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In Chronic Kidney Disease, Protein-Energy Wasting and Mortality

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Abstract

Protein-energy wasting (PEW) is a common complication of chronic kidney disease (CKD) and is linked to an increased risk of death from cardiovascular illnesses. Despite the fact that even minor renal impairment is an independent predictor of poor cardiovascular prognosis, PEW manifests clinically at a later stage, either before or during dialysis. Loss of muscle protein and fat is caused by a variety of abnormalities that stimulate protein degradation and/or decrease protein synthesis. These abnormalities are not always linked to anorexia, but they are linked to several abnormalities that stimulate protein degradation and/or decrease protein synthesis. Furthermore, data from experimental CKD shows that uremia selectively inhibits the regeneration ability of skeletal muscle stem cells. The loss of kidney excretory and metabolic functions occurs in the course of CKD, along with the activation of endothelial damage, inflammation, acidosis, insulin signalling changes, and anorexia, all of which are believed to orchestrate net protein catabolism and the PEW syndrome.

Keywords: Protein-energy wasting • Malnutrition • Chronic kidney disease • Cardiovascular risk • Skeletal muscle

Introduction

Despite advances in current renal replacement therapy approaches, death rates in patients with CKD remain high [1]. This rise in mortality is not confined to dialysis patients, but affects people with all GFR levels as CKD progresses, and is mostly caused by cardiovascular disease (CVD) and, in advanced stages, infections [2-4]. Protein energy waste (PEW), a disease characterised by a loss of muscle and visceral protein reserves that is not totally explained by insufficient nutritional intake [5], worsens with the loss of residual renal function and is particularly prevalent in dialysis patients. Uremia-induced changes in protein metabolism and gastrointestinal tract function can lead to poor nutritional status, which raises the risk of cardiovascular disease and infection. The traditional CVD risk factors (such as age, lifestyle, smoking, hypertension, dyslipidemia, diabetes, left ventricular hypertrophy, and heart failure) are over-expressed in CKD patients, partly due to the clinical characteristics of the CKD population (which consists primarily of elderly people, many of whom have CVD or type II diabetes) [6]. The increased cardiovascular risk associated with CKD may be attributable in part to a higher prevalence of non-traditional risk factors unique to CKD, which may promote endothelial dysfunction and/or atherogenesis in and of itself. The phenomenon of "reverse epidemiology" among dialysis patients is an example of the importance of non-traditional risk variables. While a high BMI (kg/m2) is associated with increased cardiovascular risk and all-cause mortality in the general population, the effect of overweight or obesity in dialysis patients is surprisingly in the other direction, with a higher BMI leading to enhanced survival. Several other established risk factors, including as blood pressure and serum cholesterol, homocysteine, and creatinine concentrations, are also involved in the "reverse epidemiology" phenomena [7]. Furthermore, due to the development of other risk factors, such as progressive wasting, the profile of risk for death may shift over time as renal function declines. Only in the short run, according to Chmielewski et al., the apoB/apoA-I ratio is related with improved survival in hemodialysis (HD) patients (1-year mortality). Another study found that the reverse link between hypercholesterolemia and all-cause mortality gradually decreased after the first year of follow-up. Due to the time impact of competing hazards, this is most likely the case. The contradictory link between cholesterol levels and mortality, according to Liu et al., could be explained by the existence of complicated malnutrition-inflammation (defined as BMI 23 kg/m2 or C-reactive protein > 10 mg/L) in the dialysis population. Contreras et al. recently investigated the prevalence of malnutrition-inflammation and its moderating effects on the risk-relationship of cholesterol levels with later CVD events in African Americans with hypertensive CKD. They discovered that in participants without malnutrition-inflammation, the hazard ratio for the primary CVD outcome increased as total cholesterol increased, whereas it tended to decrease in those with malnutrition-inflammation. It's worth noting that the phenomena of “reverse epidemiology” aren’t limited to renal patients; it's also seen in ageing sarcopenia. The goal of this study is to look at the mechanisms that cause PEW as well as a list of non-traditional factors that enhance cardiovascular risk in CKD patients. The loss of kidney metabolism and function, as well as the activation of pathways of endothelial damage, inflammation, acidosis, and altered intracellular IGF-1 and insulin signalling, are among the mechanisms underlying the causes of the wasting syndrome. These elements are expected to orchestrate the PEW syndrome, as they overlap with those that currently operate in ageing and concomitant illnesses like diabetes and sepsis. Several biomarkers have been linked to poorer outcomes in individuals with CKD and dialysis. Those of PEW appear to be the most effective predictors of survival. In dialysis patients, lower levels of serum albumin, prealbumin, cholesterol, serum transferrin, creatinine, and bicarbonate are linked to death. Hormones such as testosterone, leptin, visfatin, adiponectin, and thyroid hormones are other biochemical indicators that are directly or indirectly connected to PEW and outcomes. The mechanisms of action that causes the negative outcomes associated with PEW markers are unknown: it is more likely that a mix of factors, rather than a single etiologic process, is to blame.

Hypoalbuminemia

In dialysis patients, hypoalbuminemia is the most often utilised surrogate for PEW, and it has a clear link to increased mortality and morbidity. In HD and CAPD patients, hypoalbuminemia is linked to the development of de novo and recurrent heart failure. In dialysis patients, serum prealbumin has been suggested as a superior proxy of nutritional status than albumin. The fact that serum albumin and prealbumin are both negative acute phase reactants whose serum levels are greatly influenced by the existence of an inflammatory response is a confusing element. When nutritional intake is restricted, albumin levels are conserved while fat and muscle mass are reduced, according to experiments conducted in the 1940s (the "Minnesota Experiment"). A significant drop in blood albumin levels is not seen in CKD patients who adhere to a reduced protein and calorie consumption. Hypoalbuminemia may be aided in dialysis patients by the loss of amino acids and/or protein during renal replacement therapy. As a result, it's unclear if the poor clinical outcome associated with hypoalbuminemia in advanced CKD patients is due to nutrition, the inflammatory response, or both. It's also unclear if the link between hypoalbuminemia and increased mortality in dialysis patients is due to albumin's intrinsic effects or whether hypoalbuminemia is the result of a series of events linked to an increased mortality risk. Low albumin levels have been linked to hypercoagulable conditions and high blood viscosity. Low oncotic pressure may also have an unfavourable effect on water transfer between the intravascular and interstitial spaces. Albumin also serves as a free radical scavenger, a binding agent for hazardous chemicals, and a transporter for a number of medicines and hormones. Uremia is characterised by decreased albumin binding of medications and endogenous ligands. Persons over the age of 65 are predicted to soon make up the majority of people requiring renal replacement treatment in several Western countries [8]. Nutritional issues are widespread in senior dialysis patients with ESRD, and they contribute to their debility and morbidity. Decreased BUN and serum creatinine levels can occur even in the midst of severe renal failure due to low food intake and decreasing muscle mass in the elderly. One of the most noticeable signs of

ageing is a decrease in body protein. It mostly affects muscle proteins and is linked to a loss of muscle strength and functional impairment. When results are expressed per lean body mass, whole-body protein production and breakdown are similar in young and elderly persons. However, some muscle protein components, such as myosin heavy chain and mitochondrial protein, are associated with specific deficiencies. Furthermore, a decline in insulin sensitivity in relation to protein metabolism has been seen in aged people. Senescence-related changes in protein metabolism are expected to amplify the effects of uremia. Weight loss in elderly people is linked to an increased risk of morbidity and mortality. Weight loss in elderly persons is influenced by a number of factors. Excess cytokine elaboration appears to be a key role in the induction of unintentional weight loss in older persons, according to available evidence. Increased levels of TNF-alfa, IL-6, IL1 receptor antagonist, and soluble TNF receptor are linked to ageing. Acute phase proteins like C-reactive protein and serum amyloid are also high, indicating that the full inflammatory cascade has been activated. Chronic uremia is a kind of acquired immunodeficiency, and CKD patients are more vulnerable to infection [9]. Infection was the leading cause of death in 23% of patients in the HEMO Study who died during follow-up. During an infection-related hospitalisation, the overall chance of death was 15%. CKD patients are susceptible to infections for a variety of reasons, including advanced age, diabetes, hypoalbuminemia, immunosuppressive therapy, dialysis catheters, the dialysis technique, and uremia. Malnutrition impairs immune function by increasing susceptibility to infections and slowing the healing of wounds. Nutrients like arginine and glutamine have been shown to boost immunological response. Uremia-induced changes in muscle metabolism of particular amino acids may impede muscle regeneration. Reduced muscle release of valine and leucine is believed to be the cause of their lower blood levels in CKD patients. The poor release of this amino acid from peripheral tissues has been attributed to increased muscle valine breakdown, which is thought to be caused by metabolic acidosis and/or decreased glucose use. The treatment of metabolic acidosis raises both plasma and muscle BCAA levels via reducing transamination and decarboxylation in muscle, according to studies in rats and humans with CKD. During the course of CKD, anomalies induced by decreased food intake overlap those caused by acidosis, and lowering plasma valine levels have been described as a sign of inadequate nutrition and a loss of lean body mass. It's worth noting that leucine works in tandem with IGF-1 to activate myogenic satellite cells. In a variety of scenarios, such as damage-induced muscle loss, ageing, and progressive neuromuscular disorders, these cells are important for muscle regeneration. Satellite cells are activated by leucine via the mammalian target of rapamycin (mTOR) signalling pathway, which is one of the most important mechanisms for protein synthesis and cell proliferation [10]. These effects appear to be caused by Beta-hydroxy-beta-methilbutyrate (HMB), a leucine catabolite that can cause myoblast proliferation, Akt phosphorylation, and muscle wasting prevention. Finally, PEW is frequent in people with CKD and is linked to an increased risk of death. Despite the fact that even minor renal impairment is an independent predictor of poor cardiovascular prognosis, PEW manifests clinically at a later stage, either before or during dialysis. Loss of muscle protein and fat is caused by a variety of abnormalities that stimulate protein degradation and/or decrease protein synthesis. These abnormalities are not always linked to anorexia, but they are linked to several abnormalities that stimulate protein degradation and/or decrease protein synthesis. Furthermore, data from experimental CKD shows that uremia selectively inhibits the regeneration ability of skeletal muscle stem cells. The loss of renal excretory and metabolic functions occurs as CKD progresses, along with the activation of endothelial damage and inflammatory pathways.

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New Bioactive Lipids in Pathophysiology and Membrane Lipid Therapy

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Abstract

Membranes are primarily made up of a lipid bilayer and proteins, and they serve as a checkpoint for signals and other chemicals entering and exiting the body. Diet, pathophysiological processes, and nutritional/pharmaceutical therapies can all influence their composition. Lipids play essential structural and functional roles in addition to serving as an energy source. For example, fatty acyl moieties in phospholipids have different effects on human health depending on their saturation, carbon length, and isometry. These and other membrane lipids have very precise impacts on the lipid bilayer structure, which controls how signalling proteins interact with one other. Normalization of these modifications or regulatory actions that control membrane lipid composition have therapeutic potential because lipid changes have been linked to major illnesses. Membrane lipid treatment, also known as membrane lipid replacement, has emerged as a cutting-edge technology platform for nutraceutical interventions and drug development. This technology has been verified by several clinical trials and medicinal treatments based on a better understanding of membrane structure and function. The molecular underpinning of this novel method is examined in this review, which describes how membrane lipid composition and structure affect protein-lipid interactions, cell signalling, disease, and therapy (e.g., fatigue and cardiovascular, neurodegenerative, tumor, infectious diseases).

Keywords: Melitherapy • Lipid replacement • Lipid switches • Pathophysiology

Introduction

The human body is made up of trillions of cells that work together to keep everything running smoothly. In this setting, health problems are caused by cellular changes that impact physiological processes [1], and these changes might result in macromolecule malfunctions and/or aberrant levels of metabolites, hormones, and other substances. Despite the fact that membrane lipid changes play a role in many diseases [2,3], most pathophysiological research have focused on protein function or gene expression. As a result, the majority of disease-fighting medicines have focused on proteins and nucleic acids, according to our understanding of their structure and function. New ways to controlling membrane shape and lipid composition have recently emerged. A number of different therapeutic strategies fall under the umbrella of lipid replacement (LRT) [4] or membrane lipid therapy (MLT or melitherapy), all of which share the common feature of regulating cell physiology by inducing relevant changes to the plasma membrane (PM) or the lipids in organelles. The importance of lipids in biological membranes, their participation in pathophysiological processes, and the development of therapeutics focusing on membrane lipid control and/or replacement are all discussed in this article. Despite the fact that cell signalling has primarily been studied from the perspective of proteins that drive and transmit signals, as well as the resulting regulation of gene expression, lipids play an important role in message transmission. Membrane lipids have a number of functions, one of which is to co-localize signalling partners in order to amplify incoming signals via productive protein-protein interactions in specific membrane microdomains. As a result, alterations in membrane lipids have an impact on critical cellular processes as proliferation [5,6], cell migration [7], cytokinesis [8], programmed cell death [9], and so on. Protein-lipid interactions, particularly those involved in the translocation of proteins to or from the membrane to form the signals at this cell barrier, can be drastically altered by changes in membrane lipid composition or structure. These changes can be quite small for some reactions, involving only a few number of membrane lipids and proteins, such as phosphatidylinositol 3,4,5-triphosphate (PI3K) interactions [10]. Regulating the lipid composition of the cell membrane and the translocation of signalling membrane proteins, on the other hand, constitute crucial membrane lipid switches that trigger events critical to physiological processes for activities that cause considerable changes in cells. The presence of lipid structures in cellular membranes, especially organelle membranes, is determined by the lipid content of those membranes. Membrane lipids can take on a variety of supramolecular shapes because they are polymorphic. The most prevalent arrangement of lipids in cells is the lamellar phase (lipid bilayer), particularly the L fluid lamellar phase (or liquid crystalline or liquid disordered -Ld), which is linked with substantial lipid and protein mobility. Lipids form various more tightly packed lamellar structures under different conditions, such as the gel phase (L), pseudo-crystalline phase (Lc), torn membranes (P), and ordered solid or liquid phases (So or Lo). Temperature, lipid composition, water content, lateral pressure, pH, and ionic strength are all factors that influence the varied circumstances and lipid membrane phases. Phospholipids with a cylindric shape, such as phosphatidylcholine (PC) and sphingomyelin, create a lamellar phase and can pack tightly (SM). Nonlamellar phases are formed when lipids with an inverted cone structure (e.g., lysophospholipids) or a truncated cone with a short polar head (e.g., phosphatidylethanolamine (PE) or diacylglycerol (DAG) induce curvature in the membrane. These phases, which can be structured into hexagonal (HI or HII) or cubic phases, are uncommon in healthy cells and provide favourable sites for the localization of certain signalling proteins involved in biological processes including budding and fusion/fission. Lipids keep the structure and composition of the cell's numerous organelles in check, and they're structured into fine-tuned lipid phases that help them do their jobs. PC and PE, glycerophospholipids, are key components of the endoplasmic reticulum (ER), Golgi, and mitochondria, whereas cholesterol (Cho), PC, and SM, as well as endosomes and lysosomes, are major components of the PM. Cardiolipin, for example, is a unique lipid found in mitochondriA. Different lipids can be generated in specific organelles and transported to their final destination to serve as a barrier, scaffold (for integral and peripheral membrane proteins, for example), and/or active lipids. Furthermore, the remaining lipid species, such as the frequency of sphingolipids in the renal cortex, acylcarnitines in skeletal muscle, and ubiquinone in cardiac tissue, fluctuate more quantitatively than qualitatively. In mice models, SM is mostly found in the brain and kidney, whereas PE is mostly found in the spleen. Furthermore, the lipidome often corresponds with the expression of genes involved in lipid metabolism, implying that lipidomics could be used to identify metabolic diseases and link them to specific enzymatic activity abnormalities. Specific lipid species can be packed and structured in small domains that influence diverse cell processes while generating lipidic structures in membranes. Lipid rafts, caveolae, and clathrin-coated pits are examples of these domains that can be found in the PM and various organelles. Lipid rafts are membrane microdomains rich in sphingolipids and Cho, which provide favourable conditions for particular proteins' activity. Some protein receptors important for homeostasis and lipid metabolism regulation, such as the TNFR1 (tumour necrosis factor receptor 1) or the insulin receptor, are found in lipid rafts or Cho-enriched microdomains (IR). Furthermore, one of the primary trans fatty acids, elaidic acid, causes inflammation by interacting with lipid rafts and their toll-like receptors (TLRs). In contrast, lipid rafts have been suggested to sequester epidermal growth factor receptors (EGFRs), preventing their activation, despite the fact that lipid rafts can also activate these receptors. These structures can be observed in the interior membranes of cells that regulate many cell processes, such as raft-like microdomains in mitochondria following Chol and disialoganglioside GD3 buildup in response to apoptotic signalling in neurodegenerative diseases.

Membrane Lipid Therapy in Historical Perspective

The recognition of the role of lipids and lipid structures in molecular and cellular events; (2) the identification of membrane lipid composition and structural alterations in human diseases; (3) a description of the molecular, cellular, physiological, and pharmacological actions of lipids and their analogues to combat pathological processes; and finally, (4) the integration of this knowledge into the rational use of lipids and their analogues to combat pathological processesEarly discoveries revealed the importance of lipid membranes in pathophysiological processes from a historical perspective. In platelet membranes from patients with haematological diseases, significant lipid changes were discovered in 1939. Similarly, the beneficial and harmful effects of certain lipids in cardiovascular disease have long been recognised. Furthermore, a link between inflammation and lipids in both blood (plasma) and cell membranes has long been established. Numerous studies support the role of lipids in cardiovascular disease and related metabolic syndrome-related illnesses such diabetes and obesity. The abundance of literature linking lipid changes to human diseases motivated researchers to dig deeper into the involvement of lipids and lipid structures in these pathological occurrences. Following the description of the fluid mosaic model of the structure of cell membranes, a fundamental aspect relevant to the development of melitherapy, the involvement of lipids and lipid structures in molecular and cellular events, was first addressed.

Arthropod-Borne Pathogens

Viruses, on the other hand, aren't the only pathogens that utilise the host cell's lipids to infect it and may be vulnerable to LRT. For arthropod-borne pathogens, for example, lipid control is critical regardless of whether they are viruses, bacteria, or protozoa, or whether they operate extracellularly or intracellularly. Bacteria from the genera Anaplasma, Ehrlichia, and Borrelia have been found to utilise host cell Cho and various fatty acids to proliferate. The usage of host phospholipids is also required for Anaplasma and Ehrlichia to survive. Plasmidium, Leishmania, and Trypanosoma are among the arthropod-borne protists that require at least one of the lipid groups indicated above for survival and growth. Cho, fatty acids, phospholipids, and sphingolipids from the host cell are required for flavivirus replication when transmitted by arthropods. These findings have inspired the development of innovative vector-borne illness medicines that rely on lipid composition manipulation, and LRT falls into this category. In fact, medications that target lipid metabolism have been proven in mouse models to reduce arboviral and parasite infection. Free Cho; fatty acid production; LDs; particular lipids in the membrane; membrane fluidity; the distribution of receptors and co-receptors; lipid rafts; lipid-based defence systems in human hosts are all targets and chances for treating or preventing pathogen infections. Controlling inflammatory processes is utilised as a symptomatic treatment in addition to fighting the pathogen. Overall, chemicals implicated in LRT or that change the nature of the membrane, weakening pathogen infection, are currently available. Crosstalk between lipid metabolism and inflammatory signalling pathways presents promising therapeutic prospects when contemplating lipid-based defence methods in human hosts. Cho production is inhibited when type I interferon (IFN) signalling is activated, and vice versa. As a result, inhibiting Cho biosynthesis in vitro appears to protect against MHV-68 and HIV-1. Reduced lipid production also reduces lipid raft stability, and Miglustat-Zavesca (a drug now used to treat hereditary illnesses affecting fat metabolism) has shown promise in inhibiting harmful pro-inflammatory activity in vitro. In conclusion, LRT and other techniques focused at targeting lipids on the infectious agent or the host present a promising landscape, especially since many of them are currently on the market for other purposes.

Conclusion

The composition of lipids is critical for cellular homeostasis. Lipid abnormalities are linked to a variety of disorders, and lowering their levels offers therapeutic promise. Membrane lipid treatment, also known as membrane lipid replacement, is currently being used in medication development and nutraceutical therapies. This technology, which is founded on an understanding of cell membrane composition, structure, and functions, has been verified by several clinical trials and medicinal products. The molecular and cellular basis of this therapeutic approach is described in this review, which explains how membrane lipid composition and structure affect protein-lipid interactions, cell signalling, cell physiology, pathophysiology, and therapy, with a focus on oncology, neurodegeneration, and infectious diseases.

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Ultrasound's Current Role in Medicine

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Abstract

Ultrasound (US) is a vital imaging technique that is the most widely utilised imaging modality on the planet. Although US exams require competence to be done at the highest quality levels, most physicians and medical technologists with understanding of human anatomy and physical examination skills may master basic US exams. When US is more than just a "imaging modality," but rather an integrated clinical, physical, and imaging examination in which the examiner interacts directly and intimately with the patient, it reaches its full potential. For expert training in clinical areas, specific diagnostic US knowledge is strongly encouraged. Ultrasound (US) is a vital imaging technique that is the most widely utilised imaging modality on the planet.

Keywords: Ultrasound • Point-of-care ultrasound • training

Introduction

Ultrasound is a very appealing tool for clinical diagnostics because of its lack of ionising radiation, low cost, great portability, and non-invasive nature. Ultrasound exams cost more than computed tomography (CT) and magnetic resonance imaging (MRI) (MRI). According to the World Health Organization (WHO), almost two-thirds of the global population lack access to any type of imaging [1,2]. The United States, as a front-line modality, is a vital component in any strategic strategy to fixing this massive worldwide problem due to its portability and relatively reduced purchasing and maintenance costs. Although US exams require expertise to be done at the greatest levels of quality, most physicians and medical technologists with understanding of human anatomy and physical examination abilities may master basic US exams. Hand-held devices, point-of-care ultrasound cart-based systems, and larger and more expensive high-resolution ultrasound systems with advanced features are typically used in student teaching. Standardized educational material is publicly available to aid training (e.g., the EFSUMB website) [3,4]. When US is more than just a "imaging modality," but rather an integrated clinical, physical, and imaging examination in which the examiner interacts directly and intimately with the patient, it reaches its full potential. Ultrasound has a number of advantages as an imaging tool: It has a higher spatial resolution than CT and MRI, excellent anatomical definition for superficial and many deeper structures, real-time imaging capabilities, widespread availability, and a wide range of clinical applications, including surveillance, diagnosis, disease monitoring, and intervention guidance [5]. Additionally, US emit no ionising radiation and is substantially less expensive than comparable imaging modalities such as MRI and CT, with lower purchase and maintenance costs. The belly can be evaluated by gastroenterologists and surgeons, the pelvic by gynaecologists, the heart by cardiologists [6], the mediastinum and lung by pneumologists, and other anatomical regions examined by their respective specialists using ultrasound. Comprehensive or conventional ultrasonography is the phrase used to describe the standard manner of performing ultrasound examinations. Unlike traditional ultrasound, mobile and portable US scanners provide examiners with immediate access to clinical imaging for quick and direct solutions. The World Federation for Ultrasound in Medicine and Biology (WFUMB) has released a position paper on the current state and future prospects of point-of-care ultrasound [7]. Point-of-care ultrasound is defined by this organisation as "ultrasound performed at the bedside and interpreted directly by the treating clinician or other specialist" [8]. The authors of this editorial have inserted the qualifier "or other specialists" to recognise that clinician-performed portable US may not be viable in some circumstances (battlefields, ambulances, isolated rural clinics, etc.). Karl-Heinz Seitz [9] presents a compelling case for physician-performed US in a recent publication. "The major message of G. Rettenmaier's seminal 1976 book was that fast B-mode ultrasound constitutes a technological enlargement of physical examination known as "clinical ultrasound" and a "dialog-based examination approach". While the physician talks with the patient verbally, the probe works as a palpating hand. This enables the clinician to record a more detailed case history as well as a more specific diagnosis of the issue. The critical synthesis of imaging and symptoms enables conclusive diagnosis that would not be feasible without the use of ultrasound, clinical knowledge, and physician consultation [10]. Many, but not all, clinical practise recommendations recommend US as a first-line imaging tool or an extensive physical examination. While the European Association for the Study of the Liver (EASL) guidelines propose contrast enhanced ultrasonography for the workup and management of incidentally identified localised liver lesions, the American College of Gastroenterology (ACG) guidelines completely disregard US. In previous EFSUMB and WFUMB guidelines, the role of specific ultrasound techniques—contrast enhanced ultrasonography, elastography, and interventional ultrasound—was explored. For acceptable and evidence-based purposes, there is a need for more uniform incorporation of US in worldwide clinical practise guidelines. General practitioners, medical experts and subspecialists, radiologists, and in some countries, non-medical sonographers with formal ultrasound training, do US around the world. Both physician-performed and sonographer-performed ultrasounds are discussed here. US can be conducted as part of a routine physical examination by physicians, including general practitioners, medical specialists, and subspecialists. The services of a radiologist or sonographer are not usually necessary in this situation. Many European countries, like Germany, Italy, Romania, and others, use this type of US. Many medical specialties integrate US in their educational programmes, and specialists conduct unique US exams in their areas of specialisation. Thus, cardiologists conduct echocardiography, gastroenterologists perform hepatic and endoscopic ultrasonography, obstetricians perform obstetrical ultrasound, and endobronchial ultrasound is performed by endobronchial ultrasound. In English-speaking countries around the world, such as the United States, Canada, and Australia, radiological services are traditionally provided by physicians and sometimes by sonographers. In such cases, US is conducted as a radiological procedure comparable to CT or MRI and reported as such. Physicians or sonographers can do the evaluation in this radiological setting. The latter are highly specialised imaging techs who operate in a radiology department under the direction of one or more radiologists and have had extensive formal training and regulatory certification in ultrasound. According to the Society of Diagnostic Medical Sonography, despite their lengthy training and great procedural expertise, sonographers work as "delegated agents of the physician and do not perform independently". Sonographers in the United Kingdom, on the other hand, are independent reporting practitioners in the National Health Service (NHS). The majority of US services are conducted and reported independently by sonographers in the NHS (about 80%). Radiologists (19%) and other medically qualified practitioners (1%), respectively, do the few remaining US examinations. Since non-medical sonographers have less medical education, general knowledge, and independence than medical doctors, the position of the United States in the United Kingdom is debatable. The non-medical sonographer is unlikely to become completely self-sufficient in the face of rising healthcare costs. In other parts of the world, such as China, the sonographer is a non-radiologist physician who specialises in ultrasound. As previously said, there are numerous advantages to ultrasonography performed by a physician. Ultrasound scanning by highly skilled sonographers under the supervision of radiologists and operating within a radiology department, however, has obvious advantages.

First and foremost, this strategy improves efficiency, flexibility, and coverage. When the scanning is done by a team of skilled sonographers, a

single radiologist can fairly and accurately report over 100 ultrasound exams every day. A clinician would not be able to scan nearly as many patients as this. Furthermore, because all of the team's sonographers are capable of completing a wide range of tests involving various organ systems, exams can be scheduled flexibly based on urgency and patient convenience. Second, because all exams are performed using established institutional protocols and reviewed by radiologists, which offers a channel for feedback to the sonographers, this technique allows for standardisation and rigorous quality assurance. In addition, one of the more experienced sonographers can take on the role of personnel supervisor, organising and leading frequent quality improvement projects involving all sonographers in the department. Finally, it is important to note that sonographers have a tremendous amount of sonographic talent, experience, and competence. They gain a mastery of their trade that would be difficult to duplicate by a busy physician who handles many complex responsibilities in addition to sonography by scanning for several hours every day for many years. Third, this strategy makes it easier to get and maintain high-quality, cutting-edge scanners. Because departments frequently purchase many scanners, scanner manufacturers may offer them competitive prices, allowing them to purchase high-end scanners at reasonable prices. Furthermore, departments may have greater access to physics and technical support, either from their own staff or through the manufacturers, allowing the scanners to be maintained at peak performance levels. The most effective use of US equipment necessitates intensive education and hands-on training. One of our main objectives is to make US available to every patient who need our services. This will increase diagnostic efficiency and, potentially, patient management. Training in the United States varies widely and is influenced by a variety of factors. It is critical that US be taught from the outset of medical education, that is, in medical schools and universities, in regions where US is conducted primarily by physicians. During anatomy classes, practical teaching could commence. The usage of US student medical education is currently being reported on by WFUMB, and the papers will be published soon. Following the curriculum suggested by EFSUMB and WFUMB, physicians in training should develop their US examination abilities by following EFSUMB and WFUMB. Even radiologists who practise in areas where sonography is regularly conducted by sonographers, such as the United States, should study US. Knowledge of US scanning improves a radiologist's picture interpretation ability, allows the radiologist to interact successfully with the sonographer, and allows the radiologist to scan patients with particularly complex or puzzling anatomy or findings. As a result, US scanning is required as part of the curriculum in radiology residency programmes. It also necessitates multiple dedicated rotations on the US service, comparable to CT and MRI rotations. Finally, in areas where ultrasound is conducted by sonographers, imaging technologists with the ability and willingness to complete intensive formal training in ultrasound should learn it. When US is more than just a "imaging modality," but rather an integrated clinical, physical, and imaging examination in which the examiner interacts directly and intimately with the patient, it reaches its full potential. For expert training in clinical areas, specific diagnostic US knowledge is strongly encouraged. All medical specialty should have US education, which includes contrast enhanced US and other specialised procedures. Medical education in the United States should begin in medical school for aspiring physicians. Point-of-care ultrasound is widely acknowledged as a realistic way to track a pregnant patient's progress from five weeks until term. Obstetricians have created global standards for diagnosis, training, and quality control in foetal imaging; comparable models should be established in other areas.

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With Diabetes in Mind: A Thiol Signaling Network

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Abstract

The redox regulation system is in charge of maintaining normal cellular activities. Similar to the phosphorylation cascade, controlled variations in redox couples potential act as signal transduction components. The thermodynamic disequilibrium of the primary redox switches allows rapid and sensitive reactions to changes in redox environments, therefore cellular redox biology necessitates both compartmentalization and communication of redox systems. Numerous sulphur species with distinct functional groups (thiols, disulphides, polysulphides, sulphenic, sulphinic, and sulphonic acids, etc.) participate in a sophisticated network of sulphur-based redox processes, resulting in the multiple oxidation states of sulphur. Increased generation of reactive oxygen species and disruptions of thiol redox homeostasis have been linked to human diseases such as diabetes mellitus and its cardiovascular consequences. The review examines the literature on some etiopathogenic elements as well as treatment possibilities. In experimental contexts, the dual toxic-protective feature of sulphydryl-donor compounds raises the general difficulty of developing antioxidants for therapeutic application.

Keywords: Oxidation-reduction • Sulphydryl compounds • N-acetylcysteine • Diabetes mellitus • Arterial hypertension

Introduction

Sulphur (S) is found in the body of the reference man in roughly 140 g. Liquids (SO42 in drinking water) and solid food products are the two main dietary sources of S-containing molecules in human nutrition (organic S in the form of cysteine and methionine). Because cysteine is a metabolic product of methionine catabolism, methionine consumption may be adequate to meet an adult's metabolic needs for exogenous sulphur. However, considering the literature's uncertainty, WHO/FAO/UNU Experts determined that methionine and cysteine intake should be separated (10.4 mg/kg per day and 4.1 mg/kg per day, respectively). Sulphur in the body is divided into three compartments: 1) a nonmetabolic, poorly exchangeable pool found in keratin, collagen, connective tissue, cartilage, tendons, and other tissues; 2) labile molecules and non-protein-bound thiols such as glutathione (GSH); and 3) muscle mass. Methionine is broken down into homocysteine, which can then be remethylated back into methionine by the folate and vitamin B12-dependent methionine synthase. Homocysteine can give serine a sulphur group, resulting in cystathionine [1]. Cystathionine is made up of cysteine and -ketoglutarate. The carbon skeleton of cysteine, cystine, and methionine can be totally oxidised, and the amino nitrogens can be integrated into urea via the Krebs-Henseleit cycle. For S-containing amino acid insufficiency, there is currently no validated biomarker. Despite its several disadvantages, GSH plasma or intracellular concentrations and redox state are currently used as surrogate endpoints in clinical trials [2]. The GSH/GSSG (glutathione disulphide) ratio can be used to estimate a sy--stem's redox status. The redox environment can be assessed by measuring the molar concentrations of GSH and GSSG in homogeneous fluids like plasma, but compartmentation in cells or tissues might be problematic. The total concentration of GSH and GSSG in many cell types is mostly a reflection of the cytosol's redox environment (depending on the portion of cell volume occupied by the nucleus).

Disulphide Redox Systems

Numerous sulphur compounds with unique S-containing functional groups (thiols, disulphides, polysulphides, sulphenic, sulphinic, and sulphonic acids, among others) participate in a complex network of sulphur-based redox processes, whose compartmentation has been widely examined. Furthermore, sulphur compounds' metal-binding properties enable the formation of bioinorganic metal complexes, and iron-sulphur (Fe-S) clusters are important electron carriers and enzyme cofactors in the mitochondrial respiratory chain, iron homeostasis, tricarboxylic acid cycle enzymes, and DNA repair. In cysteine, the sulphur has an oxidation state of -2. As a result, cysteine in proteins can participate in redox reactions such as thiol-disulphide exchange, single- or two-electron transfer, hydrogen-atom transfer, and nucleophilic substitution in addition to structural responsibilities. When protein folding offers a favourable environment for the stability of the cysteine sulphydryl group in the anionic state, these redox processes are favoured. The electrostatic environment of cysteine thiols in proteins can, in fact, have a significant impact on thiol-disulphide exchange reaction rates. Disulphides, which are typically thought of as structurally stabilising components in proteins, have recently been discovered to be members of the redox-sensitive thiol-based regulatory switch family, which is involved in protein function preservation, restoration, and modulation. Thiol/disulphide oxidoreductases like thioredoxins, glutaredoxins, and protein disulphide isomerases have a conserved thioredoxin domain with the classic Cys-X-X-Cys active site motif [3,4]. The big thioredoxin-like superfamily, on the other hand, contains both protein disulphide oxidoreductases with a traditional thioredoxin domain and non-oxidoreductases with a thioredoxin-fold domain. Because changes in the oxidation/reduction state of redox couples affect protein structure, function, interactions, trafficking, and degradation, the redox regulatory system regulates normal cellular activities. Furthermore, cell compartments have varied redox properties, and thiol/disulphide control mechanisms are not in thermodynamic equilibrium within each compartment. Cellular redox biology necessitates redox system compartmentation and communication such that the thermodynamic disequilibrium of the primary redox control nodes or switches (acting as sensor or rheostat) allows for rapid and sensitive responses to redox environment disturbances. In human plasma, cystine and cystine is the most common low-molecular-weight thiol/disulphide pair. The average redox value of Cys/CySS in plasma is around 80 mV. This means that the Cys/CySS couple is out of balance with the plasma GSH/GSSG pool, which has a redox state of around 140 mV. Plasma also includes intact thioredoxin-1 and its truncated version, both of which is released to the extracellular compartment by cells and has cytokine and chemokine-like properties. It's worth mentioning that a lack of essential cysteines impacts numerous mammalian transactivators in this regard. Thioredoxins are engaged in the regulation of transcription factors such as AP-1, NFkB, p53, and Sp1, which can influence expression from the thioredoxin gene promoter (through direct and/or indirect pathways). The redox status of cytoplasm can be changed by physiologic stimulation at the plasma membrane, as evaluated by cytosolic GSH/GSSG and thioredoxin-1. Similar to the phosphorylation cascade, controlled variations in redox couples potential act as signal transduction components. In erythrocytes (which lack intracellular organelles), the steady-state redox potential (Eh) of GSH/GSSG is 193 mV, but in cells with nuclei and mitochondria, it is 200 mV. Cellular thioredoxin-1 has an Eh value of 280 mV. Because oxidative stress is expected to have a role in diabetic complications, notably vascular dysfunction, innovative antioxidant treatment techniques are gaining popularity. Agents that inhibit ROS, such as vitamin E, C, and alpha lipoic acid, showed promise in animal models and early human research, but larger trials have failed to show improved cardiovascular outcomes [5,6]. Other drugs used for various clinical purposes, such as statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and thiazolinediones, appeared to be more effective in improving cardiovascular outcomes, likely due to their success in reducing ROS production at an earlier part of the cascade. We'll concentrate on NAC, which has been proposed as a promising treatment in this field. NAC has predominantly been used in the treatment of chronic obstructive

pulmonary disease as a mucolytic and chemopreventive drug, with therapeutic effects attributed to its capacity to transport cysteine to the portal circulation and thereby restore GSH levels. Second, the impacts on endothelial function have been researched, with mixed results. In patients with coronary artery disease, supplementing with NAC (600 mg/day) reduced homocysteine levels and enhanced endothelium-dependent dilation. In stable cardiac transplant recipients, however, oral NAC supplementation (500 mg/day) had no effect on plasma homocysteine levels or flow-mediated dilation of the brachial artery. In patients with type 2 diabetes and hypertension, oral supplementation with NAC (1200 mg/day) and arginine (1200 mg/day) for six months reduced mean systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, oxidised LDLs, high-sensitive C-reactive protein, intercellular and vascular-cell adhesion molecules, nytrotyrosine, fibrinogen, plasminogen activator inhibitor-1, and intim The combined administration raised HDL cholesterol and nitrites/ nitrates levels in the blood. As a result, the intervention appeared to improve NO bioavailability by lowering oxidative stress and increasing NO synthesis. The effects of varying doses of NAC (0-5 mmol/L) on the action potentials of rat sciatic nerve fibres were studied in vitro and found to be dose-dependent acute inhibition. Because ROS plays a role in cell activity at very low concentrations, total depletion of ROS was expected to disrupt nerve fibre function. Surprisingly, at 1 mmol/L, NAC provided 100% neuroprotection against cadmium-induced neurotoxicity. NAC treatment reduced both post-prandial oxidative state and endothelial activation in patients with type 2 diabetes mellitus. In experimental contexts, NAC's dual toxic-protective feature raises the general difficulty of developing antioxidants for therapeutic application. Indeed, the fundamental principles of free radical chemistry reveal that (1) chain-breaking antioxidants can have pro-oxidant capabilities and accelerate oxidative damage under certain conditions, and (2) extracellular and intracellular redox control interact in a complex way. Although NAC looks to be promising in some therapeutic contexts, long-term randomised clinical trials are still needed to assess the efficacy and safety of chronic NAC administration in humans, taking into consideration some unanticipated adverse effects seen in vitro and in animals. Despite the fact that cardiovascular disease is the leading cause of morbidity and mortality in diabetics, lowering cardiovascular risk factors can successfully prevent or reduce cardiovascular disease [7-10].

Post-translational modifications of proteins are used in signal sensing and transmission. Modulation of thiol-based redox switches in enzymes, receptors, transport proteins, and transcription factors is a well-known signal transduction pathway, and its dysregulation as a result of oxidative stress is linked to cardiovascular disease in diabetes mellitus. Unfortunately, the chemical mechanisms that underpin thiol-based redox regulation are still unknown.

Conclusion

Insulin has metabolic and haemodynamic effects, with the latter being mediated principally by increased NO availability. Insulin resistance is linked to decreased endothelial-mediated vasodilation, which is caused by insulin's failure to drive NO synthesis as well as increased NO consumption. Endothelial dysfunction, in turn, is both a cause and a result of the metabolic abnormalities that characterise insulin resistance. The expression of vascular and intercellular adhesion molecules, the regulation of procoagulant and anticoagulant characteristics of the artery wall, and the maintenance of oxidant/antioxidant balance are all affected by changes in vascular homeostasis. By upregulating adhesion molecules, inflammatory cytokines, and chemokines, oxidant stress increases the inflammatory response. In high-risk people, therapies that improve carbohydrate and lipid metabolism, insulin resistance, vascular function, blood pressure, and procoagulant and inflammatory responses all at the same time can reduce cardiovascular morbidity and death. Every long-term medical therapy, however, requires a careful assessment of the benefits and drawbacks.

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The COVID-19 Pandemic: An Opportunity to Assess the Global Health Status

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Abstract

For those researchers like us, who started practicing medicine and have been involved in global health since the late seventies, the picture of the latter given by the COVID-19 pandemic is a vivid indication of its condition and it is a global mess.

Keywords: COVID-19 • Pandemic • Opportunity • Global • Health • Assessment

Introduction

There were many reasons for optimism and enthusiasm after the WHO Alma Ata declaration early September 1978. They included the apparent leadership from WHO, efficient public health tools, for example: wells and filters, mosquito nets, insecticides, swamp drainage, efficient immunization against several very lethal diseases like yellow fever and meningitis and efficient treatment against various diseases like malaria and TB [1, 2].

This led to spectacular achievements such as the eradication of smallpox [3, 4, 5]. However, in 2022, the results are dismal despite trillions of dollars spent on global health for decades on all fronts by international organizations (like WHO, The World Bank, PAHO, UNICEF, etc.), NGOs, bilateral aid, private funds (like the Gates and the Clinton foundations):-

- Polio remains endemic in Afghanistan and Pakistan. Malawi reported the first case in Africa since 2016 on February 17, 2022. According to WHO: “As long as one child is infected all countries are at risk to get 200,000 new cases per year” [6, 7].
- TB claims 1.5 million lives each year. Only one third of the people with multi-drug-resistant TB had access to treatment in 2020. Three million cases were missed by the detection systems and the funding to combat the disease was back to the 2016 level that year [8-10].
- The number of cholera cases remains high and many are not reported. Moreover, it can be re-introduced into many countries like it was in Haiti in the 2010 [11-13].
- Due to the sylvatic cycle in Africa yellow fever cannot be realistically eradicated [14-17].
- Because of the cattle and wild animal reservoirs of *Trypanosoma rhodesiense* in East Africa, sleeping sickness cannot be practically eradicated.
- In 2007, WHO announced a renewed strategy to eliminate Chagas’ disease by 2010. On April 1, 2021, there were 6 to 7 million people infected by *Trypanosoma cruzi* and the disease was found in 21 continental Latin American countries [18,19].
- Meningitis is now extending outside of the Lapeysonnie’s belt, which includes 26 countries, and into more forested regions of Africa [20-22].
- Globally after 2015, the ASRs (Age-Standardized incidence Rate) in high-middle, middle, and low-middle SDI (Socio-Demographic Index) regions began to rise and the uptrend remained in 2019. Central, Western, and Eastern Sub-Saharan Africa had the highest ASRs rate in 2019 since 1990 [23]. The main problems linked to the elimination of malaria have not been tackled like: deforestation, agricultural expansion, infrastructure development, the biological differences in *Anopheles* species adapted to different landscapes, human and mosquito migrations, travelers, climate change [24-26].
- The discovery of a dog-fish cycle in Chad renders a lasting elimination of dracunculiasis improbable [27-28].

I have identified historically wrong priorities and 54 common denominators between the causes of mismanagement of the COVID-19 pandemic in the United States and the disastrous state of global health [29].

Most worrisome are the trends for the diseases mentioned above and there is no sign of imminent or short term eradication. Moreover, lack of capacity is the main obstacle to adequate healthcare in developing countries [30].

- Quantitatively, data are dismal [31].
- Quality wise, the gap is huge and increasing [32].
- Unfortunately, the evolution in various places is not toward improvement particularly in Sub-Saharan Africa.
- Questions have not been raised on the unreliable origin and misutilization of resources. For example:
- On November 30, 2021, the Clinton Foundation donations had plummeted 75% since Hillary Clinton was Secretary of State [33].
- On February 2, 2022, Melinda Gates said she will stop donating the bulk of her wealth to the Gates Foundation [34]
- How many lives could be saved by buying vaccines instead of life-long, viral-suppressive treatments for HIV/AIDS?

It takes courage and vision to make tough and right choices. Unfortunately, those are the ones leaders must make in resource-limited environments.

I believe that history will not be kind to deciders who fail their people in this regard. Guidelines should be given by international institutions on the establishment of healthcare budget priorities in developing countries [35].

With all the means that we had at our disposal, in 2022 we should have eliminated cholera, polio, malaria, meningitis, Chagas’ disease, TB, and HIV/AIDS from the face of the earth.

It is an ignominy for the human race that we did not and it reflects poorly on our level of consciousness, ability to mobilize and organize, and degree of evolution.

It is clear that global health has been and still is a huge convoluted nexus wasting lives and treasury [36]. It is high time for it to be transformed radically. I have designed a road map for drastically transforming it with the simplifications required to tackle all healthcare issues much more efficiently and effectively, including: Three values, one need, one urgency, two priorities, three strategies, and seven suggestions [37]

Given the status of global health, it should be considered and implemented without any delay.

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