. One of the first theoretical considerations of immune surveillance in oncology was published in 1970 [314]. At this time, check-point inhibitors became the great hope as reagents in cancer therapies [315]. Soon it became obvious again that single-sided action could have serious consequences, causing the opposite effect (hyper-progression) on cancer to that desired [42], connected to immune-related adverse effects [43]. The apparent problem was obvious from the point of view of systemic complexity: a single action may modify a parameter in the complex balance, but many other conditional parameters have to be considered. The effect could be limited by simple factor too: the majority of the targeted receptors are activated, and the useful effect is saturated [316]. To avoid this problem a low dose check-point blockade has been proposed [317].

Due to the frequently mentioned complexity of homeostasis, regular immune surveillance is not the only factor which could act to achieve dynamic equilibrium. When the immune-surveillance does not recognize the malignant tumour, the well induced injury current (see above) may have the possibility to maintain some immune-attacks on the "unhealed wound" by its electromagnetic interactions.

As we have shown above, despite the disability of immune-surveillance to carry out tumour-destructive action in some cases, the general immune status of the patient is important. A well-maintained immune system keeps the general wellbeing of the patient high, could prevent comorbidities, and reduces the side effects of the therapies applied [318], and by these effects the quality of life of the patient is improved. In this sense, general immune support has to be part of the CTA and must be provided as early as the ePT starts.

2.3. Electro-Chemical Complexity—A Part of the Supportive and Palliative Care

The largest group of the components of early CTA interventions is comprised of pharma-products [319] [320] [321]. A new kind of treatment is emerging though: the bioelectromagnetic [245] [322]. The properly applied electromagnetic intervention promotes ePT in oncotherapies, as a complementary intervention to conventional therapies in any lines, including in the cases of naïve patients too. The magnetic component of the field established the popularity in

these treatments of nano-particle technologies [323], where the energy-absorption can certainly be declared heterogenic [324] in a decisive shift away from the conventional homogeneous heating concept in hyperthermic oncology [325]. The change is not drastic because the traditionally expected temperature homogeneity (isothermal heating) is quasi ensured by the rapid thermal equalization of the target. The selectively targeted nanoparticles heat up their environment, unifying macroscopically the microscopic differences.

Another nanotechnology method uses the electric field, with [326] or without [327] additional artificial nano-targets, using the absorbed energy of the field. The preclinical results show feasibility in both the artificial [328] and natural [329] nanoparticle targeting methods. The electromagnetic fields effectively arrest the malignant proliferative activities [330] by blocking cellular division [331], developing a complete therapy by an alternating electric tumour-treating field (TTF) [322]. The effect of TTF is clearly shown in clinical practice too [332] [333]. TTF is currently settled as an FDA- and EMA-approved, reimbursed tumor therapeutic intervention. A further advantage of the electric field effect is that it can decrease effusions [334], proven by a clinical trial too [335].

Healthy and malignant cells show a lot of differences from the electromagnetic point of view (**Figure 3**), giving rise to the possibility of recognizing them by biophysical, bio-electrodynamical methods.

The electromagnetic interactions have the particular advantage of being selective due to the electromagnetic differentiation of the malignant cells from those of their healthy neighbourhood. The more prolific than usual tumour-cells are well distinguishable by their electrolyte structure in the microenvironment of the cells. The malignant proliferation uses a massive amount of nourishments and produces more waste from them too [336]. The ionic concentration increases in the electrolytes where the chemical reactions occur, allowing the recognition of them by their lowered electric resistivity [337]. Furthermore, the characteristically autonomous tumour-cells lose their networking connections, modifying the structure of their microenvironment, and allowing their recognition by this property too [338]. These distinctive characteristics are complexly interconnected [249] and give rise to the special electro-impedance differences between the cells, permitting us to focus the energy on the malignant ones selectively [339]. In this way the absorbed energy shows heterogeneity according to the varied electromagnetic characteristics of the tissues.

There is another advantage of the electric field that could further our attempts to kill the malignant cells selectively [340]. The electrical component of the field is expected to be involved in molecular excitations by the absorption of energy [341] [342]. Using the electric field interactions with the excitable molecules defines a principally different nanotechnology, as the nanoparticles are naturally present in the tumour-cells and are used for the desired molecular excitations [343] for the well selected heating of the malignant cells and through these of the complete lesion [344] [345].

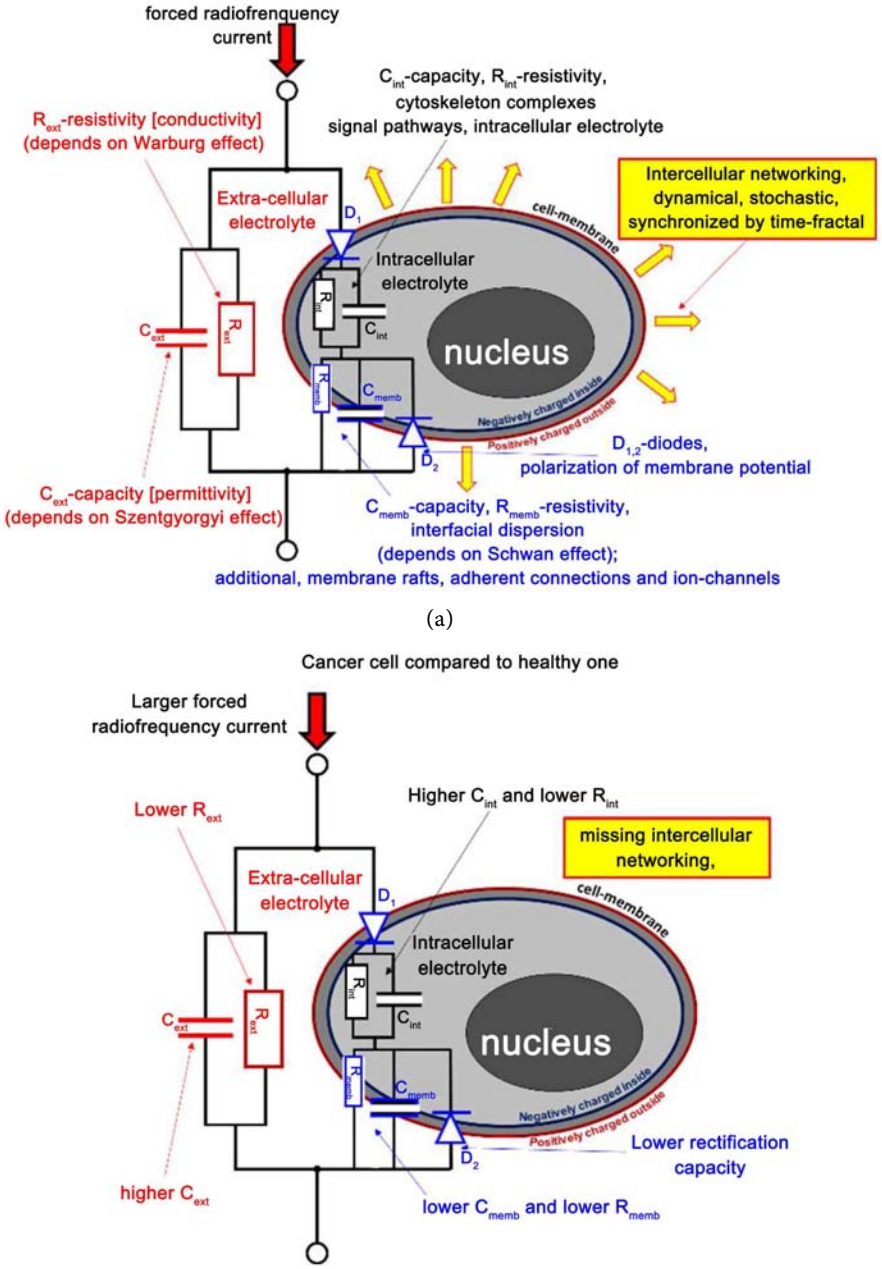

Figure 3. The electromagnetic difference between (a) healthy and (b) malignant cells is remarkable.

The impedance guided electric field opens a new paradigm of nanotechnologies by the targeting of the excitable molecular branches on the membrane of the selected malignant cells [346]. The selection is supported by the modulation of the radiofrequency carrier [347], a method named modulated electrohyperthermia (mEHT, tradename: oncothermia®) [348]. This method uses the electric field in a precisely selective way [349], there being a strong interconnection of thermal and electrical effects [350]. The transmembrane proteins of cancer cells which assure the interconnections in a healthy network remain un-bonded due

to the cellular autonomy in a tumour structure. These proteins form membrane rafts [351], which are highly populated in the membrane of malignant cells [352]. The energy is concentrated on the specific transmembrane proteins clustered in membrane rafts [353], producing the extrinsic excitation of intracellular signals [354].

The excitation of the transmembrane protein compounds helps to ignite variants of apoptotic signal pathways, destroying the tumour by the specific molecular selection of malignancies [355]. The externally oriented energy absorption may choose various pathways:

- caspase independent route through apoptotic inducing factor (AIF) [356];
- extrinsic pathway through caspase-8 (Casp8) and Casp3 [357];
- intrinsic pathway thorough the mitochondria followed by Cas9 and ending on Cas3 [358].

Additionally, the excited Septin4 [359] and Smac/Diabolo [360] proteins neutralize the apoptosis blocker XIAP helping the "avalanche-like" branches of the apoptotic signal to dominate. This complex process reintroduces the sorely missing apoptosis in tumorous development. This apoptotic method has found its way directly from the laboratory to clinical beds [361], being introduced in broad clinical practice [362] [363], and even Phase III trials have been published on electromagnetic methods in oncology [364].

The temperature dependence of the energy-absorption clearly follows the Arrhenius chemical reaction-rate in exponential development by rising temperature [365]. Certain similarities between the temperature dependence and the action of the electric field exist [366], a similar expression of chemical reaction rate being seen in both the solely temperature dependent and the solely field dependent cases. The strict similarity of the relationships defines the electromagnetic energy absorption as hyperthermia. The reality of the electromagnetic treatment is that the energy-consumption is expended on a mixture of heating and excitation. Energy analysis of the heating processes shows complexity even in consideration [367] solely from the conventional hyperthermia (heating) point of view. The comparison of conventional and mEHT heating shows well distinguishable differences [368] [369]. The temperature, however, is only a conditional parameter for the phase-transition-like excitation process while the action is physiological [370].

The electromagnetic treatments have further advantages. These are less harmful than the chemo- or radiotherapies and their H/B is lower, so their application well improves the quality of life of the patients [371] [372], which highlights again its excellence for the ePT application in CTA therapy. mEHT works complementarily with radio- [373] and chemotherapies [374] [375], increasing its already broad oncological application spectrum. The well applied electromagnetic therapy solves the long-debated problem of electromagnetic energy-absorption used in oncological hyperthermia [376]. In the conventional mode of electromagnetic energy absorption, the goal is isothermal (homogene-

ous) heating focused on the tumour as a mass in the body. Unfortunately, this heating affects homeostatic blood-flow, and by this regulation the body tries to re-establish thermal homeostasis by cooling with extra blood from the non-heated part or from the surface of the body. The extra blood-flow, however, could have the risk of supporting the tumour with glucose, this effect thus starting to compete with the anti-tumorous thermal effect. The increased blood-flow around the tumour helps the invasion of malignant cells to the vessels, distant metastases forming by dissemination of the cancer-cells [377], causing controversies in regard of clinical applications in cases where the advantage of thermal cell-killing provided excellent local control but without benefit for overall survival [378] [379]. This contradictory problem has been reported by others too [380] [381] [382]. The results show that it was probably the increased metastases that were causing the contradictions [383]. This contradictory effect of isothermal heating in the traditional hyperthermia protocol is solved by heterogenic heating, attacking the malignant cells by energy, as realized in the mEHT methodology. The selective heating could drastically reduce this risk as the complete mass is not isothermally heated, the energy absorption targeting the malignant cells.

Another electromagnetic effect is the injury current. It is a factor of natural wound healing that is physiological [384]: the injury current, which promotes redifferentiation [385], has a definite role in natural wound healing [291]; consequently, it is used for wound healing [291]. The typical value of the injury current is approximately 100 $\mu A/cm^2$ with a voltage drop of approximately 100 mV/cm in an mm extension from the wound [386]. The weak power of the current-flow (~0.01 mW/g) does not increase the local temperature [387], but it is measurable during the progression of the wound-healing [388] [389] [390]. This current is physiologically controlled and endures for as long as the wound is healing. The electric field which induces the current determines the orientation [391] and the dynamics of the cell division [392], and it forces cells to migrate [393] to heal the wound [394]. In this way a biological charge transfer promotes the tissue repair [395] [396]. Some invasive [387] [397] and non-invasive [388] [389] [390] experimental results prove the injury current experimentally.

Malignant diseases are systemic. The localization of a tumour is only a visible manifestation but not the complete disease (**Figure 4**). To achieve a complete cure, the goal has to be increasing survival time, with an acceptable quality of life, of course.

Circulating tumour cells (CTCs) are presented by invasion/intravasation from primary tumours independently of their localization, carrying the risk of metastatic developments. The sentinel lymph-nodes of the tumour are sensitive and vulnerable for the transport of malignant cells from the lesion. CTCs start their dangerous voyage from the very beginning of the malignancy, and the risk of distant extravasation in vital organs grows with time. The goal of conventional local hyperthermia is to eliminate the tumour, seeking the highest goal of complete remission (CR). Nevertheless, the disease-free status differs from local

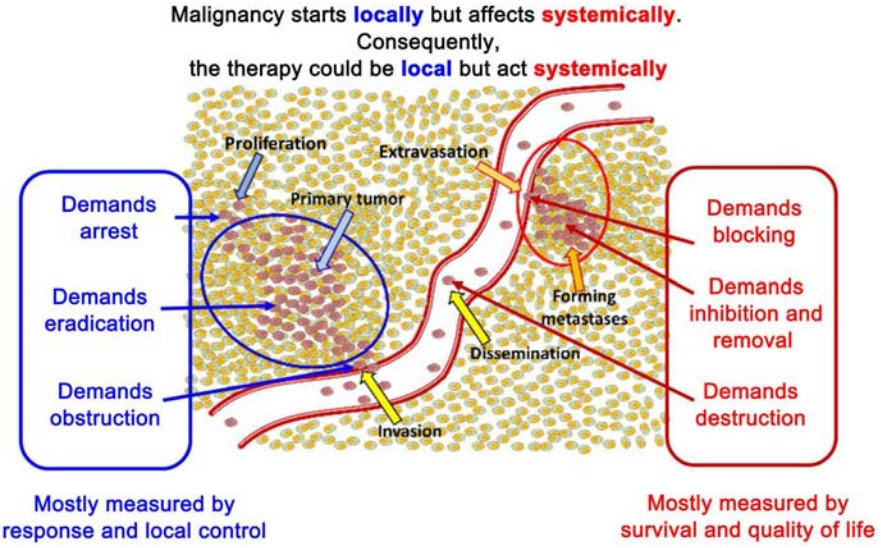

Figure 4. The tumour is a systemic disease; treating only the local tumour does not offer a complete cure, but could achieve a status of "no evidence of disease (NED)", meaning that the diseases is not visible, the malignant lesions remaining but beyond our measuring resolution.

measures. The CR alone does not guarantee the clearing of the malignancy from the whole body. This could be the reason that despite improving results with regard to local remission rates, overall survival does not necessarily increase. The development of metastases and/or local relapses considerably limits the patient's overall survival.

The conventional chemotherapies or other systematically administered compounds (check-point inhibitors, enzymes, etc.) target some products and compounds of malignant formations, but the process which produces these targets remains intact. Modern cancer-therapy needs a shift of paradigm to focus on the dynamism of the malignancy and to concentrate on the activities which form the malignant phenomena [398]. This new demand again turns our attention to the complexity of the cancer and the living objects which carry it. The previous parts of this article have emphasized the demand for a complex approach regardless of which particularity is being investigated. A review of preclinical and clinical data [399] discovered that several old anticancer chemotherapy drugs, together with radiotherapy, had effects on immune responses. Three categories of immune effects could be identified: 1) direct immune-stimulation of effector cells (like NK and cytotoxic T-cells), 2) increased immunogenicity to poorly immunogenic malignancies, and 3) blocking the immunosuppressive cells (like Treg). Among others, Gemcitabine was identified as helpful in all categories. Paclitaxel was effective in 1) and 3), and Oxaliplatin was in 2) and 3). Interestingly, even such old drugs as 5-Fluorouracil and Cyclophosphamide were active in categories 2) and 3) respectively, and the antibiotic-related Doxorubicin and Idarubicin were active in category 2).

The homeostatic dynamic equilibrium is too complex for outside constraints

to be effective in repairing it. Compactly connected feedback mechanisms regulate the system, and the reaction of the homeostatic control will be against any simple restraints. A good example of this is the response to conventional hyperthermia, which aims to kill the tumour by thermal effect. It is a valid aim, but unfortunately homeostatic control mechanisms start correcting this heating by various actions to maintain thermal equilibrium. The most effective reaction is the increased blood-flow and perfusion, pursuing the cooling down of the heated lesion. However, this feedback carries a danger, increasing the delivery of nutrients to the tumour, as well as promoting metastases by cellular invasion to the bloodstream. Consequently, any winning strategy must work together with homeostatic controls, using the natural processes and supporting the immune system in recognizing and destroying the malignant cells throughout the entire body.

Many variants exist that aim to activate personal immune defences against cancer. The key point is the immune recognition of the malignancy. The immune system needs recognizable signs to direct its actions. However, the highly adaptive hiding strategy of the malignant cells protects them from being identified by the immune cells. One effective possibility for the invading of the cancer is the NK cell's innate antitumoural immune action [400] [401]. The NK does not need information by way of MCH-I molecules of the host, and acts in case of a lack of priming too. The cytotoxic activity of NK potentially controls tumour growth [402]. As a component of phytomedicine, Panax ginseng increases NK activity [140]. Complicating the complementing of the available positive effect of NK cells, it might also promote the tumour-progression and angiogenesis [403] inducing a dysfunction by ROS [404].

Also a possibility is to initialize the innate immune action by toll-like receptors (TLR) forcing suitable signal pathways (e.g. through the Tumour-necrosis factor Related Apoptosis Inducing Ligand (TRAIL) and its death receptors (DRs) [405]) to trigger cell death, eliminating the cancer cells [406], as when helping in the fight against infectious diseases [407].

The other possible immune attack could be promoted by adaptive immune reaction. The key is to form antigen presenting cells (APCs) and produce adaptive immune-fighting against the cancer-cells all over the body. The appropriate tumour-specific genetic information has to be obtained from tumours, presenting their malignant behaviour to the immune-surveillance. The process acts through immunogenic cell-death, which is a kind of apoptosis, freeing the genetic information from the tumour. This information may mature the dendritic cells (DCs). The matured DC forms CD4+ and CD8+ (helper and killer) T-cells with appropriate tumour-specific information, preparing them for tumour-specific immune attack. We may realize in this way how to get "back to complexity", as has been recognized as a demand in medicine generally [35].

Complementary mEHT therapy is a perfect tool with which to accomplish the CTA, completing it with appropriate immune support in both the innate and

adaptive mechanisms. The heterogenic targeted energy-absorption excites a branch of apoptotic signals, as described above. The main excitation is extrinsic through TLR by TRAIL-R2/DR5, which has the possibility of innate immuno-attack on cancer [408]. The mEHT therapy has an effect on adaptive immune stimulation as well. It produces immunogenic cell death (ICD) with the help of a damage associated molecular pattern (DAMP) [358]. The molecular set of DAMP gives all the necessary tumour-specific information for APC production. The extrinsic signal-excitation triggers the release of calreticulin (CRT, an "eat me signal"), adeno-triphosphate (ATP, a "find me signal"), high-mobility group protein 1 (HMGB1, a "danger signal"), and extracellular heat-shock protein 70 (HSP70, an "info signal"). The APC (mature DC) produces the necessary tumour-specific fighters: the CD4 (helper) and CD8 (killer) T-cells. The maturation of DC cells can be actively supported by the immune-stimulatory effect of b-glucan [409]. It has been shown that the mushroom G. lucidum simultaneously increases the percentages of CD3, CD4, and CD8, with a marginal elevation of NK-cell activity [169]. Assembling and stimulating the immune system against malignancy is a direct way to eliminate the cancer and avoid recurrence and metastases. The activated tumour specific cytotoxic T cells have the ability to recognize and destroy the cancer-cells all over the body. The NK cells, as the front-line defensive fighters, are intensified also by the general enhancing of the immune surveillance. Some cytokines, like IFN-gamma and TNF, could make a decisional addition to the tumour-destructive processes, and in this sense the old kind of anthracyclines [410] and/or electrodynamic therapy like mEHT could boost the immune cells and could create ICD by cytokine response to the treatment. The homeostatic balance is again clear with regard to the DAMP action, which may ignite the tumour-attack but on the other hand may trigger chronic inflammation, promoting tumour-growth [411] [412].

Enhancing the temperature of tumour-cells could increase their sensitivity to immune cell recognition and killing [413]. The naturally developed intracellular heat-shock proteins (HSPs) protect the cancer cells against any attacks, but the expression of them on the outside cellular membrane may activate the NK cells to attack the cell, promoting NK-cell cytotoxicity. When HSP70 is liberated to the extracellular electrolyte, it could tumour-specifically carry genetic information and prepare an orchestrated adaptive immune action against the tumour. In general, an induced immune-effect is observed in mild hyperthermia [414], even in preoperative application too [415]. The cytotoxic activity of NK-cells sharply reduces when the temperature growth is to over 41˚C [416] [417], and the general immune activity also drops at over 40˚C [418]. Due to the "only local" blocking of immune activity in high-temperature heating, it is neglected in local/regional hyperthermia (LRH) due to an assumption that new immune cells from the non-heated areas will be delivered and substitute for the blocked activity. This effect, however, does not help to form in-situ, real time immune actions. The time delay in presenting active immune-cells in the treated area could

be crucial, as genetic information needs to be available promptly for the possibility to mature the dendritic cells to form antigen presentation for a tumour-specific immune effect.

After the precise selection of the clusters, the transmembrane proteins (rafts) on the membranes of the cancer cells absorb the energy [368]. The malignant cells have relatively high raft density compared to their non-malignant neighbours [419], helping the selection by this additional factor and the energy-absorption heats the membrane to at least 3˚C higher than its surrounding extracellular electrolyte. The full process from the temperature point of view shows the growing temperature to the raft, representing the gradient responsible for mEHT's action [420].

There are a lot of natural compounds, herbal immunostimulants that support the immune system, enhancing its effects [140]. Evidence indicates that several anticancer drugs stimulate the immune system [399]. Antioxidants and phytomedical compounds, enzymes, etc., are all good candidates for the complex improvement of the immune actions against cancer development. However, again and again we have to emphasize that the homeostatic, healthy complexity needs a balancing equilibrium, that the interconnected feedback mechanisms can be counterproductive, and that a lack of expected benefits or even serious adverse effects can be observed. The complexity could be controlled by dosing (quantity of the taken compounds) and, in the same regard, by their relative applications in dose and time, considering their strong interconnections. One lucky situation is that phytomedical processes (nourishment) involving the taking of herbal and other effectors are usually harmless, because the quantity of the active drugs in the food is generally lower than dangerous levels. High quantity consumption of such nourishments tends to be limited by the stomach's capacity and by healthy lifestyle. However, even natural nourishments are not completely without side effects, especially since interactions between agents can cause side effects, though again, the healthy body will often avoid such problems by quick elimination (usually by the vomiting of drastically interacting contents). The real challenge, which could be dangerous with high dosing of compounds extracted from natural products, is not only quantitative, but deeply qualitative; the homeostatic dynamism is complex in time, and the SOC mechanisms and the fractal interactions redress imbalances in relatively narrow time bands. The observed fractal noise (1/f noise) is the fingerprint of the balance, and its dynamic support could have the same benefit as the variants of herbal or other immunostimulants. This is what is recognized by mEHT, and it applies electromagnetic fluctuations to stimulate the healthy dynamism of the complex interactions. The applied electric field, which transports information to the cellular level, induces chemical changes, but when the energy-absorption is not lethal for the cells by necrosis, it will not cause notable side effects.

The well applied electromagnetic effects are not too strong, causing necrosis by their absorbed energy, and not too weak to cause signal pathway excitations.

Of course, it is frequency dependent, so there is no excitation limit for the zeroth component of fluctuations [421]. The electric field could be associated with injury currents, which orients cellular migration and wound healing in general, as was discussed above. In reactions to injury, immune actions have a pivotal role. Injuries produce a higher population of immune cells. Modifying the injury currents could act as a healing factor by physical effects, helping the natural biological processes, which has a probable role in the effect of mEHT too. A continuous injury current, which stimulates cell-proliferation (intending to heal the wound) and promotes the tumour-infiltration of immune-cells, promotes the malignant proliferation [422]. However, the fluctuating current intensity of mEHT and its directional constraint blocks the negative effects of injury currents, blocking the proliferation stimuli.

The primary goal of the local therapies like radiation and local-regional hyperthermia is to eliminate the tumour, measured by the local response of the therapy. Cancer patients with multiple distant metastatic lesions have multiple local therapies as macroscopic tumours are observed. However, most metastases, at least in their early stages, are microscopic, and there is no fine enough resolution of imaging diagnosis to recognize them. A change of paradigm away from these local treatments looks mandatory to solve the consequence of the spreading of malignancy. Intensive research is targeting the challenge to treat distant metastatic lesions even in their microscopic state. The expected appropriate tool to meet these requirements would be a local effect far away from the treatment's actual application location. Radiation generates "danger" signals, transmitting from irradiated to non-irradiated cells, which could lead to off-target effects.

The explanation of radiotherapy by traditional radiobiology has focused on DNA damage to avoid the repair of the targeted tissue. This effect is clearly localized on the irradiated area. The first published observation on a systemic effect of local radiotherapy was made by R. H. Mole, who proposed the term "abscopal effect" in 1953 [423]. The word abscopal is derived from the Latin ab, meaning "positioned away from", and scopos, meaning "a target for shooting at". The abscopal effect is defined as a systemic action of radiation therapy observed in apparently untreated tumour locations distant from the site of irradiation field. These distal effects were neglected for a long time after their first detection; they were "rediscovered" [424] outside the treated field of ionizing radiation [425], but were generally under-recognized in clinical practice [424]. Similar, but certainly much shorter in their effective distance, are bystander effects, which are communicated from an irradiated cell to a non-irradiated bystander cell via cell-to-cell gap junctions [426] or by the secretion or shedding of soluble factors [427] [428]. Important information was provided by case reports showing that despite the radiosensitivity of hypoxic lesion being suppressed, when targeting the hypoxic centre of the tumour the non-targeted bystander area is also affected [429]. The precise nature of factors that mediate the bystander effect is unknown, but reactive oxygen and nitrogen species and various cytokines have

been implicated. The short distance bystander information transfer has been ascribed to redox mechanisms, which may produce transmission of ROS, various cytokines, and reactive nitrogen species (RNS), making the off-target response similar to inflammation [430]. The propagation of bystander effects among cancer cells additionally to inflammatory mechanisms involves cellular communication under irradiation with non-uniform dose distribution nearby, and probably immune action in far-away localizations [431].

Radiation-induced long-distance abscopal effects have been extensively documented in several recent reviews [432] [433], which have described both detrimental (e.g., DNA strand cleavage, chromosomal damage, and cytotoxicity [434]) and potentially beneficial abscopal effects. The explanation of abscopal effects has well distinguished it from the bystander effects in the traditional sense [435], having no direct short communication pathway between the treated and untreated cells. Much of the observed physiological abscopal effect has been associated with splenic irradiation [436], but intensive development in using it for solid tumours had been started. In the early period of applications, the explanation of the effect related to the immune response mediated by cytokines, but the mechanism remained unclear because this phenomenon was so rare and poorly understood in clinical practice, also giving rise to many controversies [433]; and sometimes being used complementary to other types of local therapies including surgery, hyperthermia, and immunotherapy.

Evidence is piling up that radiotherapy in the appropriate dose stimulates the immune system. In consequence, the abscopal effect has recently been revised, receiving attention as a new therapeutic facility [437]. Intensive application in the clinical setting has been started in a variety of malignancies including lymphoma [438], papillary adenocarcinoma [439], melanoma [440], adenocarcinoma [441] [442], chronic lymphocytic leukaemia [443] [444], lung malignancies [445] [446], and hepatocellular carcinoma [447] [448]. Low-dose radiation delivers clinical benefits by abscopal effect [449]. The application of emerging immunotherapies by check-point inhibitors combined with radiotherapy has also been tried [450] [451]. This complementary application did not give clear clinical evidence for the benefit of this combination [452] not delivering stable results [453], but the positive promise remains [454]. Despite the incomplete understanding and sometimes controversial results, the present results show clearly the trend of cancer therapy development: cytotoxic drugs used for systemic therapies will be replaced by more complex combined therapies involving the immune-system, providing systemic, abscopal facility [455].

The abscopal effect is probably of the same complex as other living phenomena, tumour-specific mechanisms being seen which are defined by the type of the tumour, and there also being observed general immune responses which could be connected to the distant effects [456]. The role of non-uniform dose could be essential to take account of the mechanism of the distant actions, because it opens a wide spectrum of doses, among which the optimal value need be found

from the "offered" quasi-linearly changing dose-spectrum. This is probably the reason why the definitely necrotic ablation technology has observable off-target effects [457] showing a broad range of electromagnetic interactions, from the necrotic to the weak, negligible effect in the far distance, which may include the necessary optimum for abscopal applications. Probably the same could happen with local high temperature heating too [458]. However, in account of the complexity it is important that the critical homeostatic regulator, the immune system, has a pivotal role in the new paradigm of oncology.

One possible part of the complex approach could be the electrical field, which has no direct macroscopic physiological effects. In in vivo experiments to clarify abscopal effects in rats in combination with radiotherapy, a pulsed electrical field was successfully investigated [459]. These experiments support the idea of trying the mEHT method in the same way, giving reason to expect positive results from the abscopal application of mEHT. The immune-stimulation approach in hyperthermia was well demonstrated earlier [460], and so it is high time to try it with mEHT too. We have to consider also that the old challenge of the homogeneous heating paradigm of conventional hyperthermia, described above, has appeared again using an updated combination of methods: a complex protocol of radiotherapy check-point inhibitors and nanoparticle hyperthermia were applied in a mice model with controversies observed: there was no increase of survival time, and metastatic dissemination to the lung of the model animal was observed [461].

mEHT is immunogenic [462]. Our main idea was based directly on the immune effects of mEHT, which induces ICD by DAMP, as we have shown above. It was however obvious that for a tumour-specific immune action we need APC, which needs a proper immune system, where un-matured DCs are available. An immuno-boosting, as others have used with radiation [463], could be the solution. We report a case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. We learned earlier that a cytokine that activates dendritic cells, the granuloceyte-macrophage colony stimulating factor (GM-CSF) as immune-boost, was earlier used with hyperthermia for inoperable pancreatic tumours with success [460]. The boosting of radiation therapy for abscopal effect used this method too [464] [465] [466]. Following this line, the patient was treated with fractional radiotherapy, modulated electro-hyperthermia (oncothermia), and GM-CSF. The success was significant, and the distant metastases disappeared while the treated primary lung lesion had good shrinking [467].

Our direct goal remained the simple tumour-specific immune attack, as was described above: to develop T-cells to perform action against the malignant cells all over the body, irrespective of their distance from the treated primary lesion [468]. One of the effective methods of inducing abscopal effect starts with ICD [469]. This was clearly demonstrated in murine model in vivo, when the abscopal effect appeared far away from the locally, mEHT treated tumour lesion, all the

DAMP molecules of the pattern—CRT, HMGB1, HSP70, and ATP—being measured, and being liberated into the extracellular electrolyte [470]. The model was tried in the situation where the originally available immune system is too weak to produce enough APC. The experiments in vivo showed the excellence of the injection of general un-matured DC-cells to produce clear abscopal effect [471]. Note, the injection of DC cells alone did not show abscopal effect without mEHT application. The immune action works like vaccination, and the re-challenging by the same tumour was ineffective [472]. The vaccination idea was patented [473].

The general abscopal effect by mEHT could be induced not only by DC [471] [472] or GM-CSF immune stimuli [467], as was shown above, but a general treatment complexity including diet and life-style change could work well with mEHT too [474]. Other complex immune-stimuli can be effectively produced by virus application [475] [476], there being excellent case-reports showing the results [477] [478], as well as there being statistically evaluable significance with the serious glioblastoma multiform showing the excellence of the virus-supported mEHT method [479], engineering the bacterial "Trojan horse" [480] to carry out a viral trick. Low-dose check-point inhibition with IL-2 support in combination with mEHT is also successful [481].

A Phase III clinical trial was performed for advanced cervical cancer treated with radio-chemotherapy with and without mEHT [464]. The abscopal effect was also evaluated beside the evaluation of the primary and secondary endpoints [482]; a significant abscopal effect was shown to be induced by mEHT compared to in the control arm. Positron emission tomography-controlled results show clearance of the metastases in the not directly treated pelvic area in more than 25% of the patients, while complete, all disease resolved results were observed in 24% of the cases on the active, mEHT treated arm, compared to just 5.6% in the radio-chemotherapy only control. The result is remarkable, because no extra immune-support was used to obtain these results in such advanced stages.

Elongated survival time, together with the improved quality of life, has been measured with mEHT in many Phase II trials with secondary endpoints of the local response. The joint positive result of the response and survival [362] [479] [483]-[489], even in cases when no conventional complementary treatment was applicable and mEHT monotherapy was performed [490], indirectly justifies the abscopal effect by the method, which was missing in conventional hyperthermia in many cases.

The best SC and PT depend on many and complex factors. The most important factors to consider:

1) First is the patient's characteristics:

a) the dosing of the treatment drugs, considering the patient's sensitivity to SC/PT;

b) general immune status;

c) kind of disease (morbidity);

d) stage and severity of disease;

e) without medical aid, home applied SC/PT.

2) Interactions with conventional, standard treatments:

a) pharmacological properties of the concomitantly applied standard treatments;

b) previously applied conventional, standard treatments;

c) comorbidities, or adverse effects of the applied standard treatments;

d) biological or physiological reasons for limiting or blocking the standard treatments.

3) Availability of SC/PT in the therapy process:

a) availability of optimal palliative and supportive drugs;

b) preparedness and SC/PT knowledge of the medical staff;

c) sufficient and accepted confidence of the patient in the physician and the therapies prescribed;

d) availability and intensity of follow-up.

For example, the IV application of high dose vitamin C with mEHT for non-small cell lung cancer was safe [206] had provided significant improvements in a well-selected and controlled cohort of the patients [372]. One of the controlled studies of the best SC for glioblastoma and astrocytoma [486] and pancreas carcinomas [362] shows the necessity of mEHT for significant results [486].

3. Conclusions

The war against cancer [491] is not over yet. There have been many good results and year-by-year new chemotherapies show improvements, but we are far from a final solution. Probably we need a change of paradigm from tumour-oriented therapy strategies to patient-oriented ones and also from product targeted to process targeted treatments, from static distortion to dynamic blockade. The focus of therapy must be reoriented from the products of the tumour (hallmarks, which appear, and are chosen to target) to the process which produces the malignancy [398]. Due to the complexity of the living object the blocking of one product or of a group of them helps only temporarily, because the complex bodily regulation mechanisms soon substitute the absent means for the tumour to develop. We know very well that a single finger as a barrier to overflowing water cannot stop the process itself; we must act at the source of the flow

We have to stop concentrating on the tumour alone and instead focus on the integrity of the patient. Integrative thinking is necessary with regard to the complex structure of life-processes. We believe that, as mathematics has no "alternative mathematics", medicine also has no alternative medicine. When we see the limits of current medical approaches, we have to change the paradigm to meet the challenges. Treatments, and not just medicine, could have alternatives, forcing us in the same direction: towards regarding the patient as a whole, integrative unity.

We propose three goals as a result of this "prospective review":

1) An early palliative therapy should support the conventional therapies, increasing their effects together with decreasing their adverse effects. This has to be a part of the CTA, using early palliation and vigilant supportive care. This point must be measured according to the elongation of survival time with improved quality of life.

2) Care should be taken to restart and replenish the hampered immune system, which is below its normal capability due to cytostatic effects and disease burden resulting in overloaded immune functions. This refers not only to the possibility of inducing the desired abscopal effect, but to general surveillance too, avoiding comorbidities and new challenges generally in the life-quality of the patient.

3) Complete the revitalization of the immune-system and the whole body in the follow-up period. This goal contains physiological, psychological, and social components too, helping to form a new and convenient lifestyle for the patient.

The key to the new paradigm is the helping of natural complex processes to solve the challenges, and not forcing upon the system something which explodes the homeostatic dynamic balance and which causes the body's regulatory mechanisms to fight against the applied treatment. There are some desired rules on how to discuss the problems of herb–drug interactions with cancer patients [492]:

- Clarify what type of herbs the patient takes regularly, counting that some herbs are considered as food or spices, and the possible similar ingredients in these that could have a commutative effect;
- The health professional has to have an open mind, not refusing immediately those herbs which have no proven useful effect. Concentrate on the explanation of proven negative effects. Despite few herbs having evidence of usefulness in treating malignancies, some of them may help relieve symptoms, and many eases the psychological pressure on the patient;
- When the herb has proven disadvantages, explain for the patients why it is so (for example, it reduces the effectivity of the applied therapy or increases the side-effects, or interacts with other useful herbs in a negative way). It is of great help when a similar herb without contraindications can be proposed;
- Educate the patient on the general pros and cons of supplementary drugs;
- Monitor the adverse effects of the herbs which you have agreed to their taking during the therapy and follow-up period;
- When there is no choice of herbal supplements, other therapies like meditation, yoga, or acupuncture could be suggested to improve the quality of life of the patient;
- It would be fine to refer to a specialist who could make a professional balancing of the risks/benefits of the supplemental therapies, and who could offer herbal therapy in the specific circumstances, properly considering the cancer therapy.

All preventive steps have to concentrate on a healthy lifestyle, including a well-balanced diet, care for acid-alkaline balance with intensive liquid consumption, regular daily exercises, and low chronic stress. Nevertheless, the acute daily stresses could be helpful [493] [494]. The hypothalamus-pituitary gland-adrenal-glands (HPA axis) has a complex homeostatic dependence [495]. Its primary function involves the body's reaction to stress involving the sympathetic nervous system and could involve the psychological self-suggestion [496]. The healthy circadian rhythm also affects the HPA axis [497]. Consequently, physiological and psychological health is strongly connected and has an essential role in preventing cancer. No further preventive action is required in the case of a well-working immune system and balanced psychologic status. The homeostatic surveillance actively regulates.

We may follow how the change in paradigms has been mirrored in the adjudgment of oncological hyperthermia:

1) First cames the conclusion regarding unsolved challenges in early applications: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment" [498].

2) "The biological effects are impressive, but physically the heat delivery is problematic" stated an editorial of the European Journal of Cancer in 2001 [499]. They invoked a shortage of technical knowledge: "The biology is with us, the physics are against us".

3) Later, when no significant development was possible in technical solutions, physiology became the target: "The biology and the physics are with us, but the physiology is against us" [500].

4) In a recent physical analysis of mEHT [347] it was well formulated, as emphasized in two conferences as well, that "physics is our friend, but we have not noticed it" [501] [502].

We have to conclude that the new paradigm is the way back to complexity, using biology, physics, and physiology in their interconnection. Nature takes no consideration that we have divided the phenomena into categories and disciplines, and natural processes involve all aspects, which we are not able to consider in such complexity as is the reality. Cancer as a phenomenon does not distinguish between the human-created disciplines. It is as complex as all the nature around us. We may surmount the gap of the missing complexity by modulated electrohyperthermia (mEHT), answering the question as to "where medicine went wrong" [35]. Thinking on the hyperthermia paradigm has to be complex like the malignancies it aims to treat. The mEHT treatment has shown a wide range of applications from in the laboratory to the clinic [361]. A clinical review was recently published [363] showing excellent results in advanced diseases, mostly in cases where the conventional protocols offer palliation only.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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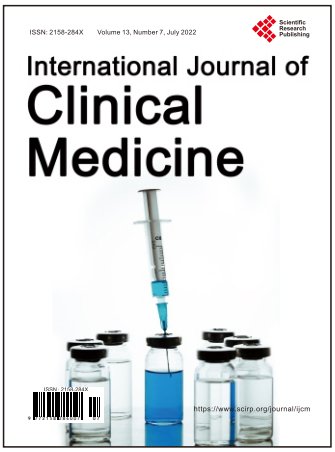

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