LYMPHATIC PATHOLOGIES IN CANCER PATIENTS

STRATEGIES FOR PREVENTION, EARLY DIAGNOSIS AND TREATMENT

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Associazione
Volontari Assistenza
Pazienti Oncologici
Venezia OdV

Lymphedema is a widespread and little known pathology with very few reference centres for research and cure; worldwide there are about 300 million cases (one person in twenty) of this disease, of which about 15% are post surgical especially secondary to the treatment of breast cancer.

This factor induced A.V.A.P.O.Venezia OdV (Association of volunteers for assistance to cancer patients) to finance the research described in the attached text.

A.V.A.P,O, Venezia was formed in 1988 with the objective of assisting cancer patients and their families. The Association is active in Venice and in the surrounding islands.

The areas in which the Association operates are: domicile hospitalization (NCP - Palliative Care Unit), assistance in hospital and at home, oncological research and senology.

The senology sector was introduced with the specific objective of sustaining, physically and psychologically, women who have undergone breast cancer operations, during the various phases of diagnosis, operation and therapy.

A.V.A.P.O. Venezia has always sustained the fundamental importance of clinical research and has contributed, from the very beginning, by financing studies conducted by eminent doctors and in the promotion of scholarships.

Consequently the decision was taken to accept the proposal to finance the scholarship assigned by the University of Siena, for two years, to the lymphologist Dr Lorenzo Ricolfi, one of the principal experts, at national level, in the diagnosis and treatment of the of lymphatic system diseases. The research of Dr Ricolfi and his team of researchers has resulted in the attached publication.

The research is divided in three parts:

- **The lymphatic system**
- **Prevention and support of lymphedema**
- **Nutrition and life style of cancer patients**

We thank Professor Guido Gabriele, scientific head of the research programme of the University of Siena, Dr.Ricolfi and the medical participants in the research as well as the patients who contributed to the research and the volunteers of A.V.A.P.O. Venezia who dedicated their time.

Last but not least, we thank LE&RN (Lymphatic Education & Research Network) USA who through their spokesperson sparked the inspiration in A.V.A.P.O. Venezia to finance this research.

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A.V.A.P.O. Venezia has funded this research work as it refers to pathologies falling within its specific activity of support to people suffering from oncological diseases, without however in any way participating directly in it. In this regard, we would like to specify that the content and text of this paper are the exclusive responsibility of the researchers who have dedicated themselves to it and who are indicated in the text.

The English text of this pubblication is a free translation of the original text in Italian.

THE LYMPHATIC SYSTEM

THE LYMPHATIC SYSTEM

The lymphatic system runs parallel to the cardiovascular system and consists of lymph, lymphatic vessels, lymph nodes and lymphoid organs. Its main function is the transport of proteins, liquids, lipids, cellular catabolites and macromolecules of various kinds from the interstitium to the blood circulatory system, but not only that, among other roles it also has a function of filtering and transporting antigens to peripheral lymphoid organs, which is essential for the proper functioning of the immune system. The chyliferous vessels located in the intestinal villi of the small intestine and on which the absorption of processed dietary fats and fat-soluble vitamins depends are also part of the lymphatic system.

The lymphatic system is divided into superficial and deep, the two systems are separated by the muscle fascia. The superficial or suprafascial system is responsible for draining the skin and subcutaneous tissue, while the deep lymphatic or subfascial system drains lymph from deeper tissues, such as in the limbs, muscle, tendon sheaths, nerve tissues, periosteum, and joint structures (some distal joints of the extremities drain through the surface layer). The transport vessels of the superficial system are embedded in the subcutaneous connective tissue while the deep transport vessels generally follow the course of the blood vessels. The lymphatic system of internal organs represents a subcategory of the deep system.

The two systems are not completely separate, they are in fact in communication through the perforating vessels.

THE LYMPH

Lymph is a colorless coagulable fluid produced at the interstitium by capillary ultrafiltration and represents the outflow route of numerous cellular catabolites. It is mainly composed of water (about 96% of the total) and a corpuscular part containing micromolecules and protein macromolecules, lipids, carbohydrates, electrolytes and non-electrolytes, leukocytes and also fragments of viruses, bacteria, mutated cells, etc. About 4 liters of lymph are produced throughout the day; the hourly flow rate is around 120 ml/h, of which 100 ml/h through the thoracic duct and 20 ml/h through other routes.

THE FORMATION OF THE LYMPH

The precursor of lymph is interstitial fluid, a fluid contained in all connective tissues in each space not occupied by cells or structures, which is formed as ultrafiltrate by the capillary microcirculation. Fluids, proteins, and small molecules, except for large macromolecules, filter through the walls of microvessels into the interstitium. The exchange takes place through the glycocalyx, a matrix of glycoproteins and glycosaminoglycans with a thickness between 50 and 500 nm that is present on the luminal (i.e. internal) surface of endothelial cells and extends over the intercellular fissures. The glycocalyx, therefore, acts as a molecular sieve and influences the filtration rate from the capillary lumen to the interstitium.

Everything between cells outside of blood and lymphatic vessels makes up the extracellular matrix (ECM). Depending on its composition, the ECM can perform different functions such as, for example, that of supporting cells and their anchoring and division between the different tissues, but also of protection from trauma, communication between cells, regulation of cell growth, and is the site of an incessant flow of molecules. It is mainly composed of adhesion proteins, such as proteoglycans and glycosamninoglycans, structural proteins such as elastic fibers and collagen and interstitial fluid and can also constitute the main component of a tissue, as in the case of connective tissue. These substances create a substance with a gelatinous composition that can be more or less solid depending on physiological and pathological conditions. Physiologically, during the daytime there is a greater permanence of cations in the matrix that are retained and neutralized by the negatively charged proteoglycans, this determines a temporary physiological acidosis of the matrix and a parallel dehydration of the cells with an effect of “imbibition” of the ECM itself, i.e. a gel phase. This is different at night, when the cations leave the matrix and pass directly into the plasma (binding directly to haemoglobin): this phenomenon causes the start of a solubilisation phase of the matrix, which becomes more liquid in a state of alkalosis. In the case of chronic lymphostasis, a pathological condition, an alteration of this balance is created which leads to a progressive acidosis and persistent gelation of the ECM, a consequent reduction in capillary perfusion from which hypoxia derives which leads to an unregulated activity of cells, including fibroblasts, responsible for initiating a fibrotic reaction.

THE COMPOSITION OF THE LYMPH

In general, the chemical composition of lymph is very similar to that of plasma, and many components differ only in concentration. The main components of the lymph are the following:

Proteins: the lymph contains all the protein fractions of plasma but in lower concentrations. The lymph of the thoracic duct in humans has been found to have a protein concentration of about 66% of that of serum. The ratios of lymph concentration to blood plasma (L/W) for albumin and total globulin were approximately 0.75 and 0.5, respectively.

Enzymes: Many of the enzymes found in plasma are also found in lymph, although generally in lower concentrations. However, in lymphatic drainage of a tissue in which the enzyme is produced, the concentration may be higher than that of plasma. The concentration of alkaline phosphatase in intestinal lymph is higher than that of plasma. Enzymes measured in human thoracic duct lymph include alkaline phosphatase, acid phosphatase, lactic dehydrogenase, glutamic oxaloacetic transaminases, glutamic-pyruvic transaminases, and aldolases

Clotting factors: Lymph from all regions of the body clots, but generally less easily than plasma. Concentrations of fibrinogen and prothrombin in lymph are lower than in plasma and vary considerably in different parts of the body.

Lipids: the lipids present in the lymph are similar to those in plasma. Concentrations in the lymph are lower, except in the case of intestinal lymph (CHYLE). These lipids, including triglycerides, phospholipids, cholesterol esters, and free cholesterol, are present in the lymph as lipoproteins. When mesenteric lymph collected after fat ingestion was examined by sequential gradient ultracentrifugation, lipoproteins including chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) were detected. These lipoproteins differ in size and lipid and apoprotein composition. Chylomicrons are the largest particles (75 to 600 nm) that carry lipids into the mesenteric lymph. The production of chylomicrons is phasic and depends on the amount of absorbable lipids. However, it is generally assumed that the concentration of chylomicron lipids in the intestinal lymph is about 1-2%. Chylomicrons have the following approximate composition: 86 to 92% triglycerides, 0.8 to 1.4% cholesterol esters, 0.8 to 1.6% free cholesterol, 6 to 8%

phospholipids, and 1 to 1.5% protein. The chylomicron core contains most of the triglycerides and cholesterol esters along with about 30% free cholesterol. The surface of chylomicron is composed of a monolayer of phospholipids, apoproteins, free cholesterol and a small amount of saturated cholesterol triglycerides.

Electrolytes and non-electrolytes: the electrolyte content of lymph is not significantly different from that of plasma. Generally, concentrations of cations including sodium, potassium, calcium, and magnesium are slightly lower, while anions, chloride, and bicarbonate are higher in lymph than in plasma. The level of non-electrolytes, including non-protein nitrogen, urea, amino acids, and creatinine, are all roughly the same in both plasma and lymph. An exception occurs in renal lymph where the creatinine level is lower than the plasma level. Glucose levels in both thoracic and intestinal lymph are similar to plasma lymph, although higher glucose levels have been found in hepatic lymph.

STRUCTURE OF THE LYMPHATIC SYSTEM

INITIAL LYMPHATICS

Also defined by some authors as lymphatic capillaries, they are blind-ended, highly absorbent vessels composed of a single layer of endothelial cells without a basal lamina. They have a diameter between 20 and 70 µm, they are not provided with valves and muscle fibers.
The lymphatic endothelial cells within the initial lymphatic vessels are interconnected through discontinuous "button-like junctions" through which the absorption takes place of interstitial fluid and macromolecules of various kinds. Endothelial cells are anchored to the extracellular matrix by **Leak fibers**. Leack fibers (or anchor filaments) are very fragile structures; they are stretched by the increase in pressure dictated by the interstitial fluid and therefore favor the opening of the interendothelial junctions, facilitating the absorption of the lymph with the outflow of the lymph contained in the initial lymphatic vessel. Gradually the endoluminal pressure of the capillary increases and the Leack fibers stretch until the emptying of the initial capillary is completed.

PRECOLLECTORS

Precollectors connect the initial lymphatic vessels with the collectors, have a diameter between 70 and 150 µm and have **valve structures and smooth muscle cells inside them**. The precollectors also include vessels that cross the muscle fascia and create connections between the deep lymphatic circulation and the superficial lymphatic circulation, also called perforating vessels (*perforating precollectors).*

COLLECTORS

They have maximum transport function and a diameter between 0.1 and 0.6 mm. Their structure is similar to the venous structure and they consist of tunica intima (endothelial cells and continuous basement membrane), tunica media (smooth muscle) and

tunica adventitia (fibro-elastic connective tissue) and are divided into afferent lymph nodes, inter-lymph nodes and efferent lymph nodes, which group in the lymphatic trunks. The collectors are provided with valves that regulate the one-way flow of lymph. The segment of the lymphatic vessel between two swallow's nest valves represents the propulsive motor functional unit of the vessel and is called lymphangion. Lymphangions motor skills are also impacted by the Vegetative Nervous System (NVS) which determines the regulation of the frequency, amplitude and synchrony of the contraction of lymphangions. The inotropy and chronotropy of a lymphangion also depend on its filling state: once the intravascular pressure of 5-6mmHg is reached, the stretching of the walls initiates muscle contraction (systolic phase), the frequency of which in physiological conditions of rest is 10-12 contractions/minute with pauses of about 5-6 seconds. In lymphatic collectors, lymphatic endothelial cells are connected to each other through more continuous *zipper-like junctions* and are covered by specialized muscle cells (SMCs).

LYMPH NODES

The lymph nodes are located along the lymphatic drainage pathways and can be divided into regional if associated with the extremities (e.g. the axillary lymph node group), or intercalated if associated with the course of deep collectors (e.g. the popliteal lymph nodes). In our body there are about 900 lymph nodes, of which 600 / 700 only between the abdominal region and the neck and are grouped in conglomerates or chains. The main function of the lymph nodes is to filter and eliminate unwanted substances (proteins, fats, cellular debris of various kinds including viruses, bacteria and mutated cells). All this is possible thanks to a high concentration of macrophages, plasma cells and T lymphocytes (produced and matured within the lymph nodes) which initiate the intranodal immune-mediated response. In addition, the lymph is concentrated through the lymph nodes, with the absorption of water that is made possible by the presence of venular structures. The lymph of the afferent lymphatic vessel spreads over the apical surface of the lobule in the subcapsular area, moves along its sides through the lateral transverse sinuses and then flows through the medullary sinuses surrounding the medullary septa, crosses the cortex and exits through

the efferent lymphatic vessel into the hilum. The sinuses are crossed by a delicate vascular network. The body districts drained by superficial lymphatic vessels belonging to a single lymph node group are called lymphosomes.

LYMPHATIC TRUNKS AND THORACIC DUCT

The lymphatic trunks are structures that originate from the confluence of numerous lymphatic collectors efferent from the lymph nodes. The right and left lumbar lymphatic trunks collect lymph from the lower limbs, pelvis, subumbilical portion of the abdominal wall and the organs of the genital system. The intestinal lymphatic trunk collects lymph from the stomach, intestine (via the chyliferous vessels), spleen, pancreas and part of the liver. The right and left lumbar lymphatic trunks and the intestinal lymphatic trunk flow into the Cisterna Chyli located at the II-III lumbar vertebra. From the Cisterna Chyli (Pecquet's Cisterna) the left thoracic duct originates, which continues its course crossing the diaphragm through the passage of Larrey, crossing the spinal column, receiving afferents from the left hemithorax and in its last part from the left upper part of the neck and the left hemiface and then flows through a valved lymphatic-venous anastomosis, at the level of the left jugular-subclavian angle in the internal jugular vein. The right lymphatic duct is formed from the union of the broncho-mediastinal trunk (collects the lymph from the right hemithorax), the right jugular lymphatic trunk (drains the right hemiface and the right side of the neck) and the right subclavian lymphatic trunk (drains the subclavian region and the right upper limb).

Distributed along the major and minor lymphatic pathways, as we have already said, are the lymph nodes, grouped in lymphnode chains located along the course of the main venous structures. They partially slow down the course of the lymph and have different functions, among which immunological functions (production and formation of lymphocytes), circulatory functions (concentration of the lymph with reabsorption of about 50% of the water and biological filtration of the lymph) and metabolic functions (regulation of the protein rate of the lymph).

LYMPHEDEMA

Lymphedema is a clinical condition characterized by the slowing down or blockage of the lymphatic circulation of one or more body districts, with progressively worsening evolution and the appearance of recurrent dermatological or infectious complications called lymphangitis (mostly erysipeloid in nature) and responsible for a further and rapid increase in the volume and consistency of the edema. The incidence of lymphedema in the world is 300 million cases (about one in 20 people). Of these, about 50% are of primary origin, on a congenital lymphangioadenodysplastic basis, i.e. due to a malformation, with consequent malfunction of the lymph nodes and/or lymphatic vessels; 25% are of parasitic origin (mainly caused by Filaria Bancrofti), present in tropical and subtropical areas (India, Brazil, South Africa); 15% are post-surgical, especially secondary to the treatment of breast cancer; 10% are mainly caused by functional problems of overload of the lymphatic circulation (e.g. resulting from important venous diseases, liver failure, nephrotic syndrome or arteriovenous fistulas). The incidence is higher in women and most affected are women between 30 and 40 years of age.

Dwelling on the incidence of lymphedema of the upper limb, secondary to mastectomy or quadrantectomy with axillary lymphadenectomy, it is estimated that it can affect 20-25% of cases and up to 35-40% if radiotherapy has been performed. Even in the case of sentinel lymph node technique, we have an incidence ranging from 3% to 22%. If we consider the cases in gynecological and urological oncology, where lymphedema affects the lower limbs, it is estimated that the incidence ranges from 5% to 30% .

It is therefore appropriate to highlight the importance of preventing the lymphostatic disease, both in terms of diagnostic and therapeutic treatment of lymphedema but also of its complications. Among these, for example, one of the most frequent is lymphangitis, which can occur very frequently and for which prolonged antibiotic treatments may be necessary, both for therapeutic and prophylactic purposes.

The pathophysiology of lymphedema is known and can result from low output failure, i.e. a general reduction in lymphatic transport capacity. This type of alteration can be due to direct damage to the lymphatic system, for example secondary to repeated infections, a lymphonodal removal or a defect in the genesis of one or more structures

of the lymphatic system. The common denominator is identified with the reduction of the lymphatic transport capacity necessary to manage the drainage of lymph formation in the tissues. High output failure, on the other hand, occurs when a normal transport capacity is overwhelmed by excessive formation of interstitial fluid (histolymph). This clinical condition can occur, for example, during liver cirrhosis (ascites), heart or kidney problems such as in nephrotic syndrome and deep venous insufficiency of the lower limbs (post-thrombophlebitic syndrome).

HOW TO RECOGNIZE LYMPHEDEMA

With an accurate medical history and a scrupulous physical examination, it is possible for a suitably trained and prepared physician to reach the diagnosis of lymphedema. This pathology presents itself as an edema that is temporary at first, then persistent, localized in one or more body districts. In most cases, the consistency of the affected limb is increased, depending on the greater or lesser fibrosclerotic tissue component. Pathognomonic signs are the foveal sign, that can be detected in the earliest stages of the disease and can be obtained through the evaluation of the imprintability of acupressure carried out in the affected limbs, and the Stemmer's sign, i.e. the non-plicability of the skin at the base of the 2nd toe resulting from a thickening of the skin and subcutaneous tissue due to continued lymphostasis over time. Complications may be present as dystrophic skin lesions, such as postlymphangitic sequelae, hyperkeratosis, papillomatosis, lymphostatic warts, lymphorrhea (exudation of lymph from the skin) or lymphorrhagia (leakage of lymph from a skin lesion), or dermato-lymphangioadenitis (DLA) complications due to occasional or repeated infections. It is also advisable to carefully evaluate the lymph node stations, for the possible association of acute or chronic lymphadenopathies. In some cases, the presence of overlapping clinical conditions such as morbid obesity, venous insufficiency, more or less evident trauma, recurrent infections, lipedema, heart failure, arterial hypertension and cerebrovascular pathologies, can complicate the clinical situation. In these cases, multidisciplinary management of lymphedema is essential. In addition, in the search for the origin of uni- or bilateral lymphedema of the extremities, especially in adults, it is necessary to consider the possibility of an undetected cancer or a relapse of the disease.

RISK FACTORS OF LYMPHEDEMA

Breast cancer-related lymphedema (BCRL) is one of the most debilitating complications that can occur after treatment of the disease. This chronic condition, characterized by the abnormal accumulation of fluid in the interstitial tissue, results from damage or impairment of the lymphatic system. Numerous factors, both related to cancer treatment and to the individual characteristics of patients, influence the risk of developing this complication, requiring an integrated understanding of its causes to optimize prevention and treatment.

A central element in the genesis of lymphedema is axillary lymph node dissection (ALND), a surgical procedure used to treat breast cancer. ALND, compared to sentinel lymph node biopsy (SLNB), involves the removal of a much larger number of lymph nodes, significantly increasing the risk of damaging the lymphatic system. Clinical data show that the probability of developing lymphedema increases in proportion to the number of lymph nodes removed. Regional radiotherapy (RLNR), which is often administered as an adjuvant treatment, also fits into this context. The combination of lymph node dissection and radiation therapy amplifies the risk of lymphedema, as radiation therapy can cause fibrosis and further structural damage to lymphatic vessels, irreversibly impairing lymphatic drainage.

These interventions, in addition to representing an essential part of cancer treatment, highlight the importance of careful planning to minimize collateral damage. Research shows that the absence of breast reconstruction, especially when not performed immediately, is an additional risk factor. In particular, autologous reconstruction techniques, which use the patient's own tissues, can help to partially preserve lymphatic function, reducing scar formation and improving lymphatic drainage. These benefits are less evident in patients who do not receive any type of breast reconstruction or undergo delayed reconstruction.

In addition to these risk factors, taxane-based chemotherapy has to be included, commonly used in the adjuvant treatment of breast cancer. Although evidence remains partially conflicting, some studies suggest that taxanes may contribute to the onset of generalized or localized edema, which in some cases evolves into chronic lymphedema. Although not all patients treated with taxanes develop this complication, the role of such drugs requires further investigation to elucidate the mechanisms involved and potential

preventive strategies. Despite the importance of cancer treatments, the individual characteristics of patients play a crucial role in the onset of lymphedema. Genetic and anatomical factors, such as the conformation of lymphatic vessels and familial predisposition, can significantly influence vulnerability to lymphedema. Although genetic research in this field is still in its early stage, specific mutations have been identified as potential causes of increased susceptibility. This highlights the need to develop personalized approaches, which take into account the unique characteristics of each patient.

Fundamentally important are infections and local inflammations, such as cellulite. These conditions can greatly aggravate lymphedema or even trigger it in at-risk patients by further damaging an already compromised lymphatic system, creating a cycle of inflammation and damage that progressively worsens the ability to drain lymphatically.

Finally, extensive or repeated surgeries can significantly increase the risk of lymphedema, according to some authors. Any additional procedure, whether oncological or reconstructive, involves potential damage to the lymphatic system, making careful preoperative planning critical. Post-operative monitoring and the implementation of innovative techniques to reduce lymphatic damage, such as axillary reverse mapping (ARM) or the LYMPHA method, can also help mitigate the risk. As for the risk factors inherent in the worsening of lymphedema, several are reported in literature and some of the most discussed will be explored below.

The relationship between air travel and lymphedema has been the subject of numerous studies, but the results obtained are often conflicting. For example, a retrospective study conducted by Casley-Smith in 1996 showed an increased risk of lymphedema in 6% of patients who had travelled by air. This risk was mainly attributed to reduced cabin pressure during the flight, which could promote lymphatic stasis. However, more recent studies have offered less worrying results. Ferguson et al., in a 2016 prospective study, found no significant correlation between air travel and increased arm volume in a large cohort of patients. Similarly, Mak et al., in 2009, in a case-control analysis, found no evidence associating air flights with a significant risk of developing lymphedema. These results suggest that while there is no solid evidence to support the use of compression garments during flights, they can be recommended by doctors to reassure patients and reduce their anxiety.

Another analysed factor is exposure to extreme

temperatures, both high and low. Although data are limited, some evidence indicates that high temperatures, such as those in saunas, can increase the risk of lymphedema. A prospective study conducted by Showalter et al. in 2013 found a significant correlation between sauna use and the risk of developing lymphedema, but found that interaction with factors such as skin cuts on the affected limb can play a decisive role. This suggests that it is not so much the temperature itself that poses a risk, but rather the presence of conditions that facilitate local inflammation.

Blood pressure measurements on the ipsilateral limb are also frequently avoided in patients at risk of lymphedema, although scientific evidence does not fully support this precaution. Studies such as those conducted by Mak et al. in 2009 and Ferguson et al. in 2016 have found no significant associations between measuring pressure on the limb at risk and increasing its volume. Another retrospective study, conducted by Hayes et al. in 2005, suggested a weak, but not statistically significant, association between blood pressure measurement and lymphedema. These results indicate that the risk associated with an isolated blood pressure measurement is likely to be very low, and that the often recommended precautions may not be necessary in all cases.

A traditionally considered risk factor is the possibility of skin punctures on the affected limb, often avoided to reduce the risk of infections such as cellulitis. However, studies provide conflicting results on this point as well. Clark et al., in 2005, in a prospective study, showed a relative risk of 2.44 for the development of lymphedema associated with hospital skin punctures. In contrast, studies such as those by Showalter et al. (2013) and Ferguson et al. (2016) have not found a significant increase in risk related to skin bites or infusions. On the other hand, skin infections, particularly cellulitis, represent a well-documented risk factor for lymphedema. Retrospective studies, such as those conducted by Mak et al. (2008) and Soran et al. (2006), show that cellulite can not only aggravate existing lymphedema, but also contribute to its development, triggering a cycle of progressive damage to the lymphatic system. In summary, the overall analysis of risk factors shows some significant differences. As for air travel, there is no clear evidence linking it directly to lymphedema, although the use of compression garments can be useful to reassure patients. Exposure to extreme temperatures, such as saunas or very hot environments, appears to pose a greater risk, especially in the presence of cuts or local inflammation. Blood pressure measurements on the ipsilateral limb are not supported by significant evidence as a risk

factor, as are skin punctures, which only in specific cases seem to increase the likelihood of lymphedema. However, infections, such as cellulite, remain one of the most significant and well-documented factors, with a strong impact on the progression of the disease. These findings underscore the importance of personalized, evidence-based management to reduce the risk of lymphedema in at-risk patients.

In conclusion, breast cancer-related lymphedema is a complex, multifactorial complication, in which surgery, radiation treatment, individual factors, and infections contribute to varying degrees to the overall risk. A thorough understanding of these risk factors not only helps prevent the onset of the disease, but also allows treatment to be optimized, improving patients' quality of life. The adoption of a multidisciplinary approach, integrating oncologists, surgeons, physiotherapists and lymphology specialists, is essential to provide personalized and effective care. This approach, based on a holistic view of the disease, is the key to proactively addressing this condition and reducing its impact.

LYMPHEDEMA STAGING

In addition to the analysis of risk factors, it is advisable to complete the clinical evaluation with a careful staging of lymphedema. Clinical staging of lymphedema, according to the International Society of Lymphology (ISL), offers a standardized classification system based on clinical features and disease evolution. This subdivision allows a detailed assessment of the severity of lymphedema and can guide treatment decisions.

Stage 0 (ISL Stage 0) represents a subclinical phase, in which lymphatic transport is compromised, but no visible signs of edema are yet evident. This stage can persist for months or even years before the obvious symptoms of fluid accumulation appear.

Stage I (ISL Stage I) marks the early onset of the condition, with a buildup of fluid in the tissues that decreases with limb elevation. At this stage, the edema can be pitting, i.e. pressing on the skin forms a depression that tends to remain for a short time.

In Stage II (ISL Stage II), elevation of the limb alone is no longer sufficient to reduce swelling. Pitting is present, indicating more fluid trapped in the tissues, but as the stage progresses, an increase in fibrosis, or hardening of the tissue, is observed.

The Late Stage II (ISL Late Stage II) is characterized by additional tissue fibrosis, where pitting may be less evident or even absent. This evolution indicates a progression of chronic and irreversible damage to lymphatic tissues.

Finally, **Stage III (ISL Stage III),** also known as elephantiasis, is the most serious. At this stage the tissue is fibrotic and hard, and pitting is absent. Significant skin changes are observed, such as thickening of the skin, hyperpigmentation, increased skin folds, fat deposits and warty overgrowths. These skin changes, combined with the deformity of the limb, make the treatment much more complex.

ISL staging is a fundamental tool for the diagnosis and management of lymphedema, as it allows for the monitoring of the progression of the disease and the planning of targeted and timely therapeutic interventions. Once the clinical classification of the patient has been completed, it is possible to refine the evaluation by performing some instrumental examinations.

The first choice instrumental examination is *lymphoscintigraphy*, useful to provide the diagnostic definition of edema,

to confirm the nature and characteristics of lymphostasis, to search for the cause of the edema (from obstacle or reflux), to assess its extension (dermal back flow), the greater or lesser impairment of the deep lymphatic circulation compared to the superficial one, and the drainage through the lymph node stations. Lymphoscintigraphy is a minimally invasive diagnostic technique that plays a crucial role in the functional assessment of the lymphatic system. It is based on the injection of a radioactive tracer, usually labelled with technetium-99m, into the dermis, usually in the patient's hand or foot, depending on the affected area. Although it involves an injection, the associated risk is minimal and the procedure is well tolerated by most patients. Once administered, the tracer is followed on its way through the lymphatic vessels to the lymph nodes using a gamma camera, which allows detailed images of lymphatic flow and lymph node stations to be obtained. This technique is widely used to distinguish between primary and secondary lymphedema. In primary lymphedema, which is often congenital or hereditary, lymphoscintigraphy may highlight abnormalities such as the absence of major lymphatic vessels or alterations in tracer distribution. In secondary lymphedema, generally caused by surgery, radiotherapy, infection or trauma, obstructions, lymphatic reflux or a significant slowing of flow are frequently observed. An additional benefit of lymphoscintigraphy is the ability to assess the severity of lymphatic dysfunction and to stage lymphedema. In early cases (Stage 0 and I according to ISL), the tracer may show reduced but still functioning lymphatic flow, while in advanced stages (II and III) the tracer may show significant reflux or accumulation in the tissues, with no or severely impaired lymphatic drainage. This information is crucial not only for diagnosing the condition, but also for monitoring its progression and evaluating the effectiveness of treatments. Lymphoscintigraphy is particularly useful for guiding therapeutic choices. In patients with early-stage lymphedema, the results may suggest effective conservative approaches, such as complex decongestive therapy (CDT), which includes manual lymphatic drainage, compression, and physical exercise.

A distinguishing aspect of lymphoscintigraphy compared to other imaging methods, such as MRI or ultrasound, is its ability to provide a functional representation of the lymphatic system, showing the tracer path in real time. However, the interpretation of the results requires specific experience on the part of the professional, since the sensitivity and reliability of the examination depend largely on the quality of the

procedure and the skill of the operator. Despite its diagnostic value, lymphoscintigraphy has some limitations. It is less detailed in identifying microscopic changes in lymphatic tissues and requires specific equipment and trained personnel, making it less accessible in some clinical settings. However, its use remains indispensable in the management of lymphedema, providing crucial data for early diagnosis, optimal treatment planning and accurate monitoring of the condition.

The study of lymphedema may require a combination of diagnostic tests in addition to lymphoscintigraphy that provide a better understanding of both functional and structural alterations of the lymphatic system. Among the available techniques, Lymphangio-Magnetic Resonance Imaging (Lymphangio-MRI) is an advanced non-invasive method, capable of providing detailed images of the lymphatic vessels and surrounding tissues. This technology makes it possible to identify anatomical abnormalities and to assess the presence of tissue edema, which is particularly useful in complex cases with a malformation basis or in the presence of suspected combined alterations between the lymphatic and vascular systems.

Another innovative technique is Lymphofluoroscopy, utilizing a fluorescent dye, indocyanine green, injected into the superficial dermis to obtain a real-time mapping of the superficial lymphatic flow using an infrared camera. This method makes it possible to accurately identify reflux, obstructions or abnormalities of lymphatic drainage. The ability to dynamically observe the behaviour of the lymphatic system makes lymphofluoroscopy particularly useful for planning targeted surgical interventions, such as lymphatic-venous anastomoses, and for monitoring the effectiveness of conservative or surgical treatments.

ULTRASOUND

Ultrasound, on the other hand, stands out for its ability to study the soft tissues and satellite lymph node structures of the affected limb. This non-invasive technique is often used as a first-line examination due to its simplicity and speed. With ultrasound, it is possible to assess the presence of fibrosis, tissue edema and lymph node changes, such as inflammation or enlargement. In addition, its use is particularly suitable for monitoring the evolution of lymphedema and identifying any local complications.

At the same time, Echo-Color Doppler is essential for distinguishing lymphedema from other conditions that can cause swelling, such as chronic venous insufficiency or deep vein thrombosis. This method allows for blood flow in the venous and arterial vessels to be analyzed, providing essential information to rule out possible vascular causes of edema, which often manifest themselves with symptoms similar to lymphedema.

Each of these diagnostic techniques has a specific role and can be used in combination to provide a complete clinical picture. The choice of the most appropriate method depends on the clinical setting, patient characteristics, and diagnostic goals. Together, these technologies are indispensable tools to ensure accurate diagnosis and personalized management of lymphedema, helping to significantly improve the quality of life of patients.

THE THERAPY

The treatment of lymphedema includes conservative treatment and surgical methods. Conservative treatment consists of Combined Physical Therapy (CPT) focused on two phases.

The first phase is based on skin care, manual lymphatic drainage, a series of specific exercises with disto-proximal muscle activation and elastic compression applied with multi-layer multi-component functional bandages. These are bandages in which the patient must continue to move the limb in the most natural way possible.

The second phase aims at maintaining and optimizing the results obtained in phase 1. It includes the continuation of skin care, elastic compression by means of day or night compressive restraints (bracelet or stocking) with a low degree of elasticity, repeated sessions of manual lymphatic drainage depending on individual cases and specific gymnastics. In some cases, it may be necessary to repeat cycles of functional bandaging on an annual or six-monthly basis before applying the daytime elastic compressive brace.

Pressotherapy can be a possible tool to be integrated into the therapeutic options during phase 1, but it should never be implemented as monotherapy and must always be carried out upon physician's recommendation. As far as physical activity is concerned, there are different methods of application and execution, as will be

described in the following chapters. Surgical methods include methods of microsurgery or derivative or reconstructive supermicrosurgery.
The surgical treatment of lymphedema has evolved in recent decades. With the addition of new technologies and surgical, microsurgical and supermicrosurgical techniques, new treatment options are available for patients with lymphedema. The various microsurgical techniques promote improvement of limb drainage by improving the outflow of lymph that accumulates in the periphery, in fact diverting the flow of lymph into the venous stream. Over the years, various microsurgical techniques have been proposed that involved only the superficial lymphatic system or the superficial and deep lymphatic system, creating single venous lymphatic anastomoses (a single lymphatic vessel joined to a single venous vessel) or multiple venous lymphatic anastomoses(several lymphatic vessels united into a single venous vessel). The surgical intervention does not exclude the use of a suitable daytime and/or night-time elastic compression therapy with different times and methods of use varying from case to case.

• SUPERMICROSURGICAL LYMPHATICO-VENOUS SHUNTS

The development of ultra-high magnification microscopes, superfine atraumatic sutures and high-resolution instrumental examinations such as infrared lymphography has opened new possibilities for lymphatic surgery in particular for the creation of anastomoses between the superficial venous and lymphatic systems, thus achieving the union between small superficial lymphatic vessels and adjacent venular structures. Various technical modifications of anastomoses have been proposed leading to satisfactory results, especially for patients with early-stage lymphedema and patients previously treated with a conservative therapy. However, only long-term follow-up will further confirm the effectiveness of these methods.

• DEBULKING PROCEDURES

These surgical methods are the option for particularly advanced stages of lymphedema, where the patient has significant functional limitations of movement due to the volume of the limbs, and does not respond satisfactorily to conservative therapy nor completely to microsurgical options. These methods mainly consist in the excision of fibro-adipose tissue that forms as a result of prolonged lymphostasis and is removed en bloc during surgery. Even in these cases the patient must be accurately

clinically examined and in preparation for the operation the recurrence of infectious complications (lymphangitic) must be reduced as much as possible.

• LIPOSUCTION

Liposuction is a surgical method generally applied in plastic surgery that has recently gained an increasing role in lymphology. In long-term lymphedema the formation of fibro-adipose tissue can be found as a consequence of protracted lymphostasis, making the limb not completely responsive to microsurgical or conservative methods as, although the peripheral lymphatic circulation is restored, a portion of volume remains as a “solid component” that impacts on the volumetric increase of the limb. Liposuction methods can therefore be applied to stages of lymphedema that are not particularly advanced, but with a marked fibro-adipose component that involves the permanence of asymmetry between the affected and the contralateral limb.

• LYMPHATIC VESSEL TRANSPLANTATION

Lymphatic vessel transplantation was developed by Baumeister several years ago and consists of the partial transposition of lymphatic vessels from the healthy limb to create an anastomosis with the lymphatic vessels of the affected limb while maintaining the outflow pathway through the vessels of the unaffected limb to the lymph node stations of the healthy limb. This method has proven to be valid through lymphoscintigraphic findings, but to date it is not largely used because of the very high complexity of the surgery.

• LYMPH NODE TRANSPLANTATION

Lymph node transplantation is a recently introduced surgical method that has proved successful for the treatment of lymphedema. However, the improvement obtained can vary and it is not clear whether this depends on the type of technique used, the site from which the lymph nodes are taken or the site where they are transplanted. The mechanism for the alleged regrowth of both afferent and efferent lymphatic collectors of the transposed lymph node also remains to be demonstrated. For this vascular process stimulation endothelial growth factors (VEGF) seem to be promising, but for the time being only lymphatic capillarogenesis, not vasculogenesis, has been confirmed.

Although a surgical approach to lymphedema is becoming

increasingly popular, some elements should be taken into account

- The timing of surgical treatments for the various stages of lymphedema is very important; the earliest stages, free from major complications and massive tissue degeneration, can achieve better results
- Liposuction is effective for immediate volume reduction, but still requires patients to wear elastic compression devices.
- Anastomoses are effective in the early stages and less effective in the more advanced stages of lymphedema.
- Lymph node transplantation is a promising option, but scientific evidence still needs to be explored.
- The role of surgical treatment should be redefined as complementary to multimodal decongestive treatment.

DRUGS ASSOCIATED WITH LYMPHEDEMA

Numerous preclinical studies have provided convincing evidence for the edema-promoting action inherent in the therapeutic mechanism of different categories of drugs. The precise incidence of drug-related lymphedema is still being studied, however the frequency of drug-related peripheral edema, which may include lymphedema, can range from 3% to 64% depending on the drug agent, the dose employed, and the duration of therapy. (Keeley, 2008). The collective results of these studies provide strong evidence that drug-related lymphedema is a prevalent condition for many commonly used drugs, which, in their therapeutic effect, alter cellular stimulation pathways of lymphatic muscle cells necessary for rhythmic lymphangion contractions and healthy lymphatic flow. There is a growing awareness that many pharmacological agents modify the activity of ion channels and other protein structures in lymphatic muscle cells, by disrupting the cyclical contraction and relaxation of lymphatic vessels, thereby impairing lymphatic flow and predisposing to the development of lymphedema. Other drugs can induce or worsen edema by disrupting the existing homeostasis between trans-capillary flow and lymphatic drainage capacity. Sometimes drug-induced edema may be erythematous, other times unilateral (e.g. sirolimus), or associated with petechial skin rash (e.g. CCB). Understanding the mechanisms by which drugs contribute to the development of lymphedema may provide a rational basis for planning treatment in patients at risk.

The processes that can explain the mechanism of iatrogenic edema are:

PATHOPHYSIOLOGY OF WATER EXCHANGE

The physiological forces that regulate the maintenance of the water balance between plasma and the interstitial space are represented by the gradient of hydrostatic pressures, the oncotic pressure and the permeability of the blood vessel wall. Alterations in the balance of these forces induce the filtration of fluids out of the vessels,

which, if not effectively drained by the lymphatic capillaries, will lead to the formation of an edema.

PHYSIOLOGY AND EXCITABILITY OF LYMPHATIC MUSCLE CELLS

The intrinsic lymphatic pump is the basis of spontaneous rhythmic contractions of the collecting lymphatic vessels and is believed to be coordinated by pacemaker muscle cells, which may make up 1-5% of the muscle cell population in the lymphatic vessel wall. The electrophysiological profile of lymphatic muscle cells is the basis of the physiological process of cyclical contraction and relaxation of the collecting lymphatic vessels that condition lymphatic flow. However, although the precise cellular events that mediate the current in lymphatic pacemaker cells are unclear, it is widely documented that spontaneous depolarization of lymphatic muscle cells opens voltage-sensitive L-type calcium channels in the plasma membrane, resulting in the influx of Ca2+, activation of contractile proteins, and ultimately rhythmic contractions of lymphatic vessels (Azu, 2021). Numerous studies have also reported the role of potassium channels in the regulation of rhythmic contractions of lymphatic vessels (Mizuno et al., 1999;Mathias and von der Weid, 2021). The strict cyclic regulation of membrane potential and intracellular calcium flow in lymphatic muscle cells ensures the presence of robust rhythmic contractions and relaxations, which ultimately provide the intrinsic driving force for lymphatic flow. The effects of edema drugs on lymphatic flow are due to the impact on the flow of intracellular calcium which is the basis of the cycle of contraction and relaxation of the lymphatic collectors. It is easy to understand, therefore, how calcium channel antagonists, which are widely used cardiovascular drugs, reduce the cyclic influx of calcium through L-type calcium channels into lymphatic muscle cells, thus interrupting rhythmic contractions, compromising lymphatic flow and effectively inhibiting lymphatic contractions.

PATIENT-RELATED SUSCEPTIBILITY FACTORS

• SEX: Some studies report a higher incidence of peripheral edema induced by calcium channel blockers (both dihydropyridine and non-dihydropyridine), in females compared to males. The mechanism underlying this gender difference is unclear. Some authors have related it to venous insufficiency, more frequent in females than males, partly due to the effect of estrogens and pregnancies on the promotion of venous-lymphatic stasis; other authors suggest the pharmacokinetics of drugs: actually, with an equivalent dose of amlodipine, females reach higher plasma concentrations than males.

• AGE*:* Aging is associated with a more precarious balance between transcapillary flow, compensatory mechanisms and lymphatic drainage capacity. A reduction in venous valve continence leads to a condition of valvular reflux, stasis, increased capillary hydrostatic pressure, and edema. Aging is also associated with an alteration in the efficiency of calcium channels involved in myogenic tone, a reduction in the pump capacity of the lymphatic collector, and fluid accumulation in the interstitial space. Finally, ageing is a risk factor for microvascular dysfunction and hyperpermeability, due to age-dependent remodelling of the vascular wall and reduction of endothelial integrity and barrier. Although few drugs have been studied and associated with the risk of edema (calcium channel blockers, Gabapentin, sutinib), all these factors suggest a more relevant risk of edema in the elderly.

• COMORBIDITY: The comorbidity burden lowers the threshold of edema formation. A striking example is diabetes, where all the forces that regulate fluid homeostasis can be altered. The effect of proteinuria on capillary oncotic pressure, the microvascular alteration caused by diabetic microangiopathy, leads to an increase in capillary fluid filtration. Diabetic neuropathy can also lead to an insufficiency of lymphatic motor skills that prevents the reabsorption of albumin and the transport of fluid into the lymphatic vessels. Drug-induced edema in comorbid patients predisposed to edema, if not recognized, can be attributed to the underlying pathology and might lead to pharmacological overprescription, harmful to the patient.

CARDIOVASCULAR DRUGS

a. Antiarrhythmic drugs

Antiarrhythmic agents are divided into four classes based on the mechanism of action on distinct ion channels or receptors expressed by myocardial cells to restore normal rhythm and conduction in the heart. Four classes are recognized which include sodium channel blockers (class I), beta adrenergic receptor blockers (βblockers) (class II), potassium channel blockers (class III) and calcium channel blockers (class IV). Epidemiological studies suggest that the administration of calcium channel blockers (CCBs) increases the risk of lymphedema (Stolarz et al., 2019a) and moreover class I and class III antiarrhythmic drugs can have the effect of interrupting the generation of action potentials and thus rhythmic contractions in lymphatic muscle cells.

b. Sodium channel blockers: ranolazine (class I)

Although calcium influx through L-type calcium channels is the main contributing factor to the increase in action potential and amplitude of rhythmic contractions in isolated lymphatic vessels, voltage-gated sodium channel antagonists have also been reported to attenuate the amplitude of contractions in isolated lymphatic vessels in different animal models (Smith, 1949; McHale et al., 1980;Ohhashi et al., 1980;Russell et al., 1980;Ohhashi and Roddie, 1981;Harty et al., 1993;Hollywood MA. et al., 1997; Igarashiet al., 1998). In studies conducted on this family of drugs, the sodium channel blocker commonly used in clinical practice, ranolazine, did not show any significant effect, unlike TTX (tetrodotoxin, not used in clinical practice), which instead demonstrated a clear attenuation of the rhythmic contractions of the lymphatic vessels, a difference due to the selective inhibition on the different isoforms of sodium channels exerted by ranolazine (, Na v 1.4, 1.5, 1.7 and 1.8), while TTX is a non-selective antagonist of sodium channels and inhibits all isoforms. As a result, the clinical use of ranolazine and other sodium channel blockers has not been associated with lymphedema (Dokken and Fairley, 2021).

c. Beta-adrenergic receptor blockers: metoprolol, atenolol, bisoprolol (class II)

β adrenergic blockers (β-blockers) are a class of antiarrhythmic and antihypertensive drugs that are widely used and have been studied for their sodium-retentive action. Currently, it is unclear whether the edematous action is related to an effect of β-blockers on lymphatic circulation or whether it can be completely attributed to cardioactive effects. In this regard, peripheral edema associated with β-blocker administration has traditionally been attributed to the negative chronotropic and inotropic effects of these drugs on the heart, which can increase venous blood volume and subsequently elevate capillary pressure resulting in hyperfiltration and increased fluid in the interstitial space. In addition, some β-blockers including labetalol, carvedilol and nebivolol have direct vasodilator properties, which is an additional mechanism increasing capillary pressure. Since evidence suggests that lymphatic vessels are also innervated by sympathetic nerves and express βadrenergic receptors and as such may play a role in the speed of rhythmic contractions and lymphatic muscle tone, it is plausible that this category of drugs may produce an edematous effect by acting directly on the lymphatic vessel.

d. Potassium channel blockers: amiodarone and sotalol (class III)

Potassium channels are densely expressed in cardiac myocytes, and Class III antiarrhythmic agents attenuate potassium efflux primarily by blocking voltage-gated potassium channels to prolong the repolarization phase of cardiac action potential. Low concentrations of antagonists increase the frequency of contraction of the lymphatic myocyte without altering other contractile parameters, while higher concentrations of antagonists transiently increase the frequency of contraction and progressively improve the amplitude of the contraction (Telinius et al., 2014b). Both of these effects caused by blocking voltage-gated potassium channels increase rather than decrease lymphatic flow. Consequently, the administration of class III antiarrhythmic drugs has not been associated with peripheral edema/lymphedema.

e. Calcium channel blockers (class IV)

Peripheral edema is a well-known effect of this class of antiarrhythmic/antihypertensive drugs, which are used to control heart rate and slow conduction through the atrioventricular node.

These drugs are also effective vasodilatory agents, and in particular **dihydropyridine vasodilators (Nifedipine, Nicardipine, Amlodipine, Lercanidipine) and non-dihydropyridine vasodilators**

(Verapamil, Diltiazem). Calcium channel blockers (CCBs) are of enormous interest as the main class of vasodilator drugs associated with drug-related lymphedema. As already mentioned, calcium influx through L-type calcium channels is clearly a critical contributing factor to rhythmic contraction in lymphatic collectors, and clinically used CCBs potently inhibit these contractions by depressing lymphatic flow. A predominant side effect of CCBs is the formation of peripheral edema (Makani et al., 2011). A mechanism of edema formation may be related to the ability of CCBs to selectively dilate arterioles in the absence of venular dilation, which results in increased capillary pressure (Noll and Lüscher,1998;Weir, 2003;Major et al., 2008). For this reason, these drugs are often associated with a sartan or an ACE inhibitor, which, by dilating the arteriolar and venular side in the same way, attenuates the edema effect of the calcium channel blocker. However, CCB-induced antagonism on L-type calcium channels in lymphatic muscle cells also attenuates the influx of voltage-gated calcium necessary for rhythmic contractions; therefore, reduced lymphatic flow may further contribute to the peripheral edema observed in patients receiving CCB therapy. Curiously, a number of studies have shown that spontaneous contractions of the bovine mesenteric lymphatic vessels are inhibited by nifedipine and diltiazem, which represent CCBs of the distinctly different dihydropyridine and non-dihydropyridine classes (Atchison and Johnston,1997). The calculated intraluminal flux was also reduced by both CCBs in the same studies. However, it is important to emphasise that therapeutic concentrations of the dihydropyridine CCB, nifedipine, inhibit spontaneous contractions of the human thoracic duct and mesenteric lymphatic vessels, while the non-dihydropyridine calcium channel blocker verapamil, although also inhibiting, exerts an inhibitory action at concentrations significantly higher than those prescribed clinically (Telinius et al., 2014c). We can therefore conclude that the class of edemic CCBs with a direct effect on lymphatic flow is the class of dihydropyridines. Another randomized placebo-controlled follow-up trial in sixteen healthy postmenopausal women investigated the effect of CCBs on lymphatic function (Mohanakumar et al., 2020), suggesting that both classes of CCB may not directly impair lymphatic function *in vivo* , but patients with impaired lymphatic function may be predisposed to CCB-associated edema/lymphedema.

f. K_{ATP} Channel Opener (KCO): diazoxide, minoxidil, nicorandil, pinacidil, retigabine

Adenosine triphosphate-sensitive potassium channel (K ATP) drug dilators , often referred to as KCOs, are another class of drugs strongly associated with peripheral edema (Sica, 2004;Nichols et al., 2013). KCOs are primarily used to treat hypertension and to relieve persistent hypoglycemia caused by excessive insulin secretion from pancreatic β cells (Nichols et al., 2013;Welters et al.,2015;Rubaiy, 2016). The following drugs belong to this category:

- Diazoxide, a vasodilator used in the treatment of hypertension, with muscle relaxant activity on smooth muscle cells
- Minoxidil, a vasodilator used to treat high blood pressure as well as alopecia
- Nicorandil , vasodilator used to treat angina
- Pinacidil.
- Retigabine, an anticonvulsant

ATP K channels are, on the contrary, selectively inhibited by sulfonylureas, antidiabetic drugs such as glibenclamide and tolbutamide. In vascular smooth muscle, binding of KCOs results in ATP K-channel opening , potassium efflux and membrane hyperpolarization, closure of voltage-gated calcium channels, and vasodilation. This cascade of events leading to vasodilation explains the potent antihypertensive effect of some KCOs and their efficacy in lowering blood pressure during hypertensive emergencies (Thirstrup and Nielsen-Kudsk, 1992). However, two important side effects of KCOs limit their value as drugs of choice for the treatment of hypertension and persistent hypoglycemia: peripheral edema and pericardial exudation, both conditions due to an altered fluid balance (Sica, 2004;Nichols et al., 2013). Similar to CCBs and other vasodilator drugs, the development of peripheral edema during administration of KCOs may be related to vasodilator-induced increase in capillary pressure and subsequent fluid displacement from the capillaries to the interstitial space. However, growing scientific evidence suggests that KCOs at therapeutic dosages also inhibit rhythmic contractions of isolated lymphatic vessels and reduce lymphatic flow *in vivo*, contributing to the development of edema. (Garner et al., 2021). (Pohl and Thurston, 1973;The International Association of Forensic Toxicologists, 2013). (Thirstrup and Nielsen-Kudsk, 1992;Bang et al., 1998), (MacleanNinewells Hospital and Vallance, 1986;Cohn et al., 2011)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

They are divided into non-selective (acetylsalicylic acid, ibuprofen, naproxen, ketoprofen diclofenac) and selective (COX 2). NSAIDs can affect sodium and water retention by increasing sodium reabsorption from the renal tubule. Individuals at risk of edema are more sensitive to the potentially edemic effect of NSAIDs, especially patients who are more susceptible to the vasoconstrictive effect induced by NSAIDs (e.g. elderly patients, with volume depletion). Fluid retention is observed in up to 2-5% of patients taking NSAIDs, and NSAIDs may make diuretic therapy less effective. These statistics are significant when we consider how often NSAIDs are prescribed or purchased even as an over-the-counter drug. NSAIDs inhibit the renin-angiotensin-aldosterone (RAAS) system, inhibit cyclooxygenase-dependent (COX)-dependent prostaglandin (PG) generation, and this is the primary jatrogenic effect. Nephron expresses all COX isoforms (Cox 1 and COX 2) at different levels, and synthesizes several prostaglandins (PGs) including PGE1 and PGI2. Prostaglandin inhibition is involved in the formation of NSAID-associated peripheral edema. For example, the reduced synthesis of PGE2 NSAIDs induced decreases both natriuresis at the level of the ascending loop of Henle and aquaresis in the collecting duct. The reduction of PGI2 results in an inhibition of the afferent arteriole, and the reduction of the glomerular filtration rate by increasing proximal tubular resorption.

COX2-selective NSAIDs have similar incidences of peripheral edema, which is usually mild (weight gain 1-2 kg), has an early onset (within the first week of use), and is readily reversible upon discontinuation of the drug.

ANTIDIABETIC DRUGS

Diabetes and metabolic syndrome are known to be associated with vascular dysfunction, including vasoconstriction, inflammation, thrombosis, and atherosclerosis (Creager et al., 2003). In contrast, the prevalence of lymphatic dysfunction in diabetes is poorly understood, although a correlation has been suggested (Mcintosh and Green,2009), recently studied in animal models (Zawieja et al., 2012,2015,2016;Lee et al., 2020). In a study conducted on rats with metabolic syndrome, some authors have demonstrated a reduced expression of endothelial nitric oxide synthesis in lymphatic vessels, which is associated with thoracic duct contraction (Zawieja et al., 2015). Another study reported alterations in macrophage concentration and increased K-channel activity ATP associated with impaired lymphatic contractility, also in rats with metabolic syndrome (Zawieja et al., 2016). To date, it is unclear whether these abnormalities of lymphatic function discovered by preclinical studies are also characteristic of the lymphatic circulation of diabetic patients, nor whether the administration of common antidiabetic agents designed to control plasma glucose levels may have undesirable effects on lymphatic flow. There is some evidence, however, that at least one class of antidiabetic agents, thiazidolinediones, may impair lymphatic function and contribute to the development of drug-induced secondary lymphedema.

a.Thiazolidinediones

Thiazolidinediones (TZDs: pioglitazone, rosiglitazone) are hypoglycaemic agents used in patients with type 2 diabetes mellitus. These drugs increase insulin sensitivity (by activating the peroxisome proliferator gamma receptor (PPARγ), which is a transcription factor that upregulates genes responsible for glucose uptake (Vieira et al., 2019), and improve lipid metabolism, reducing, thanks to their combined effects, the cardiovascular risk of the diabetic patient. TZDs are widely used for the treatment of type II diabetes, but one of their side effects is water retention and edema that is dose-dependent (DeFronzo, 1981;Yamanouchi, 2010;Yau et al., 2013). The incidence of edema is 5-10% in patients taking TZD as a single drug. However, administration of TZD in combination with daily insulin increases the incidence of edema to 15-20% via an unknown interaction (Scheen, 2004). The mechanisms responsible for this drug-related edema are unclear, but a limited number

of studies indicate that TZDs may directly affect lymphatic function. For example, rosiglitazone TZD is reported to inhibit lymphangiogenesis in a mouse model (Chen et al.,2013). In this study, rosiglitazone dose-dependently reduced the density of lymphatic vessels of implanted gastric tumors and decreased the expression of VEGF-C and VEGFR-3, common lymphangiogenic markers (Chen et al., 2013). It is possible that TZDs may act in multiple ways to disrupt local fluid dynamics, acting on lymphatic vessel density, capillary filtration, lymph uptake, and other processes that maintain the delicate balance of fluids in the interstitial space.

CHEMOTHERAPY AGENTS

Cancer-related lymphedema is one of the most common types of secondary lymphedema. This type of lymphedema is often attributed to surgeries that physically damage lymphatic vessels to disrupt lymphatic flow. However, cancer-related lymphedema is a "multi-hit" process, favoured by different cancer treatment strategies, such as radiation therapy and chemotherapy, which also increase the risk of lymphedema (Nguyen et al., 2017). Many prospective and retrospective observational studies have investigated the risk of lymphedema associated with the use of chemotherapy. However, only a handful of studies have investigated the direct effects of chemotherapeutic agents on lymphatic contractile function and lymphatic flow, also due to the confounding nature of epidemiological data derived from very complex clinical settings. For example, patients are often treated with a cocktail of different chemotherapy drugs, which explains the extreme difficulty of establishing the contribution of individual agents to the development of lymphedema. For example, in breast cancer, which shows a 30% incidence of arm lymphedema, patients are commonly treated with a combined drug regimen containing an anthracycline, a taxane, and an alkylating chemotherapeutic agent.

a. Anthracyclines

There is considerable evidence that anthracyclines, particularly doxorubicin, contribute significantly to the risk of lymphedema in cancer patients (Norman et al., 2010;Ahmed et al.,2011;Bevilacqua et al., 2012;Nguyen et al., 2017). Doxorubicin is

often referred to as the "red devil" not only because it forms a red solution when reconstituted into solution prior to administration, but also because of its potential adverse effects including cardiotoxicity, myelosuppression, and lymphedema. Doxorubicin is used to treat a variety of malignancies, including Hodgkin's disease, acute lymphoblastic leukaemia, breast cancer, genitourinary cancers, and gynecologic cancers (Young et al., 1981; Minottiet al., 2004;Cortés-Funes and Coronado, 2007;Bedford, 2012;Acheson, 2015).

Most studies have focused on the edema contribution of anthracyclines in patients treated for breast cancer, where doxorubicin is the anthracycline of choice. In a prospective cohort study that followed 631 breast cancer patients for 5 years, treatment with anthracyclines after surgery increased the risk of lymphedema by 4 to 5 times (Norman et al., 2010). Anthracycline treatment in non-radio treated patients undergoing sentinel lymph node biopsy increased the risk of lymphedema to levels comparable to those of patients undergoing axillary lymph node dissection procedure (Normanet al., 2010). In a more recent study, anthracycline treatment was associated with a 13.5% incidence of lymphedema within 5 years in breast cancer patients followed for a 10-year follow-up (Nguyen etal., 2017). It has been studied how doxorubicin directly impairs the rhythmic contractions of isolated lymphatic vessels and lymphatic flow in vivo as an off-target effect (Stolarz et al., 2019;Van et al., 2021). Further studies revealed that doxorubicin has a direct action on calcium L channels in lymphatic muscle cells and inhibits rhythmic contractions and normal lymphatic flow. (Stolarz et al., 2019), which is also characteristic of other anthracyclinic drugs. Olson et al., 2000; Shadle et al., 2000; Hanna et al.,2011). These observations raise the possibility of a shared effect of anthracyclines on lymphatic contractile function that could directly contribute to the development of secondary lymphedema. Other studies suggest that disruption of lymphatic contractions and subsequent lymphostasis damage the lymphatic endothelium and fragile leaflets of lymphatic valves, creating conditions for long-term impairment of lymphatic vessel contractile function (Zawieja et al., 1991;Ji and Kato, 2001;Gashev, 2002;Nipper and Dixon,2011;Choi et al., 2012).

b. Taxanes (paclitaxel, taxol)

Taxanes have emerged as important chemotherapy drugs in the treatment of patients with breast, lung, head and neck, and prostate cancer (Ojima et al., 2016). Paclitaxel (Taxol) is isolated from the bark of

the Pacific yew (*Taxusbrevifolia*) and docetaxel (Taxotere) is synthesized from European yew needles (*T. baccata*). Both have similar chemical structures, which bind to tubulin, stabilize microtubules and cause inhibition of mitosis resulting in apoptosis of the neoplastic cell (Ojima et al., 2016). Taxanes also inhibit tumor angiogenesis, an action that can be partially attributed to their ability to inhibit endothelial cell migration and proliferation (Bocci et al., 2013). They are used in adjuvant, neoadjuvant and metastatic settings. Taxane-based chemotherapy has been shown to improve disease-free survival and overall survival in early operable breast cancer. Taxanes are a common class of chemotherapy drugs that are well known to cause edema (Béhar et al.,1997;Ho and Mackey, 2014). Several epidemiological studies have linked taxane chemotherapy to an increased incidence of breast cancer-related lymphedema (Lee MJ. et al., 2014;Nguyen et al.,2017;Zhang et al., 2019). Administration of taxanes as part of the chemotherapy regimen showed an association with the development of lymphedema in 33.5 % of patients. Cox multivariate regression analysis confirmed that patients who received taxanes after axillary lymph node dissection are three times more likely to develop lymphedema than those who did not receive chemotherapy.

In a larger cohort study evaluating risk factors for lymphedema in 1794 breast cancer patients, the overall incidence of lymphedema at 5 years in patients treated with taxane chemotherapy was approximately 30% (Nguyen et al., 2017). Furthermore, the addition of taxanes to any treatment regimen resulted in an incidence of lymphedema of 33-40% at 5 years (Nguyen et al., 2017).

The association of taxane drugs with lymphedema can be partially explained by their inhibitory action on endothelial cells, although the literature fails to clarify the mechanism by which this class of drugs can damage lymphatic circulation. In this regard, a recent study suggested that paclitaxel may induce autophagy in human dermal lymphatic endothelial cells.

It has also been shown that taxanes increase vascular permeability. The increase in vascular permeability results in an increase in microvascular filtration and therefore an increase in lymphatic flow.

If the lymphatic flow cannot increase, a state of "decompensation" occurs that leads to edema.

Other studies suggest that taxanes may induce a direct inhibition of neolymphangiogenesis.

c. Tamoxifen

Edema is a common adverse event to this drug, and frequently represents a reason for discontinuation of therapy. The tendency to a positive tamoxifen/lymphedema association has been confirmed by various authors. Tamoxifen appears to promote edema through the estrogen-alpha receptor blocking mechanism. During tamoxifen therapy, transcapillary filtration may greatly exceed the lymphatic drainage capacity, resulting in edema.

Other drugs, in addition to tamoxifen, such as taxanes (already commented above), m-TOR inhibitors (rapamykinase targets: sirolimus, everolimus) and PI3K/AKT inhibitors (alpelisib, idelalisib), interfere with VEGF-C, i.e. vascular endothelial growth factors, which activate VEGF-3 through the PI3k/AKT pathway.

d. m TOR inhibitors: sirolimus, everolimus.

m-TOR inhibitors (mammalian target of rapamycin) are anticancer drugs that act by forming a "complex" with a particular protein called "mammal-specific rapamycin target" (mTOR), present in cancer cells, through which they block and inhibit mTOR. Since mTOR is involved in controlling cell division and blood vessel growth, m-TOR inhibitors prevent mitosis of cancer cells and reduce their blood supply. They are used effectively in the treatment of advanced breast cancer with hormone receptor positive, in postmenopausal women after recurrence or progression; in the treatment of well- or moderately differentiated, inoperable or metastatic neuroendocrine tumours of pancreatic origin in progression of disease in adults; in neuroendocrine tumours of gastrointestinal or pulmonary origin, well differentiated (Grade 1 or Grade 2), inoperable or metastatic, in progression of disease, in adults; in advanced renal cell carcinoma; in kidney and liver transplant patients. Since they have an interfering action on VEGF3 through the PI3k/AKT pathway, they are also used in lymphatic malformations related to the upregulation of PI3k/AKT/mTOR. A higher incidence of edema has been reported in patients receiving sirolimus therapy. The time edema onset ranges from 1 to 30 months. Sirolimus-induced lymphedema is usually unilateral or asymmetrical, and can also affect the upper limbs. Diuretics are ineffective and even harmful, as they can lead to irreversible fibrosis of the connective tissue, up to scleroderma-like lesions. In most cases, early discontinuation of the drug leads to partial or complete resolution of the edema after several months.

e. Corticosteroids administered with chemotherapy

Common clinical protocols use corticosteroid premedication prior to chemotherapy as a prophylactic strategy to prevent adverse reactions to chemotherapy infusion (Boulanger et al., 2014). The different actions of this class of drugs on the activation of mineralocorticoid receptors, a mechanism through which they promote water retention, are well known (Schimmer and Funder, 2017). A correlation between corticosteroid use and cancer-related lymphedema has only been reported anecdotally, and no dedicated studies have directly evaluated the role of corticosteroids in cancer-related lymphedema.

ANTICONVULSANTS/ANTINEURALGICS

Drugs used to treat neuropathic pain (antineuralgic) are part of the category of anticonvulsants. Two common drugs are pregabalin (Lyrica) and gabapentin (Neurontin), which are widely used in the treatment of seizure disorders and neuropathic pain. The prevalence of peripheral edema is reported in up to 15% of patients receiving chronic pregabalin treatment.

ANTIDEPRESSANTS

The specific drug that will be examined for antidepressants is trazodone, a tricyclic antidepressant that has fewer anticholinergic and cardiac side effects than other drugs in the same category. Various clinical trials have reported edema as a side effect in patients treated with trazodone, with a negative history of edema diseases. Once the administration of the drug was stopped, there was regression of the edema. The mechanism of action that causes edema in patients taking trazodone is unclear. One possible explanation could be that trazodone lowers blood pressure and decreases heart rate; This has an overall effect on reducing cardiac output, and this hemodynamic effect could promote the formation of edema. Another possible explanation could be related to a dose-dependent effect of trazodone on serotonin receptors. Although the exact mechanism of action remains elusive, the dosage of trazodone should be increased gradually in patients with underlying diseases that might produce edema.

TAB. 1
ANTI-HYPERTENSIVE DRUGS AND MECHANISMS OF ACTION

Anti-hypertensive drugs	Mechanisms
Minoxidil, hydralazine, dihydropyridine calcium channel blockers, alpha1 blockers, beta-blockers	Precapillary arteriolar dilation (minoxidil, hydralazine, calcium channel blockers) Myogenic response with inhibition of the venous-arteriolar reflex (calcium ant.) Increased arteriolar reabsorption of Na in situations of renal hypoperfusion (minoxidil, hydralazine) or reactive stimulation of RAAS (alpha1 blockers)
Diazoxide	Arteriolar vasodilation Stimulation of the RAAS resulting in water and sodium retention

TAB.2
ANTI-INFLAMMATORY AND ANALGESIC DRUGS

Anti-inflammatory and analgesic drugs	Mechanisms
Non-selective anti-inflammatory NSAIDs, Cox-2	Inhibition of PGI2-related afferent arteriole vasodilation and reduction of PGE2-related aquaresis and natriuresis with final effect of sodium and water retention.
Corticosteroids	Sodium-retention mineralocorticoid effect
Opioids: Fentanyl, Hydromorphone, Morphine, Oxycodone, Tramadol	Increased capillary permeability through non-specific histamine release effects

TAB.3
CHEMOTHERAPY DRUGS

Chemotherapy/ immunosuppressants	Mechanisms
Gemcitabine, Cyclophosphamide, trans-retinoic acids	Increased capillary permeability
Taxanes: docetaxel, paclitaxel	Increased capillary permeability Inhibition of the VEGFR-3/VEGFC pathway (anti-lymphangiogenic effect) Heart failure
SERM (tamoxifen)	Hydro saline retention due to inhibition of ENaC receptors (epithelial sodium channels), estrogen-dip. Lymphatic microvascular stability disorder mediated by alpha-estrogen receptors
Aromatase inhibitors: anastrozole, exemestane	Hydro-saline retention mediated by inhibition of ENaC receptors (epithelial sodium channels), estrogen-dip.
Antiandrogens: abiraterone	Hydro-saline retention due to mineralocorticoid effect
Protein Kinase Inhibitors Alkylating agents: ceritinib, crizotinib	Increased capillary permeability through activation of inhibition-induced VEGF signalling HGF/MET
GnRH agonists: goserelin, leuprolide	Hydro-saline retention due to lack of inhibition of estrogen-dip. ENaC receptors. And reduced mineralocorticoid effect of progesterone.
mTOR inhibitors: everolimus, sirolimus	Anti-lymphangiogenic effect by inhibition of VEGFR-3/VEGFC Increased capillary permeability
Calcineurin inhibitors: cyclosporine, tacrolimus	Increased capillary permeability (capillary leak syndrome)
PI3K/AKT: idelalisib, alpelisib	PI3K/AKT inhibition preventing lymphangiogenesis VEGFR-3/VEGF-C mediated

TAB. 4
NEUROLEPTIC DRUGS

Neuroleptics	Mechanisms
Antidepressants: mirtazapine, venlafaxine	Arteriolar vasodilation through inhibition of 5-HT2 receptors
Antipsychotics: Olanzapine, Quetiapine, Ziprasidone	Arteriolar vasodilation through an alpha1-lytic effect and/or through inhibition of the 5-HT2 receptor
Antiparkinsonians: dopaminergic agonists, L-dopa, MAOI-B	Arteriolar vasodilation through stimulation of peripheral D1 receptors Precapillary arteriolar vasodilation through ACE2 elevation induced by D3 receptor stimulation Heart failure (Pramipexole and bromocriptine)
Baclofen	Increased capillary permeability, particularly if alcohol consumption is concomitant. GABA-ergic vasodilation for inhibition of sympathetic tone Inhibition of GABA-mediated myogenic response
Antiepileptics: Carbamazepine, Valproate, Clobazam	Mechanism unknown. Heart failure (carbamazepine)
Gabapentinoids: Gabapentin, pregabalin	Precapillary vasodilation and inhibition of myogenic response through Cav1.2 inhibition

TAB.5
HORMONAL THERAPIES

Hormones	Mechanism
Androgens: danazol, testosterone	Hydro saline retention through ENaC stimulation
Estrogen	Increased capillary permeability Precapillary arteriolar vasodilation through RAAS-induced activation of Mas receptors Sodium and water retention
Progestogens	Hydro saline retention not mediated by mineralocorticoids
Insulin	Increased capillary permeability Arteriolar vasodilation Hydro saline retention due to the antinatriuretic effect and activation of the RAAS
GH growth hormone	Hydro saline retention through ENaC stimulation

TAB.6
EDEMA DRUGS WITH UNKNOWN MECHANISM.

Drugs	Mechanism
Antimicrobials: acyclovir, levofloxacin	Unknown mechanism
PPI: lansoprazole, omeprazole, Pantoprazole, Rabeprazole	Unknown mechanism
Sulfonamides	Unknown mechanism

PREVENTION AND MANAGEMENT OF LYMPHEDEMA

PREVENTION AND MANAGEMENT OF LYMPHEDEMA

Long-term management of lymphedema focuses on improving the function of the lymphatic system, limiting further worsening of the swelling and achieving long-term control of the condition. Success depends on self-management by patients and their carers, with appropriate and effective education involving:

- Daily skin care
- Physical exercise/movement
- Compression – compression garments
- Elevation of the limb
- Manual self-drainage performed by the patient or a trained assistant.
- Self-bandaging
- Self-monitoring.

It is important to take certain precautions, both to minimise the risk of developing lymphedema (in at-risk patients) and to reduce the risk of worsening in patients with established lymphedema:

- The care of skin and nails.
- Maintaining a healthy body weight.
- Following a balanced diet.
- Avoiding injury to the affected area.
- Avoiding tight underwear, clothing, watches and jewellery.
- Avoiding exposure to extreme cold or heat.
- Use of high-factor sun creams and insect repellents.
- Use of mosquito nets in areas where lymphatic filariasis is endemic
- Wearing prophylactic compression garments, if prescribed.
- Exercise/movement.

The prevention of lymphedema represents one of the main challenges in the management of this chronic condition, which affects the lymphatic system, causing fluid accumulation in the tissues and a consequent impairment of the quality of life. Preventive measures focus on reducing risk factors and adopting personalised strategies to prevent the condition from developing in susceptible individuals or to prevent

the worsening of existing lymphedema. The prevention of lymphedema is particularly important in oncological and post-surgical contexts, as well as in congenital or acquired conditions.

PRIMARY PREVENTION: REDUCING RISK FACTORS

Primary prevention aims to prevent the onset of lymphedema in patients considered at risk. Among the most common risk factors are surgical procedures involving the removal or damage of lymph nodes, such as those performed for the treatment of breast cancer, as well as trauma, infections and obesity. Excess body weight is one of the main modifiable factors: obesity increases pressure on the lymphatic vessels and reduces their drainage capacity, thereby promoting fluid retention. Promoting a healthy lifestyle, characterised by a balanced diet and regular physical activity, is crucial for maintaining an optimal weight and improving lymphatic circulation. Furthermore, patient education plays a fundamental role in the prevention of lymphedema. Informing people at risk about how to recognise the early signs of the condition, such as persistent swelling of a limb or a feeling of heaviness, can facilitate early diagnosis and prompt treatment. Patients must be made aware of the importance of avoiding skin injuries, insect bites, infections and other conditions that could trigger an inflammatory response and overload the lymphatic system. It is also essential to use moisturisers to keep the skin soft and prevent dryness or cracking, which could lead to infections. Another important aspect of primary prevention involves adopting less invasive surgical techniques, where possible, to reduce the risk of damage to the lymphatic system. Advanced techniques such as sentinel lymph node biopsy for tumour staging can reduce the risk of lymphedema as opposed to extensive lymph node removal.

SECONDARY PREVENTION: MONITORING, EARLY DETECTION AND MANAGEMENT

Secondary prevention is aimed at patients who have already undergone operations or treatments that put them at risk of developing lymphedema. In these cases, regular monitoring is essential to identify any early signs of this disease. Imaging techniques such as lymphoscintigraphy can be used to assess lymphatic function, whilst non-invasive instruments such as bioimpedance analysers provide an accurate estimate of the amount of fluid in the tissues. Regular measurement of the circumference of the affected limb and comparison with baseline values can help detect any changes at an early stage. Patients at risk should be educated on self-monitoring practices, such as daily observation of skin appearance and awareness of changes in limb volume or sensation. Furthermore, preventive compression using custom-made compression garments may be useful in reducing the risk of developing lymphedema, particularly in individuals with a predisposition or who have already experienced episodes of transient swelling.

TERTIARY PREVENTION: MANAGING RELAPSES AND REDUCING COMPLICATIONS

In patients with diagnosed lymphedema, tertiary prevention focuses on the effective management of the condition to prevent worsening and reduce the risk of complications. Complex decongestive therapy (CDT), which includes manual lymphatic drainage, compression, therapeutic exercises and skin care, represents the gold standard for the treatment of lymphedema and for the prevention of relapses. A crucial element of tertiary prevention is ongoing patient education. Learning self-bandaging techniques and the correct application of compression garments enables the patient to manage their condition independently and maintain control over the swelling. Physical activity, carried out regularly and with the use of appropriate compression, is essential for improving the function of the muscle pump and stimulating lymphatic drainage. Activities such as swimming are particularly recommended, as water provides natural compression that aids venous and lymphatic

return. Skin care is another key aspect of tertiary prevention. In patients with lymphedema, the skin is often more vulnerable to infections such as erysipelas, which can further aggravate the condition. Daily use of moisturisers, thorough hygiene and the use of pH-neutral products help maintain skin integrity. It is important for patients to avoid injuries, insect bites and trauma, as these can trigger local inflammation that overloads the lymphatic system.

EDUCATIONAL STRATEGIES AND MULTIDISCIPLINARY SUPPORT

The success of lymphedema prevention depends largely on adopting an educational and multidisciplinary approach. Patients must be actively involved in their care pathway, acquiring the knowledge needed to independently manage risk factors and implement preventive strategies. This includes learning self-monitoring techniques, the use of compression garments and participating in exercise programmes tailored to their condition.

The support of a multidisciplinary team, including physiotherapists, surgeons, specialist nurses and dietitians, is essential to ensure effective and personalised treatment. For example, the physiotherapist can provide practical guidance on specific exercises and drainage techniques, whilst the dietitian can help develop a balanced diet plan for the maintenance of an optimal body weight.

NEW APPROACHES TO LYMPHEDEMA PREVENTION

Scientific research is exploring new strategies to improve the prevention of lymphedema. These include the use of advanced technologies such as wearable sensors for continuous monitoring of changes in limb volume and the use of targeted drug therapies for the reduction of inflammation and improvement of the lymphatic function. Furthermore, recent studies have suggested that lifestyle changes, such as the adoption of anti-inflammatory diets and the use of relaxation techniques to reduce stress, can have a positive impact on the prevention and management of lymphedema. In conclusion, the prevention of

lymphedema requires an integrated approach that combine educational interventions, clinical strategies and the active involvement of the patient. Reducing risk factors, promoting a healthy lifestyle and providing multidisciplinary support are key steps in preventing the onset of lymphedema or limiting its progression in at-risk patients. With advances in research and the introduction of new technologies, the panorama of lymphedema prevention will continue to evolve, offering ever-improving opportunities to enhance patients' quality of life.

THE ROLE OF PHYSIOTHERAPY IN THE TREATMENT OF LYMPHEDEMA

Lymphedema is a chronic condition affecting the lymphatic system, characterised by an abnormal accumulation of lymph in the interstitial tissues. This phenomenon is caused by insufficient lymphatic drainage, leading to persistent swelling, stiffness and, in advanced cases, serious complications such as fibrosis, skin infections and loss of function in the affected limb. Despite the complexity of the condition, physiotherapy has established itself as an indispensable therapeutic approach, contributing significantly to symptom management and improving patients' quality of life. The lymphatic system plays an essential role in maintaining the balance of body fluids, in transporting plasma proteins and in the immune response. When this delicate balance is compromised, as in the case of lymphedema, a pathological accumulation of fluid occurs in the tissues, which can impair mobility, cause pain and profoundly alter the patient's daily life. The condition is manifest in two main forms: primary lymphedema, which is congenital and often associated with genetic defects, and secondary lymphedema, which arises following surgery, radiotherapy, trauma or infection. Physiotherapy is a central pillar in the management of both forms of lymphedema, integrating advanced and personalised techniques to address the many facets of the condition. Physiotherapy treatment is not limited to reducing swelling; it also includes strategies to prevent complications, improve limb function and promote patient independence through targeted education. This multidimensional approach not only improves physical symptoms but also addresses the psychological and social aspects of the condition, which are often overlooked.

One of the main objectives of physiotherapy is to reduce the volume of edema through specific techniques such as manual lymphatic drainage (MLD) and elastic compression therapy. These methods, combined with therapeutic exercises and proper skin care, help improve lymphatic drainage, preventing fluid accumulation and reducing the risk of various complications.

A fundamental aspect of physiotherapy is patient education, whereby patients are taught how to manage their condition

independently. This includes self-bandaging techniques, home exercises and strategies for monitoring warning signs, such as increased swelling or the appearance of redness of the skin . The aim is to provide the patient with the tools needed to maintain the results achieved during physiotherapy sessions and prevent the progression of the disease.

Another strong point of physiotherapy is its ability to adapt to the patient's specific needs. Each personalized treatment plan is tailored to the severity of the lymphedema, the presence of comorbidities, and the patient's functional needs. For example, in cases of advanced lymphedema or in areas that are difficult to treat, such as the neck or trunk, manual lymphatic drainage may be combined with innovative therapies such as pressotherapy or the use of smart compression devices.

Research in the field of lymphedema has highlighted the importance of a multidisciplinary approach, involving not only physiotherapists but also doctors, nurses and psychologists. In this context, physiotherapy, represents the hub around which the other components of the treatment revolve. Thanks to its versatility, physiotherapy allows the integration of various methods, maximising the benefits for the patient. In recent years, new technologies have been developed that have further expanded the therapeutic possibilities for lymphedema. Advanced compression devices, imaging techniques for lymphatic assessment and low-intensity laser therapies are just some of the innovations that are revolutionising treatment. These tools, combined with traditional physiotherapy techniques, offer new prospects for the long-term management of the disease. In conclusion, physiotherapy is much more than a simple treatment for lymphedema; it represents a global and integrated approach that takes into account all aspects of the condition, from the physical to the psychological and social. Through a combination of manual techniques, compression therapies, targeted exercises and educational strategies, physiotherapy significantly improves the patients' quality of life, restoring their independence and well-being. This makes physiotherapy an indispensable element in the management of lymphedema, capable of addressing the challenges of this complex condition with expertise and innovation.

PHYSIOTHERAPY ASSESSMENT

The physiotherapy assessment is a crucial stage in the management of lymphoedema, as it enables the development of a personalised rehabilitation programme tailored to the patient's needs. This process is not limited to an initial assessment, but must be repeated periodically to monitor the effectiveness of treatments and adapt them to changes in the patient's clinical condition.
A thorough understanding of the location, stage, severity and complexity of the lymphoedema is essential, alongside a holistic assessment of the patient, which should also include psychosocial aspects. From a functional perspective, it is vital to consider the impact of lymphoedema on the patient's mobility and daily activities. Standardised questionnaires, such as the Lymphoedema Quality of Life Inventory (LQOLI), can help assess the condition's impact on quality of life and psychological well-being. Particular attention must be paid to identifying any motor limitations or pain, which could affect the effectiveness of complex decongestive therapy. The physiotherapy assessment is not limited to clinical aspects but also considers the patient's adherence to therapies. The ability to apply bandages, use compression garments and perform regular exercises must be carefully monitored. Furthermore, assessing family support and the resources available for home-based treatment is crucial to ensuring the long-term success of lymphoedema management. A further key element is the analysis of the patient's nutritional status and body weight. Scientific studies have shown that obesity can exacerbate lymphoedema by increasing pressure on the lymphatic vessels and impeding lymphatic drainage. Therefore, collaboration with other professionals, such as dietitians and nutritionists, is essential for a multidisciplinary approach. Finally, the physiotherapy assessment should include an educational component, aimed at raising the patient's awareness of self-management of lymphoedema. This includes instructions on self-bandaging, the correct use of compression garments and skin care, with particular attention to the prevention of skin infections, which can be a common complication.

In summary, the physiotherapy assessment in lymphoedema is not merely a diagnostic step, but a cornerstone for establishing an effective treatment plan, monitoring its progress, and actively involving the patient in the management of their condition.

A holistic and multidisciplinary approach is essential to address the complexity of this chronic condition, thereby improving the patient's quality of life.

COMPLEX DECONGESTIVE THERAPY (CDT)

Complex Decongestive Therapy (CDT) is considered the gold standard for the management of lymphedema. This integrated approach unfolds in two main phases, each designed to address specific therapeutic needs and to maximise results over time.

The intensive phase of CDT: its primary aim is to minimise the volume of the affected limb. This is achieved through the combined application of various therapeutic techniques which work synergistically. Manual lymphatic drainage (MLD) is one of the main tools used in this phase, performed daily to stimulate lymphatic flow and promote the removal of excess fluid. This technique is complemented by the use of multi-layer bandaging, which is applied after each drainage session. The bandaging uses short-stretch bandages, capable of exerting graduated pressure on the limb, improving lymphatic circulation and preventing the return of fluid within the tissues. Alongside drainage and compression, therapeutic exercise plays a crucial role in promoting lymphatic drainage by activating the muscle pump. During this phase, exercises are performed under the supervision of a physiotherapist, with particular attention paid to maintaining active compression on the affected limb. Targeted movement, in fact, stimulates lymphatic circulation and improves the overall function of the limb. Another key element of the intensive phase is skin care. The skin in areas affected by lymphedema is particularly vulnerable to infections such as erysipelas; therefore, careful and constant management is necessary to preserve skin integrity and prevent complications.

The maintenance phase: this follows immediately after the intensive phase and focuses on consolidating the results achieved. During this phase, patients take an active role in the daily management of their condition, with a gradual transition from direct assistance by the physiotherapist to self-management. The use of compression garments replaces the multi-layer bandaging used in the previous phase. These garments, which are made to measure, guarantee continuous and graduated compression, essential for the prevention of fluid retention

and for the maintenance of control of the edema. Manual lymphatic drainage remains an important part of the maintenance phase, although performed less frequently than during the intensive phase. Regular physical exercise, which includes simple movements and activities such as walking or swimming, remains a pillar of the treatment. These activities, preferably carried out with active compression, help to stimulate the lymphatic system and maintain limb mobility. Skin care also remains essential during the maintenance phase, with the aim of preventing infections and preserving skin integrity. Patients are taught how to care personally for their skin, in the use of moisturisers and in the recognition of signs of deterioration or irritation. A crucial aspect of the maintenance phase is patient education. Through a training process, patients learn self-bandaging techniques, the correct use of compression garments and strategies for managing their lymphedema independently. This educational approach enhances patient autonomy and promotes long-term adherence to the treatment plan.

Ultimately, CDT is a complex yet highly effective treatment that integrates various therapeutic modalities to address lymphedema in a systematic and personalised manner. The combination of manual lymphatic drainage, compression, exercise and skin care offers comprehensive management of the condition, with significant benefits for patients' quality of life. Although the consistency and commitment required can be challenging, the multidisciplinary approach and the patient's active involvement are essential for achieving lasting and sustainable results.

MANUAL LYMPHATIC DRAINAGE (MLD)

Manual lymphatic drainage (MLD) is an essential technique in the management of lymphedema, aimed at stimulating and improving lymphatic flow through a series of specific and gentle manual movements. This practice is based on well-established physiological principles, which include increasing the absorption of fluids and proteins from the interstitium through the lymphatic capillaries, stimulating the contractility of the lymphatic collectors, and increasing fluid absorption in the lymph nodes. The overall aim is to increase the volume of fluid returning to the venous system, helping to reduce edema and improve associated symptoms.

THE ROLE OF MLD IN THE MANAGEMENT OF LYMPHEDEMA

MLD is used at various stages of lymphedema treatment. During the intensive phase, it is one of the main instruments for reducing edema. During this stage, MLD is combined with multi-layer bandaging and other therapies, such as therapeutic exercises, in order to achieve significant decongestion of the affected limb. In the maintenance phase, however, MLD can be used to support and maintain the results achieved in the intensive phase, particularly in patients who require periodic interventions for the control of residual swelling. MLD is also indicated in managing the transition period between the two phases of treatment, acting as a therapeutic bridge to prevent a relapse of edema during the transition to a less intensive therapy. Furthermore, in specific cases where compression therapy is not well tolerated or is difficult to apply, such as in lymphedema affecting sensitive areas like the head, neck, trunk, breasts or genital organs, MLD may represent the only viable option. In these situations, the physiotherapist's skill is crucial in adapting the technique to the patient's needs, ensuring maximum therapeutic benefit.

PHYSIOLOGICAL BENEFITS OF MLD

The MLD technique is based on slow, rhythmic movements, designed to follow the natural flow of lymph towards the lymph nodes. These movements not only stimulate the lymphatic system but can also have a relaxing effect, reducing muscle tension and the pain associated with lymphedema. Furthermore, MLD can help reduce local inflammation by facilitating the removal of pro-inflammatory mediators and promoting tissue regeneration.

LIMITATIONS AND CONTROVERSIES REGARDING THE EFFICACY OF MLD

Despite its potential benefits, the effectiveness of MLD has been the subject of debate in scientific literature. Some studies report positive results, highlighting significant improvements in edema volume, quality of life and reduction of pain in patients treated with MLD. However, other research has found no statistically significant differences compared to alternative treatments or the sole use of compression therapy. A systematic review of the literature in 2021 highlighted the importance of conducting higher-quality clinical trials to clarify the efficacy of MLD and to better define its long-term benefits.

PRACTICAL CONSIDERATIONS

The MLD technique requires specific training and a thorough understanding of the anatomy of the lymphatic system on the part of the physiotherapist. It is essential to perform the movements with precision, following the natural flow of the lymph and adapting the intensity and direction of pressure to the patient's individual condition. Furthermore, it is important to integrate MLD with other decongestive therapies to maximise its effectiveness and ensure sustainable results.

Patient involvement in the management of lymphedema is another crucial aspect. In some cases, patients can be taught self-drainage techniques, which can be used to complement professional treatment. However, self-drainage requires adequate initial supervision to ensure it is performed correctly.

FUTURE PROSPECTS

To improve the adoption and effectiveness of MLD, further studies are needed to investigate the mechanisms through which this technique influences the lymphatic system and to identify patients who may benefit most from its use. Furthermore, the integration of innovative technologies, such as imaging devices to monitor lymphatic flow in real time, could optimise the practice of MLD and increase its precision.
In conclusion, MLD represents a fundamental component of complex decongestive therapy, playing a key role in reducing edema and improving patients' quality of life. Despite controversies regarding its efficacy, MLD remains an irreplaceable technique, particularly in specific clinical situations. As research progresses and multidisciplinary approaches are adopted, it is probable that MLD will retain a central role in the management of lymphedema.

MULTILAYER BANDAGING

Multi-layer bandaging is universally recognised as the gold standard in the treatment of lymphedema, thanks to its ability to exert graduated and targeted compression on the affected limb. This technique is based on the application of short- or medium-stretch bandages, the purpose of which is to create pressure that varies during the patient's movement. The pressure generated by the bandage is in fact greater during active phases, such as walking or muscle contraction, and lower whilst resting. This pressure dynamic stimulates lymphatic flow and helps improve the efficiency of the muscle pump, two fundamental elements for reducing edema. The principle behind multi-layer bandaging is to make full use of the body's natural movement in order to enhance lymphatic drainage. When the patient moves, the compression applied by the bandage creates a 'massage' effect which promotes the flow of lymph towards the lymph nodes. This effect is particularly useful for counteracting fluid retention in the tissues and preventing the worsening of swelling. Furthermore, multi-layer bandaging is not limited to a mechanical action; scientific studies have shown that the application of graduated compression can stimulate the release of anti-inflammatory mediators, thereby reducing the inflammatory process and the risk of developing tissue fibrosis, a common complication in patients with lymphedema. The ability of multi-layer bandaging to improve lymphatic and venous flow is accompanied by further benefits, such as an increase in local temperature. This slight rise in temperature, induced by the bandage, can promote improved cellular metabolism and tissue regeneration. However, it is essential that the bandage is applied correctly by trained staff, as improper application could cause adverse effects, such as skin lesions or excessive compression that might impede blood flow. The use of multi-layer bandaging is not limited to the intensive phase of complex decongestive therapy, but can also be integrated into the long-term management of lymphedema, particularly in patients requiring additional support to maintain control of the edema. Personalisation of the treatment is a key aspect: the type of bandages, the number of layers and the application technique are adapted to the patient's specific characteristics, such as the severity of the lymphedema, the presence of comorbidities and the level of physical activity. Another advantage of multi-layer bandaging is its ability to prevent overnight fluid accumulation in the tissues, when the patient is lying down and lymphatic flow tends to slow down. For this reason, bandaging is often used as a complementary tool of compression garments, which are worn during the day. This combined approach ensures continuous and graduated compression, maximising the effectiveness of the treatment. The application of multi-layer bandaging requires specific training by a physiotherapist or healthcare professional. During treatment, the patient is also educated on the importance of compression and, in some cases, may be taught self-bandaging techniques to ensure self-management of lymphedema. However, self-bandaging is recommended only for patients with good manual dexterity and an understanding of the techniques, as an error in application could compromise the effectiveness of the treatment. Finally, it is important to emphasise that multi-layer bandaging is one of the fundamental components of a multidisciplinary approach to the treatment of lymphedema. When combined with manual lymphatic drainage, therapeutic exercises and skin care, bandaging makes an essential contribution to improving patients' quality of life, reducing symptoms and preventing long-term complications. The effectiveness of this technique is supported by numerous clinical studies, which have confirmed its usefulness in both the intensive and maintenance phases of complex decongestive therapy.

INTERMITTENT PNEUMATIC PRESSURE THERAPY (IPC)

Intermittent pneumatic compression (IPC) is an advanced technology which is increasingly used in the treatment of lymphedema, integrating effectively with other components of complex decongestive therapy. The principle behind this technique is the application of variable pneumatic pressure to the affected limb, achieved using a device comprising an electric pump connected to an inflatable garment. The garment, often consisting of separate air chambers, is worn over the affected area and subjected to cycles of inflation and deflation for a predetermined period, generally between 30 and 120 minutes. The pressure cycle generated by IPC serves a dual purpose. On the one hand, it stimulates lymphatic drainage by increasing external pressure, promoting the flow of lymph towards the lymph nodes and the venous system. On the other hand, this cyclic movement helps to reduce lymphatic stasis, improving local circulation and reducing swelling. The intensity and duration of the pressure can be adjusted according to the patient's needs and the severity of the lymphedema, making pressure therapy a highly personalised solution. IPC is distinguished for its versatility, as it can be used both in a clinical settings, under the supervision of professionals, and as a self-treatment option at home. This flexibility is particularly beneficial for patients who require ongoing support in managing lymphedema, allowing them to integrate the treatment into their daily routine. However, to ensure the safety and efficacy of the compression therapy, it is essential that the patient receives adequate training on how to use the device. Instruction provided by experienced healthcare professionals is crucial to avoid application errors, such as excessive pressure or an inappropriate treatment duration, which could cause unwanted side effects. One of the main advantages of IPC is its ability to provide uniform and repeatable treatment, reducing the physical burden on both the patient and healthcare staff. This makes compression therapy particularly useful in combination with manual lymphatic drainage and compression therapy, enhancing their effects. Furthermore, IPC can be a viable option for patients who do not tolerate well multi-layer bandaging or who have mobility difficulties that limit their ability to perform therapeutic exercises. From a clinical perspective, several studies have highlighted the effectiveness of pressure therapy in reducing edema

volume, improving mobility and alleviating the physical and symptoms associated with lymphedema, such as a sensation of heaviness and pain. Furthermore, the mechanical stimulation provided by IPC can also have beneficial effects on local inflammation, helping to reduce the risk of long-term complications, such as tissue fibrosis. Despite its numerous benefits, pressure therapy has some limitations and contraindications. For example, it is not recommended for patients with active infections, deep vein thrombosis or conditions that compromise arterial circulation. Therefore, a thorough clinical assessment is necessary before commencing treatment. Furthermore, the effectiveness of IPC depends largely on the choice of device and the settings used, which is why it is essential to rely on high-quality equipment and qualified healthcare professionals. Finally, it is important to emphasize that compression therapy does not replace the other components of complex decongestive therapy, but complements them. When used correctly, IPC can help significantly to improve the quality of life of patients with lymphedema, offering an effective and accessible therapeutic option. However, the success of this treatment depends on a multidisciplinary approach that combines compression therapy, manual lymphatic drainage, therapeutic exercises and skin care, thereby ensuring comprehensive and sustainable management of the disease.

SELF-BANDAGING

Self-bandaging represents a fundamental strategy in the long-term management of lymphedema, offering patients an effective option for maintaining control of swelling and preventing the condition from worsening. This approach is particularly suitable for patients who, due to individual needs or physical limitations, cannot use other forms of compression on a continuous basis. Thanks to its flexibility, self-bandaging allows decongestive treatment to be integrated into the daily routine, ensuring therapeutic continuity and promoting patient autonomy. The self-bandaging technique is taught by the patient's physiotherapist, who adapts the application methods to the patient's specific needs. This personalisation process is essential to ensure correct and effective application, avoiding errors that could compromise the benefits of the treatment. Simplicity is a crucial element: the physiotherapist simplifies the technique as much as possible, using easy-to-handle materials and providing clear, practical instructions. This is particularly important for patients with reduced manual dexterity or who find it difficult to understand complex techniques. Self-bandaging proves useful in various circumstances. One of the main uses is as a night-time supplement to the daytime compression provided by elastic garments. During the night, when the patient is not wearing compression garments, the bandage can provide continuous support, preventing fluid build-up that might occur due to reduced physical activity and the horizontal position. This approach helps to maintain stable the results achieved during the day and reduces the need for more intensive interventions. Another scenario in which self-bandaging is particularly beneficial involves patients with limited mobility. In such cases, the difficulty in putting on and removing compression garments can present a significant obstacle. The bandage, applied by the patients themselves or with the help of a carer, offers a practical solution that can be easily adapted to the patient's physical condition and capabilities. Furthermore, in situations where elastic compression is insufficient to control fluid accumulation, self-bandaging provides additional support which contributes in the improvement of lymphatic drainage and reduced swelling. The effectiveness of self-bandaging depends largely on the quality of the instruction received and the patient's ability to apply the technique correctly. For this reason, it is essential that patients are

supervised by experienced healthcare professionals who can monitor progress and provide ongoing support. Patient education is not limited to learning the technique, but also includes understanding the importance of compression, skin care and monitoring for signs of worsening lymphedema. Another crucial aspect of self-bandaging is the choice of materials. Low-stretch bandages are generally preferred, as they provide effective compression during movement, stimulating lymphatic drainage without exerting excessive pressure when resting. These materials, combined with protective skin layers and pads for the most sensitive areas, ensure safe and comfortable application. In addition to clinical benefits, self-bandaging offers a significant psychological advantage, promoting the patient's sense of control and independence. The ability to independently manage a key part of the treatment can boost self-confidence and reduce the anxiety associated with reliance on external support. This aspect is particularly important for patients with chronic lymphedema, for whom managing the condition represents a daily challenge. Despite its many advantages, self-bandaging is not suitable for all patients. The ability to apply the technique correctly requires a minimum level of manual dexterity and understanding, and not all patients have access to a carer who can provide assistance. In such cases, alternative solutions may be necessary, such as the use of adjustable compression devices or more frequent support from healthcare staff. In conclusion, self-bandaging is an essential component of lymphedema management for many patients, providing a flexible and effective option for maintaining control of swelling and preventing the condition from worsening. Education, ongoing support and personalisation of the technique are key elements in ensuring the success of the treatment. With the right approach, self-bandaging not only helps to improve clinical outcomes but also promotes the patient's psychological well-being and quality of life, making it a valuable ally in the management of this complex condition.

THERAPEUTIC EXERCISE AND PHYSICAL ACTIVITY

Therapeutic exercise is a key component in the management of lymphedema, thanks to its ability to promote venous and lymphatic return through muscle movement. Active exercises, in particular, are recommended for improving lymphatic circulation via the effect of the muscle pump, which is activated during muscle contraction and relaxation. This process not only aids the drainage of accumulated fluid but also helps prevent the formation of new pools of lymphatic fluid in the tissues. One of the most important aspects of therapeutic exercises for lymphedema is their combination with external compression. When exercises are performed with a compression bandage or suitable compression garments, the effectiveness of the treatment increases significantly. External compression amplifies the effect of the muscle pump, improving lymphatic flow and promoting greater pressure variation in the tissues. This dynamic effect helps to reduce local inflammation by stimulating the release of anti-inflammatory mediators and preventing progression to complications such as fibrosis. Scientific studies, such as the one conducted by Cohen et al. in 2001, have highlighted the importance of different types of exercise in the treatment of lymphedema. Resistance exercises, for example, are particularly effective in strengthening the muscle pump, thereby increasing lymphatic flow. At the same time, aerobic exercise, such as walking or using an exercise bike, plays a crucial role in increasing intra-abdominal pressure. This pressure, in turn, facilitates drainage of the thoracic duct, one of the main pathways for lymph flow into the venous system. Physical activity in the treatment of lymphedema must be carried out consistently and in a controlled manner, with particular attention to the safety of the patient. Whilst the use of compression is essential in most activities, there are exceptions such as exercise performed in water. Water, in fact, provides natural compression thanks to hydrostatic pressure, which can be particularly beneficial for patients with lymphedema. Swimming or exercising in a swimming pool allows the benefits of physical activity to be combined with those of compression, minimising stress on the joints and improving mobility.

Adopting a specific exercise programme for lymphedema not only improves lymphatic drainage but also has a positive impact on the

patient's quality of life. Regular physical activity helps maintain an optimal body weight, reducing the load on the lymphatic system and preventing the disease from worsening. Furthermore, movement improves flexibility and muscle strength, promoting greater independence in daily activities.

PHYSICAL EXERCISE ADAPTED FOR LYMPHEDEMA

Adapted physical exercise is a fundamental component of lymphedema management, as it helps improve both general well-being and specific symptoms associated with the disease. It is based on structured activity designed to meet individual and contextual needs, promoting the maintenance of physical health without worsening the symptoms of lymphedema. Its importance is highlighted by numerous studies which emphasise the role of physical activity not only in the management of lymphedema, but also in the prevention of complications and comorbidities.

CORRECTIVE EXERCISE AND THE INTENSIVE PHASE OF COMPLEX DECONGESTIVE THERAPY (CDT)

During the intensive phase of CDT, the focus is on 'corrective exercise', a targeted activity carried out under the supervision of a physiotherapist. This type of exercise is performed with compression bandages worn over the affected area, which amplify the effect of muscle movement on lymphatic drainage. Corrective exercises involve slow, controlled movements targeting specific joints and muscle groups, with the aim of stimulating lymphatic return without placing further strain on the compromised lymphatic system. Corrective exercises are generally uncontroversial within the medical community, as the benefits far outweigh the risks. However, it is crucial that they are performed under strict supervision to avoid technical errors that could worsen the patient's condition.

TRANSITION TO DAILY PHYSICAL EXERCISE

The phase following CDT emphasises 'physical exercise', understood as the adoption of habitual movements which patients can integrate into their daily lives. It is at this stage that most of the controversy arises. Some fear that unsupervised exercise may aggravate lymphedema or cause injury, whilst others argue that regular activity,

if carried out in moderation and with appropriate precautions, is not only safe but also beneficial. Scientific evidence supports the idea that exercises such as walking, swimming or practicing yoga can be successfully integrated into the daily routine. It is important that patients are educated to recognise any signs of overexertion, such as increased swelling or pain, and to adapt physical activity to their abilities and needs. Initial supervision by healthcare professionals, such as physiotherapists or lymphedema specialists, is essential to provide safe and personalised guidelines.

BENEFITS OF ADAPTED EXERCISE

Exercise adapted for lymphedema not only improves physical function but also helps prevent associated complications, such as fibrosis and loss of mobility. Furthermore, it helps prevent the worsening of the lymphedema itself and may reduce the need for more invasive medical intervention. The importance of physical exercise also extends to the management of common comorbidities in patients with lymphedema, such as obesity and diabetes. Regular physical activity has been shown to improve insulin sensitivity, reduce body weight and promote cardiovascular health. Therefore, the integration of a well-structured exercise programme is a crucial component in the long-term management of lymphedema. Physical exercise adapted for lymphedema is an essential strategy for improving patients' quality of life and supporting the effects of other treatments. The key to success lies in personalising the physical exercise programme, initial supervision by professionals, and patient education. With a balanced approach tailored to individual needs, physical activity can become a powerful ally in the management of lymphedema.

WHAT TYPE OF EXERCISE IS SAFE FOR PATIENTS WITH LYMPHEDEMA? WHEN CAN THEY START EXERCISING AND HOW MUCH EXERCISE CAN THEY UNDERTAKE?

Physical exercise is an important component in the management of lymphedema, both for patients already affected and those at risk. However, it is essential that it is carried out with care, following specific guidelines to avoid complications. A 2011 systematic review analysed 19 studies on physical exercise and lymphedema, focusing primarily on patients with breast cancer-related lymphedema . The results showed that resistance exercise is safe for both patients with established lymphedema and those at risk of developing it following cancer treatment.

Among the types of physical exercise considered safe for patients with lymphedema are:

- **Resistance exercises**: when introduced gradually and under appropriate supervision, these exercises can improve muscle strength and lymphatic drainage. Muscle contraction stimulates lymphatic return, reducing lymphatic stagnation.
- **Aerobic exercises**: activities such as walking, swimming and cycling promote blood and lymphatic circulation without placing excessive strain on the lymphatic system.
- **Corrective exercises**: as previously explained, these exercises are often performed during complex decongestive therapy and aim to stimulate lymphatic drainage through specific movements carried out under the supervision of a physiotherapist. They are generally accompanied by the use of bandages or compression garments.
- **Yoga and Pilates**: these low-impact disciplines can be useful for improving joint mobility and muscle strength, whilst always respecting the patient's physical capabilities.
- **Swimming and water-based activities**: Water provides natural compression that supports lymphatic drainage and reduces the risk of swelling.

WHEN TO START AND HOW MUCH PHYSICAL EXERCISE TO DO

Physical exercise can be started at any stage of lymphedema treatment, provided it is progressive and tailored to the patient's needs. Ideally, the exercise programme should begin under the guidance of a healthcare professional, such as a physiotherapist specialising in lymphedema. In particular, during the intensive phase of CDT, corrective physical exercises are introduced in combination with other decongestive therapies. After this phase, physical activity can be gradually integrated into the patient's daily routine. It is important to begin with moderate intensity and increase gradually, monitoring for signs of overload, such as increased swelling, pain or a feeling of heaviness in the affected area. The duration and frequency of exercise depend on the patient's clinical condition, but in general it is recommended to engage in physical activity at least three times per week for 30–45 minutes.

PRECAUTIONS AND MONITORING

Every physical exercise programme for patients with lymphedema must be carefully monitored. Assessing the affected area after physical activity is essential to identify any changes, such as swelling or stiffness. It is also important to pay attention to form and technique whilst performing the exercises, to avoid injury or unnecessary stress to the lymphatic system. Rest intervals between sets of exercise may be extended to allow for adequate recovery.

The use of compression garments during physical exercise is recommended, as they support lymphatic drainage and reduce the risk of worsening the swelling. However, compression must be appropriate and tailored to the patient's needs.

EXERCISE IN SEDENTARY PATIENTS

For patients who have never exercised or have done so only occasionally, the main objective is to incorporate a gradual exercise routine. A well-structured approach should consider:

Biomechanical characteristics: joint or muscle limitations may influence the choice of exercises. For example, in lower limb lymphedema, it is important to avoid movements that place stress on the knees or ankles, whilst for the upper limbs, maintaining a good range of motion (ROM) through gentle mobilisation exercises should be encouraged.

Conditional and coordinative abilities: strength, aerobic capacity and balance may be compromised in patients with advanced lymphedema. For this reason, light resistance exercises, such as the use of therapeutic elastic bands, and low-impact aerobic activities, such as swimming or walking, are particularly recommended. Water provides an ideal environment thanks to its uniform pressure, which aids lymphatic drainage.

Technical abilities: patients unfamiliar with physical exercise may benefit from simple, guided activities such as Pilates or Tai Chi. These approaches promote movement control and improve posture, reducing the risk of complications.

Metabolic status: in patients with obesity or insulin resistance associated with lymphedema, it is crucial to encourage exercises that improve glucose metabolism and promote body fat loss. Moderate aerobic exercises, such as cycling on a exercise bike or brisk walking, have been shown to be effective.

Anthropometric characteristics: body proportions and the specific musculoskeletal configurations can influence the choice of exercises. For example, patients with columnar lower limbs may benefit from exercises that distribute the load evenly, avoiding excessive pressure on the joints.

Posture: postural abnormalities or deformities may require specific adaptations. Postural exercises and stretching can be incorporated into the routine to improve body symmetry and prevent further overload.

A key element for success is gradual progression. Patients should start with light exercises and gradually increase the intensity, under the supervision of an experienced therapist. It is essential that each routine is tailored to the patient's specific needs, respecting individual limits and regularly monitoring the response of the lymphatic system.

HIGH-RISK SPORTS: HOW TO MANAGE THEM

Activities such as tennis, golf, football or kickboxing induce high levels of stress on the joints and an increased level of risk of injury. Nevertheless, completely banning these activities could compromise the psychological well-being of patients who derive great satisfaction from them. It is therefore advisable that these activities be carried out under close supervision, with appropriate modifications. Wearing compression garments, monitoring limb volume and paying attention to signs of discomfort (pain, tension or increased limb volume) are essential measures to minimise risks. Furthermore, patients should consult regularly with their therapists to adapt their physical exercise regime in accordance with the progression of their condition.

CONCLUSIONS

Physical exercise is not only safe for patients with lymphedema, but is also strongly recommended as part of an integrated approach to managing the condition. Regular physical activity has been shown to offer numerous benefits to patients with lymphedema, including improved quality of life and psychological well-being, and contributes to the management of common comorbidities in patients with lymphedema, such as obesity, diabetes and cardiovascular disease. However, it must be tailored to individual needs and introduced gradually, with careful monitoring by healthcare professionals. With a well-structured and supervised programme, patients can derive significant benefits from physical activity, improving both the management of their lymphedema and their quality of life.

GENERAL GUIDELINES FOR DIFFERENT TYPES OF EXERCISE

Among the various types of exercise, breathing exercises, resistance training and aerobic activity are particularly useful for stimulating the lymphatic system, strengthening muscles and supporting the patient's overall well-being.

BREATHING EXERCISES

Deep diaphragmatic breathing is essential for the return of lymph to the bloodstream. During abdominal breathing, the rhythmic up-and-down movement of the diaphragm acts as a natural pump, promoting lymphatic drainage and improving the return of venous blood to the heart. This movement involves not only the diaphragm, but also the ribcage, abdomen and lower back, promoting a beneficial effect throughout the body. Breathing exercises not only stimulate the lymphatic system, but also improve intestinal peristalsis and help reduce muscle tension and stress. Diaphragmatic breathing should be incorporated as the initial part of any exercise routine, as it prepares the body for movement, activates the core muscles and reduces edema. This practice is particularly important in sedentary patients or those showing signs of lymphatic system dysfunction. A study on the role of the diaphragm highlighted that regular activation of abdominal breathing significantly increases lymphatic flow through the thoracic duct, improving overall lymphatic drainage (Frontiers in Immunology, 2024). Therefore, regular sessions of diaphragmatic breathing, combined with light aerobic exercise, can lead to both local and systemic improvements.

RESISTANCE EXERCISES

Resistance exercises, such as those using light weights or elastic bandages, offer numerous benefits for patients with lymphedema. These exercises improve muscle strength, increase bone density and promote limb stability, whilst at the same time reducing stress on the lymphatic system. Muscle contraction during exercise applies rhythmic pressure to the lymphatic vessels, facilitating the flow of accumulated lymph towards the lymph nodes and promoting more efficient drainage. Resistance exercises must be performed with caution, especially in patients starting from low fitness levels or with functional limitations. It is essential to start with light loads and a higher number of repetitions, gradually increasing resistance according to the patient's tolerance levels. This approach minimises the risk of overload and allows for a gradual adaptation of the muscles and tissues involved. The use of compression garments during training is essential to prevent fluid accumulation in the affected limb. These garments provide external support that optimises lymphatic drainage during muscle contraction, reducing the risk of worsening edema. According to a study published in *Lymphology*, compression combined with physical exercise significantly increases lymphatic flow compared to exercise without compression.

In addition to promoting lymphatic drainage, these exercises offer other significant benefits:

- Improved muscle strength and endurance: an improved strength base enables patients to tackle daily activities with less effort, reducing fatigue and increasing functional independence.
- Restoration of intramuscular balance: strengthening the muscles around the affected area helps correct muscular imbalances, improving joint biomechanics and reducing the risk of injury.
- Weight management: increased muscle mass contributes to basal metabolic rate, promoting weight loss and the management of metabolic comorbidities, which are often present in patients with lymphedema.

Training with the use of weights should be started in a supervised environment, preferably under the guidance of a physiotherapist or a certified trainer with experience in managing lymphedema. These professionals can monitor the patients response to the exercises and adapt the programme to their needs. If symptoms such as pain, tension or increased swelling of the affected limb occur

during physical activity, the activity should be interrupted and a specialist consulted.

AEROBIC EXERCISE

Aerobic exercise is an essential component of general well-being and management of lymphedema. It stimulates the lymphatic and circulatory systems, improves cardiovascular health, and contributes to weight control. Furthermore, aerobic activity plays an important role in reducing edema and improving quality of life, whilst also promoting the patient's mental health and independence.

Aerobic conditioning involves large muscle groups in repetitive movements, promoting lymphatic and venous drainage. Key benefits include:

• Improved muscle strength: stronger muscles support venous and lymphatic return, reducing edema.

• Lower heart rate during rest periods: aerobic exercise improves the heart's efficiency, reducing cardiovascular strain.

• Weight management: calory consumption helps maintain healthy weight, reducing the burden on the lymphatic system.

• Increased general well-being: regular physical activity helps improve mood, reduce stress and improve sleep quality.

Recommended exercises

• Walking: walking is one of the simplest and most accessible exercises for patients with lymphedema. A 20-minute walk outdoors or on a tapis roulant, whilst wearing compression garments, stimulates the lymphatic system and improves circulation. It is important to maintain a normal speed and avoid dragging the affected leg or limping, as these could worsen the edema and cause pain.

• Cycling: easy. Using a exercise bike, preferably a recumbent model, offers an excellent alternative for patients with lower limb lymphedema. This position promotes venous and lymphatic return thanks to the elevation of the legs. A 20–25-minute session at a moderate pace is sufficient to improve mobility and endurance, reducing the risk of overloading.

• Swimming and aquagymn: water-based exercises are an ideal choice for patients with lymphedema. The hydrostatic pressure exerted by the water stimulates lymphatic drainage, reducing edema.

Swimming or taking part in aquagymn sessions improves muscle tone, joint mobility and aerobic capacity. However, it is essential to avoid water temperatures above 35°C, which could aggravate the edema and compromise the lymphatic system.

• Yoga: Yoga combines stretching, deep breathing and relaxation, offering significant benefits for the lymphatic and venous systems. Yoga positions can be modified to suit the patient's individual needs and physical limitations. Intense practices or positions which cause discomfort should be avoided.

Although many exercises are beneficial, certain activities pose a high risk for patients with lymphedema:

• For lower limb lymphodema: football, kickboxing and other high-impact activities.

• For upper limb lymphodema: tennis, squash and golf, which involve repetitive and intense arm movements.

These activities may increase the risk of injury or worsen the odema. However, patients who are motivated to continue these activities under the supervision of a qualified professional and by taking the necessary precautions can safely and effectively incorporate physical exercise into their daily routine, improving not only their physical condition but also their quality of life.

GENERAL GUIDELINES FOR PHYSICAL ACTIVITY

• Wear compression garments: aerobic exercises should always be performed whilst wearing an elastic compression brace, which provides support to the lymphatic system and reduces the risk of fluid build-up.

• Exercise in the morning: the ideal time to exercise is in the morning, when the affected limb is less fatigued from daily activities.

• Progress gradually: the intensity and duration of physical activity must be increased gradually, always taking into account the patient's individual limits.

• Avoid painful or stressful movements: any exercise that causes pain, discomfort or increased swelling must be stopped immediately.

• Monitor the affected limb: the affected limb should be checked regularly for any changes in size or shape during and after exercise.

NUTRITION AND LIFESTYLE IN THE VOYAGE OF CANCER PATIENTS

NUTRITION AND LIFESTYLE IN THE VOYAGE OF CANCER PATIENTS

Facing a cancer diagnosis is a profound challenge that affects the body, mind and spirit. In the context of a complex disease such as cancer, often experienced as a ‘game of chess’ against a cunning and unpredictable opponent, every choice that promotes the patient’s well-being is of crucial importance. This chapter aims to provide a practical and informative guide, primarily for cancer patients, to explore how nutrition and lifestyle can positively influence the body, supporting the fight against the disease and the management of treatment side effects. In recent decades, scientific research has highlighted the inextricable link between diet, intestinal microbiota, the immune system and physical and mental wellbeing. The microbiota, composed of trillions of microorganisms residing in the gastrointestinal tract, plays a fundamental role in modulating inflammation, digesting nutrients and producing bioactive metabolites such as short-chain fatty acids (SCFAs). Changes in the composition of the microbiota can influence not only the progression of the disease, but also the response to cancer treatments and the overall recovery. A key element of this short guide is to promote an active understanding of the role of nutrition as an integral part of the therapeutic journey. Adopting a diet rich in anti-inflammatory foods — such as high-quality animal fats, olive oil, nuts, and vegetables grown using natural methods — and limiting ultra-processed foods and refined sugars can help modulate chronic inflammation, a factor recognised for its negative influence on tumour growth. At the same time, approaches such as intermittent fasting and time-restricted eating, when well integrated into patients’ routines, have shown promising benefits. These regimes, which are based on respecting the body’s circadian rhythms, can activate cellular autophagy processes, improve insulin sensitivity and help protect healthy cells during treatment. Furthermore, the ability of fasting to reduce the side effects of chemotherapy and enhance the efficacy of treatments has been documented in several clinical studies. Sleep hygiene is another crucial aspect for cancer patients, although it will not be explored in depth in this chapter. Good-quality sleep supports physical

recovery, hormonal balance and psychological well-being, contributing to an overall improvement in quality of life.

The aim of this chapter is also to provide practical ideas for transforming the treatment path into a more active and conscious process. Eating can become a healing ritual, a moment of connection with one's body and a source of resilience. Every dietary choice can be seen as a building block that helps to build one's strength against the disease. Finally, it is important to emphasise that the suggested approach is not intended to replace conventional cancer treatments, but to complement them, highlighting the complementary role of nutrition and lifestyle. A deeper understanding of these aspects can not only improve quality of life, but also provide patients with the tools needed to face the challenge with greater awareness and determination.

CANCER AS A METABOLIC DISEASE AND THE FOUNDATIONS OF NUTRITIONAL THERAPY

Cancer is increasingly recognised as a metabolic disease, characterised by alterations in cellular metabolism that fuel tumour growth. One of the main metabolic characteristics of cancer is the Warburg effect, in which cancer cells favour anaerobic glycolysis to produce energy even in the presence of oxygen. This phenomenon allows cancer cells to accumulate intermediate metabolites essential for the synthesis of the biomass required for cell proliferation. Nutritional therapies aim to exploit these metabolic 'vulnerabilities' to hinder tumour growth and improve response to conventional therapies. A ketogenic diet, for example, reduces the availability of glucose and promotes the use of keton bodies as an energy source, a less efficient metabolic pathway for cancer cells. Clinical and preclinical studies have shown that such approaches can enhance the efficacy of chemotherapy and radiotherapy, whilst improving the patient's quality of life. Another key aspect is represented by autophagy, a cellular recycling process that is stimulated during fasting or calorie-restricted diets, particularly those restricting certain nutrients. Autophagy contributes to the removal of damaged cellular components and the maintenance of cellular homeostasis, promoting an adaptive response to therapies and reducing treatment toxicity. Oncological nutritional therapy, therefore, is not limited to

calorie restriction, but is based on personalised strategies that take into account the specific metabolism of the tumour, the patient's clinical condition and patient interactions with ongoing therapies. Supplements such as vitamin D, selenium and omega-3 fatty acids can support the immune system and modulate inflammation, offering an additional level of metabolic support. In summary, cancer as a metabolic disease presents a complex challenge but also an opportunity to integrate targeted nutritional interventions, improving therapeutic efficacy and the patient's overall well-being.

THE ROLE OF INFLAMMATION AND THE IMMUNE SYSTEM

Chronic inflammation is a key factor in tumour progression, influencing the growth, invasion and metastasis of cancer cells. Pro-inflammatory cytokines, produced by the tumour microenvironment, create a favourable environment for tumour survival and proliferation. However, inflammation can be modulated through dietary interventions and healthy lifestyles. Foods rich in antioxidants and omega-3 fatty acids can help reduce levels of systemic inflammation. The immune system plays a fundamental role in recognising and destroying cancer cells. However, many cancers develop mechanisms to evade immune surveillance. Adopting a balanced diet and targeted supplements can support immune system function, improving the body's ability to fight cancer. In particular, the gut microbiota, modulated by dietary fibre and fermented foods, contributes to the formation of beneficial metabolites, such as SCFAs, which strengthen mucosal and systemic immunity. In summary, a strategy that combines inflammation control and immune support may represent a key factor in improving the prognosis for cancer patients.

THE INTESTINAL MICROBIOME AS AN ALLY IN THE FIGHT AGAINST CANCER

The human microbiome is a complex network of microorganisms that coexist in symbiosis with the host, and its balance is crucial for the optimal functioning of our body. The main components of the human microbiome are:

Bacteria: the most abundant group, comprising major phyla such as *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. These bacteria play a role in essential functions such as digestion, vitamin production and the regulation of the immune system.

Archaea: bacteria-like microorganisms, such as *Methanobrevibacter smithii*, involved in the metabolism of intestinal gases.

Viruses: such as bacteriophages

Fungi: form part of the microbiome and include species such as *Candida* albicans and *Saccharomyces cerevisiae*, which can be commensal or opportunistic.

Protozoa: single-celled microorganisms such as *Blastocystis hominis*, whose role in physical wellbeing is still subject to studies.

The gut is the main habitat for these microorganisms, but the skin, mouth, respiratory tract and urogenital system also host microbial communities with specific functions. Among these, it is very important to highlight a few:

1. Modulation of the immune system

The intestinal microbiome is fundamental to the maturation and functioning of the immune system. It stimulates the production of regulatory lymphocite T cells, which are essential for preventing excessive immune responses against the body's own tissues (autoimmunity), and regulates the production of cytokines, small proteins that modulate inflammation. A healthy microbiome helps maintain a balanced immune system, preventing both infections and autoimmune diseases.

2. Regulation of digestion and metabolism

The intestinal microbiome plays a role in the digestion of foods that the human intestine cannot digest on its own, such as food fibre. Furthermore, certain microbes produce essential vitamins (such as vitamin K2 and vitamins of the B group) and short-chain fatty acids (SCFAs), which are important for intestinal health, appetite regulation and protection against metabolic diseases, such as type 2 diabetes.

3. Maintaining the intestinal barrier

A balanced microbiome helps maintain the integrity of the intestinal barrier, preventing 'leaky gut', a condition in which the intestinal mucosa becomes damaged, thereby allowing unwanted substances to enter the bloodstream. Dysbiosis, i.e. the loss of microbiome diversity, can compromise this barrier and promote systemic inflammation and chronic diseases.

MICROBIOME AND CANCER

Given the importance of the intestinal microbiome in regulating the immune system and its role in regulating the gastrointestinal environment, research into the link between the microbiome and cancer has intensified in recent years. Indeed, alterations in the composition and function of the microbiome – known as **dysbiosis** – have been linked to the development and progression of various types of cancer, particularly those of the gastrointestinal tract, such as colonrectal cancer. However, their influence also extends to cancers in other parts of the body, including the liver, pancreas and even the lungs. There are several mechanisms through which an alteration in the microbiome can influence the onset of cancer. The first relates to the development of a state of chronic inflammation caused by intestinal dysbiosis. Chronic inflammation is a condition that predisposes normal cells to transformation into cancer cells. If the proportion of certain bacteria in the microbiome increases, such as Escherichia coli (toxin-producing strains) and Fusobacterium nucleatum, there is an increase in the production of metabolites that promote inflammation and damage the DNA of host cells, favouring mutations that lead to the development of cancer. Furthermore, an increase in certain bacterial strains can also stimulate the secretion of inflammatory cytokines (e.g. IL-6, TNF-α),

which contribute to the proliferation of cancer cells and the formation of a microenvironment conducive to tumour growth. In addition to chronic inflammation, intestinal dysbiosis is linked to immune system dysregulation. Since the microbiome regulates the activation and suppression of the immune system, when dysbiosis occurs, there may be a reduction in the immune system's ability to recognise and destroy tumour cells , as well as interference by certain bacterial strains (for example, *Fusobacterium nucleatum*) in immune surveillance, thereby reducing the ability to protect against the development of cancer cells. Furthermore, dysbiosis can lead to excessive production of compounds that directly affect intestinal epithelial cells, such as deoxycholic acid (produced by *Clostridium spp.*), a metabolite that damages DNA and promotes hepatocellular carcinoma, or nitrosamines, which result from the metabolisation of excess animal proteins and fats by dysbiotic bacteria, thereby increasing the risk of gastrointestinal cancers. Finally, in cases of dysbiosis, certain microorganisms in the microbiome that modulate hormone production and metabolism may increase, influencing, for example, oestrogen levels, which are linked to the risk of hormone-dependent cancers such as breast and endometrial cancer.

EFFECTS OF CANCER TREATMENTS ON THE MICROBIOME

Cancer therapies, which are essential for the treatment of cancer, can profoundly affect the human microbiome. This impact can have significant consequences not only for intestinal health, but also for the immune response, for metabolism and for patients' quality of life. Understanding these effects is crucial for developing supportive strategies that reduce symptoms and improve clinical outcomes. Chemotherapy, for example, targets cancer cells but also has non-specific side effects on healthy cells, including enterocytes (the cells of the intestinal epithelium). This results in damage to the intestinal mucosa, thereby altering the barrier and promoting dysbiosis. The alteration of the intestinal barrier leads to increased permeability between enterocytes, allowing bacterial endotoxins (e.g. lipopolysaccharides) to pass into the bloodstream, triggering a systemic inflammatory response. Furthermore, the effects of chemotherapy can lead to a reduction in microbial diversity, with a decrease in beneficial bacteria such as

Lactobacillus and *Bifidobacterium*. Radiotherapy directed at the abdomen or pelvis can also severely damage the intestinal microbiome, likewise reducing microbial diversity and altering the balance between beneficial and pathogenic bacteria. Furthermore, it can cause radiation enteritis, a condition characterised by diarrhoea, abdominal pain and chronic inflammation. Finally, during cancer treatment, it may be necessary to take antibiotics to prevent or treat infections in immunocompromised patients. Their use also has a significant impact on the health of the microbiome. In fact, antibiotics do not only eliminate pathogenic bacteria, but also beneficial ones, leading to significant dysbiosis. This promotes the growth of opportunistic bacteria, such as *Clostridium difficile*, which can cause severe diarrhoea and colitis, and reduces the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), which protect intestinal integrity. These alterations to the microbiome during cancer treatments can contribute to numerous side effects, such as diarrhoea and nausea, weakness and fatigue, increased susceptibility to infection (due to greater colonisation by pathogenic bacteria) and systemic inflammation. It is therefore necessary to study and explore strategies useful for the protection and preservation of the microbiome as much as possible during oncological treatments . Among these, the most important factor is the dietary choices made by the patient. The type of diet followed, in fact, has the ability to alter the microbiome or to promote its well-being.

Let us first examine the characteristics a diet should have to promote a healthy microbiome as much as possible.

1. A good intake of fibre: fibre is the main nutrient for beneficial bacteria, as it acts as a prebiotic, i.e. as a substrate for their growth. In fact, it promotes the production of short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate, through the fermentation process. SCFAs improve the integrity of the intestinal barrier and reduce inflammation. Some foods that contain fibre include fruit and vegetables, pulses, seeds and nuts.

2. Dietary variety: A diverse microbiome is synonymous with good health. Dietary diversity promotes the growth of different bacterial strains, improving microbial balance. Some suggestions for increasing dietary variety include eating a variety of fruit and vegetables every week, alternating protein sources (fish, pulses, meat, eggs) and incorporating seeds, nuts, extra virgin olive oil, avocado, butter and other sources of good-quality dietary fats.

3. Consumption of fermented foods: these contain probiotics, live microorganisms that contribute to the balance of the microbiome. Examples of fermented foods include natural yoghurt and kefir, sauerkraut and kimchi, miso and tempeh, and kombucha.

4. Limiting sugars and ultra-processed foods: simple sugars and trans fats promote the growth of harmful bacteria and can reduce microbial diversity. This promotes inflammation and disrupts the balance of the microbiome (dysbiosis). Examples of foods to avoid therefore include sugary drinks, packaged snacks, commercially sweetened yoghurts, fruit juices, and pre-cooked and ready-made frozen foods.

5. Adequate intake of healthy fats: Healthy fats have a protective effect on the intestine and promote a balanced microbial composition, reducing inflammation and increasing the number of beneficial microbial strains. Foods in this category include extra virgin olive oil, oily fish (salmon, mackerel, sardines), avocados, and nuts and seeds (walnuts, almonds, flaxseeds and chia seeds)

6. Be mindful of the type of animal protein included in your diet: animal-based foods may, in fact, come from large industrial farms that do not guarantee proper product quality due to the way the animals are reared. For this reason, it is necessary to check the origin of meat, fish and eggs. Furthermore, a proper rotation of these foods within your weekly routine ensures a good variety of diet.

7. Limitation of alcohol: excessive alcohol is, in fact, harmful to the microbiome, as it can reduce bacterial diversity and increase intestinal inflammation. Reducing or eliminating alcoholic drinks helps to protect the intestinal microbiome, as alcohol can alter the composition of intestinal bacteria, promoting dysbiosis and inflammation; if consumed, it is preferable to limit intake to moderate amounts and opt for red wine, which contains polyphenols that may be beneficial for intestinal bacteria.

A diet low in fibre, high in sugar and processed foods, high in alcohol, lacking in variety and with low fluid intake, is, on the other hand, harmful to the microbiome, leading to the condition of dysbiosis mentioned earlier. Following these recommendations during cancer treatment therefore helps to preserve the microbiome as much as possible, as it is already subject to modification due to the therapies. Another beneficial measure for intestinal microorganisms is the supplementation of probiotics and prebiotics. Probiotics are live

microorganisms, mainly bacteria and yeasts, which act by increasing the presence of strains beneficial to the intestine's balance. Prebiotics, on the other hand, are fibres or non-digestible compounds that nourish the beneficial bacteria of the intestinal microbiome. During cancer treatment, probiotics such as *Lactobacillus rhamnosus GG* and *Bifidobacterium longum* can reduce diarrhoea caused by chemotherapy and antibiotics, whilst prebiotics, such as inulin, promote the growth of beneficial bacteria.

THE ANTI-INFLAMMATORY DIET

INFLAMMATION: A DOUBLE-EDGED SWORD

Inflammation is a natural defence mechanism of our body, essential for fighting infections, repairing damaged tissue and responding to trauma. However, when it becomes chronic, it turns into a silent problem that can contribute to the development of numerous diseases, including cancer. Chronic inflammation is a state of persistent activation of the immune system, often caused by factors such as an unbalanced diet, stress, a sedentary lifestyle or exposure to toxic substances. In the context of cancer, inflammation can promote both the onset and growth of tumours by creating an environment conducive to the proliferation of diseased cells. Furthermore, it can compromise the response to treatments and exacerbate side effects. Reducing inflammation through dietary choices and a healthy lifestyle is therefore a fundamental strategy for supporting the body during treatment and improving quality of life.

Much debate centres on the effectiveness of anti-inflammatory diets during periods of cancer; one often hears of ketogenic or low-carb diets, whilst others advocate plant-based diets, and finally there are those who argue that diet has no effect or benefit on the health of cancer patients. On one point, however, everyone is in agreement with: the importance of paying attention to diet, aiming to reduce inflammation of the body as a preventive measure. Adopting a protective lifestyle and a diet that involves moderate consumption of certain foods and a reduction in others is essential to help the body prevent the disease or a potential recurrence. During the active phases of the disease, however, diet takes on a different role, as not all patients respond in the same way and many may experience varying degrees of benefit, particularly when combined with the treatment. In many cases, patients experience nausea, diarrhoea, poor appetite, and changes in taste and smell, which do not help them to eat properly. These symptoms can lead to poor nutrient absorption and sudden weight loss, which must be avoided at all costs during treatment: body fat can be reduced, but in a controlled manner. Certain macro- and micronutrients must never be lacking, to allow the body to perform its normal functions. Alongside this, protective habits can be adopted to help the patient experience fewer side effects during treatment. Changing meal times or adjusting the frequency of meals can help manage nausea

or diarrhoea. Creating an anti-inflammatory metabolic state that can contribute to cellular autophagy can prove very useful in increasing the effectiveness of the therapy. Where the therapy primarily targets cells that replicate rapidly, whether healthy or diseased, having a metabolic state that can slow down the replicative drive of healthy cells can reduce side effects and increase the effectiveness of the therapy. This metabolic state can be managed through diet and lifestyle.

ANTI-INFLAMMATORY FOODS: NATURAL ALLIES FOR WELL-BEING

Regularly including certain foods in your diet can help strengthen the body's natural defences and create an internal environment less conducive to tumour progression.

Below are listed the main anti-inflammatory foods and their benefits:

Fruit and vegetables rich in antioxidants:

Berries (blueberries, raspberries, blackberries): contain anthocyanins, powerful antioxidants that reduce inflammation.

Citrus fruits (oranges, lemons, grapefruit): rich in vitamin C, which protects cells from oxidative damage.

Cruciferous vegetables (broccoli, cabbage, cauliflower): contain sulforaphane, a compound with anti-inflammatory and anti-carcinogenic properties.

Spinach and other leafy greens: rich in vitamin E and magnesium, known for their calming effect on the immune system.

Oily fish:

Salmon, mackerel, sardines and herring are excellent sources of omega-3 fatty acids, which reduce systemic inflammation and support cardiovascular health. Omega-3s compete with omega-6s, which in excess can promote inflammation.

Nuts and seeds:

Nuts contain alpha-linolenic acid (a type of plant-based omega-3) and antioxidants that reduce inflammation.

Flax and chia seeds: rich in fibre, lignans and omega-3s, which improve intestinal health and reduce inflammatory markers.

Spices and seasonings:

Turmeric: its active ingredient, curcumin, is one of the most

powerful natural anti-inflammatory agents. To improve its absorption, it is helpful to combine it with black pepper, which contains piperine.

Ginger: reduces levels of inflammatory cytokines and aids digestion, which is often compromised during cancer treatments.

Garlic: thanks to allicin, a bioactive compound, garlic reduces inflammation and improves immune function.

Healthy fats:

Extra virgin olive oil: rich in polyphenols and vitamin E, it is a powerful natural anti-inflammatory, ideal for dressing vegetables and salads.

Avocado: contains monounsaturated fatty acids and phenolic compounds that help reduce inflammation.

Green tea:

Rich in catechins, powerful antioxidants that help combat oxidative stress and reduce inflammation levels.

Fermented foods:

Yoghurt with no added sugar, kefir, kimchi, miso and sauerkraut help to balance the intestinal microbiome, which is crucial for keeping inflammation levels low. When discussing antioxidants, it is important to remember that molecules such as free radicals or reactive and oxidising species are often used by our immune system as a defence mechanism and should not be reduced excessively. Consuming too many antioxidants, especially in the form of supplements, becomes a risk if they are not properly balanced, as whilst it is true that an excess of oxidising substances contributes to chronic inflammation, it is equally true that without them our body would lose a powerful means of defence; therefore, it is important to seek the correct balance that allows the immune system to modulate oxidised species. Consider physical activity, which produces oxidising substances during the training phase, but which, if carried out correctly and at the right times, becomes an anti-inflammatory and protective factor for the individual.

FOODS TO AVOID: SILENT ENEMIES

Whilst there are foods that combat inflammation, there are others that promote it, damaging overall health and worsening the side effects of cancer treatments. Reducing the consumption of these foods is essential to support the body during treatment. In fact, we must

remember that cancer cells feed on glucose and glutamine, two elements that are also essential for the survival of other cells. It is impossible to completely exclude these two nutrients from our diet, as the body can produce or recover them by depleting reserve tissues if they are absent; however, we can carefully limit our intake of them. The aim should not be to have no glucose in the blood—which is incompatible with life—but to keep it as low as possible by carefully assessing what we eat throughout the day. We can regulate what we eat, when we eat it, and in what quantities. These three parameters allow the nutritionist to devise a personalised, dietary plan to support the patient on route. It is necessary to provide the right amount of nutrients to prevent sarcopenia, but useful in slowing down tumour growth.

One must be careful with certain foods:

Refined sugars: Foods such as cakes, biscuits, sugary drinks and processed snacks cause blood sugar spikes that promote inflammation and damage the intestinal microbiome. Simple sugars provide energy to cancer cells, promoting their growth.

Ultra-processed foods: Snacks, crisps, packaged foods and ready meals contain additives, preservatives and trans fats that increase levels of inflammation and oxidative stress.

Saturated and trans fats: Processed meats (cold cuts, sausages, hot dogs) and industrial baked goods contain saturated and hydrogenated fats that promote chronic inflammation.

Alcoholic drinks: Excessive alcohol consumption can alter the intestinal microbiome and increase the risk of systemic inflammation. Extreme moderation is advised, and in some cases it is preferable to avoid consumption altogether.

Refined oils: Industrial seed oils (such as palm oil, soya oil and all seed oils) are rich in omega-6, which in excess can upset the balance between omega-3 and omega-6, promoting inflammation.

Studies tell us that cancer cells require glucose and amino acids to grow; obviously, the body also needs these to fight the disease and maintain general homeostasis. Nutrition for those affected by this disease must therefore strike the right balance between macronutrients and the timing of their intake. The risk of completely excluding a macronutrient such as carbohydrates, as in the case of the ketogenic diet, is that cancer cells capable of surviving under such conditions may be selected. Studies certainly show a slowing of tumour growth, but if the exclusion is prolonged for too long, cells that manage to

replicate despite this more unfavourable environment could be selected. According to some studies, a good strategy is to train the body to make a metabolic switch from a carbohydrate-based metabolism to a lipid-based metabolism. This enables the body to manage its internal resources more effectively, alternating them through external resources introduced by the diet. If the body is trained to make this switch, it can regulate itself between mealtimes and fasting periods by alternating between the different metabolic states. Making use of these fasting windows between meals can prompt the body to activate cellular autophagy, which will make healthy cells more resistant to cancer treatment. Some studies have shown various benefits linked to mild calorie restriction and time-restricted feeding (more commonly known as intermittent fasting). These benefits tie in well with what has just been said: indeed, creating an appropriate dietary plan that incorporates these principles helps the body maintain a catabolic state that utilises cellular autophagy to recover energy and reduce systemic inflammation.

It is worth remembering that inflammation is a necessary process for the body to combat cancer, but it must be regulated when it becomes chronic and uncontrolled. Following an anti-inflammatory diet helps to avoid amplifying the inflammatory signals already present in the body. Careful management of nutrition can provide the body with the right resources to fight, without promoting tumour growth. A diet in the context of cancer treatment must be tailored to the individual; it should not be a restriction, but must have specific characteristics that are adapted to the patient's lifestyle and needs. Every choice made during meals and linked to lifestyle becomes an opportunity to strengthen the body and improve quality of life, one day at a time.

DIETARY FIBRE AND GASTROINTESTINAL CANCERS

BENEFITS OF FIBRE

As mentioned earlier, the composition of a cancer patient's diet is a decisive factor for the balance of the microbiome. Among the characteristics of the diet, one of the most influential factors for eubiosis is represented by the content of foods containing dietary fibre. This is a component of carbohydrates found in plant-based foods, which is partially digested by enzymes in the human gastrointestinal tract. Unlike sugars and starches, fibre passes intact through the stomach and the small intestine, reaching the colon, where it can be partially or fully fermented by gut bacteria. It is mainly divided into two categories: soluble fibre and insoluble fibre, each with specific characteristics and benefits.

Soluble Fibre: soluble fibre dissolves in water to form a viscous gel; it is fermentable in the colon, where it nourishes the bacteria of the microbiome and has the ability to slow down the absorption of sugars and fats, contributing to glycaemic control and an improved lipid profile. The principal source of soluble fibre includes certain whole grains such as oats and barley, certain types of fruit such as apples, pears, oranges and berries, certain pulses such as lentils, chickpeas and beans, as well as flax and chia seeds.

Insoluble fibre: insoluble fibre does not dissolve in water and passes through the digestive tract relatively intact. Its rigid structure helps to stimulate bowel movement. It is not fermentable, or only partially so, and has the ability to increase stool volume. The main sources of insoluble fibre are certain whole grains such as wheat, spelt and brown rice; certain vegetables such as spinach, artichokes, cauliflower and celery; the skin of certain fruits such as apples, pears and plums; certain types of nuts such as walnuts; and seeds such as flax or chia seeds.

Dietary fibre is essential for health, contributing to certain vital functions of the human body and represents a substance that protects against the onset of certain diseases, including cancer. The first beneficial effect that fibre has on the body is promoting regular bowel movements, by reducing the transit time of faecal matter. Dietary fibre, in fact, increases stool volume and improves its consistency, accelerating

intestinal transit. This reduces the time enterocytes are exposed to potentially carcinogenic substances, thereby lowering the risk of chronic inflammation and the formation of precancerous lesions. Furthermore, fibre intake promotes the growth of beneficial bacteria in the intestinal lumen, as it is the main substrate for bacterial fermentation in the colon. This encourages the production of SCFAs (short-chain fatty acids), molecules such as butyrate, which, as already mentioned, play a key role in protecting the intestinal mucosa. They promote the apoptosis of cancer cells and reduce systemic inflammation by modulating the immune system. Furthermore, SCFA production increases microbiome diversity, reducing the prevalence of pathogenic bacteria associated with cancer risk. Dietary fibre, furthermore, reduces chronic inflammation—a risk factor for cancer—by modulating levels of inflammatory cytokines (e.g. TNF-α, IL-6) and stimulating the production of regulatory T cells (Tregs) that help maintain immune homeostasis. Finally,the consumption of an adequate amount of fibre reduces the absorption of carcinogens, as it binds in the intestinal lumen to certain molecules such as nitrosamines—derived from foods rich in animal protein—and certain toxic metabolites produced by the fermentation of fats and proteins.

SOURCES OF FIBRE: PRACTICAL SUGGESTIONS

Incorporating a good amount of fibre into daily diet is easier than you might think. Detailed below is a practical and comprehensive guide to choosing the best sources of fibre and how to include them in meals.

Wholemeals: these are one of the most versatile and accessible sources of fibre and contain mainly insoluble fibre. Compared to refined grains, they retain the bran and germ, the parts richest in nutrients. Examples of wholegrains include: buckwheat, oats, spelt, barley and brown rice. At appropriate times or during dietary phases, one way to incorporate them into meals is to replace white rice with brown rice, or to use wholemeal or buckwheat pasta and bread instead of pasta and bread made from ‘white’ (refined) flour.

Legumes: this food group includes lentils, chickpeas, beans (borlotti, black cannellini) and peas.

Most legumes contain mainly soluble fibre, but some types, such as soya, black beans and cannellini beans, have more insoluble

fibre. Legumes available on the market are sold both dried and pre-cooked in tins or jars. The advice is to buy them dried and soak them for several hours, so as to make their fibre more digestible. There are also shelled legumes that can be used to increase fibre intake, but in limited quantities, for those who are more sensitive to their consumption.

Fruit: this contains mainly soluble fibre, particularly in the form of pectin. Its consumption can be at the end of a meal (if well tolerated) or added in a moderate amount as a snack for breakfast (if eaten). Despite its beneficial effects in terms of fibre intake (and its vitamin and mineral content), it is important not to overindulge, in its consumption using two daily portions as a guideline (one portion, according to guidelines, corresponds to approximately 150g).

Vegetables: within this food category, one can find both foods richer in soluble fibre and those containing more insoluble fibre. In particular, soluble fibre is more abundant in vegetables rich in mucilage or fermentable polysaccharides, such as carrots, broccoli, courgettes, Brussels sprouts, asparagus and pumpkin. Insoluble fibre, on the other hand, is more common in green leafy vegetables or those rich in cellulose. These include spinach, artichokes, cauliflower, celery, peppers, aubergines (with skin) and kale and cabbage. Some suggestions to encourage vegetable intake include the use of minestrone and creamed soups as accompaniments to meals (if well tolerated), always including a small amount of vegetables with the main course, and/or using vegetables as seasoning in the first course.

Seeds and Nuts: examples of seeds include flaxseeds and chia seeds, whilst examples of nuts include almonds, walnuts, hazelnuts and cashews. As well as providing fibre, these foods are rich in healthy fatty acids, such as omega-3s, which have anti-inflammatory effects and protect cardiovascular health. Flaxseeds and chia seeds, in particular, also contain mucilage, which helps regulate bowel movements. Some ways to increase ones intake include adding a small portion to yoghurt or salads, or eating a handful as a snack or at the end of a meal.

FIBRE INTAKE: AMOUNTS AND METHODS

To obtain an idea of daily fibre requirements, one can refer to guidelines recommending a daily intake of 25–30 grams of fibre for adults, with a balanced ratio of insoluble to soluble fibre. For cancer patients, it is essential to modulate fibre intake and introduce it gradually into the diet to avoid gastrointestinal disturbances and improve tolerance during treatment. Due to the sensitivity of the digestive system, caused by the side effects of chemotherapy, radiotherapy or immunotherapy, a personalised and gradual approach is essential. The consequences of excessive and rapid fibre intake can include:

Intestinal sensitivity: cancer patients may suffer from symptoms such as diarrhoea, constipation, swelling or nausea, exacerbated by sudden dietary changes.

Microbiome imbalance: a sudden increase in fibre can overstimulate intestinal bacteria, causing excessive fermentation and symptoms such as cramps and flatulence.

Failure of the microbiome to adapt: dietary fibre provides substrates for beneficial bacteria; a non-gradual introduction does not allow the microbiome to adapt and proliferate in a balanced way.

It is therefore necessary to adopt certain strategies to incorporate fibre into the diet gradually. First of all, it is necessary to start by consuming small amounts. The initial objective could be to introduce 5–10 grams of fibre daily, then increasing by 2–3 grams each week until the recommended intake (25–30 grams per day) is reached. To follow this process, it is advisable to initially choose foods rich in soluble fibre and introduce those rich in insoluble fibre (s) in small quantities: beginning with cooked vegetables such as courgettes and carrots, opt for fruit without skin or seeds or in a smoothie (e.g. cooked apples, ripe bananas) and, if consuming cereals, begin with refined cereals enriched with small amounts of whole grains (e.g. homemade bread, semi-wholemeal rice). In general, it is advisable to opt for cooked foods initially, as cooking softens the fibre and makes it easier to tolerate. Vegetables can therefore be steamed or boiled (cooking methods that reduce the insoluble fibre content whilst retaining vitamins and minerals), and fruit can be cooked. To gradually introduce fibre, it is also possible to use small quantities of legumes in a puréed and/or shelled form. This allows for the intake of fibre but in a form that is more easily digested by the intestine. Examples of such foods include velvety soups, hummus, and strictly homemade

legume-based meatballs or burgers. It is necessary to monitor the individual's response during this process, as everyone reacts differently to fibre intake. Symptoms to watch out for include bloating, cramps, and the onset of diarrhoea or constipation. Should these symptoms occur, the advice is to temporarily reduce the amount of fibre and reintroduce it more gradually. A final consideration when introducing fibre into the diet concerns fluid intake. Increasing dietary fibre must be accompanied by adequate fluid consumption, drinking at least 1.5–2 litres of water daily (to prevent constipation and promote bowel motility) and opting for still water, herbal teas or homemade broths with meals.

INTERMITTENT FASTING AND METABOLIC STRATEGIES

FASTING AND CELLULAR RESILIENCE

Intermittent fasting stimulates a series of mechanisms that contribute to cellular resilience, making the body better able to cope with metabolic stress and improving responses to cancer therapies. One of the key processes is autophagy, an intracellular recycling system that eliminates damaged components, reduces the accumulation of misfolded proteins and regenerates essential organelles such as mitochondria. This process, activated during fasting, enables healthy cells to maintain functional integrity and counteract oxidative stress. A further effect of fasting is the reduction in levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, which contribute to the modulation of the tumour microenvironment. This less inflammatory environment not only hinders tumour progression but also enhances the efficacy of treatments such as chemotherapy and immunotherapy. Several preclinical studies have shown that fasting can sensitise cancer cells to the effects of anticancer drugs, whilst reducing toxicity of healthy cells. For example, a study conducted on mouse models of breast cancer demonstrated that fasting for 48 hours prior to chemotherapy increases the treatment's efficacy whilst reducing collateral damage to healthy tissues. Another clinical trial involving patients with solid tumours found a significant reduction in side effects, such as nausea and fatigue, among those following intermittent fasting protocols. These benefits also extend to fasting's ability to stimulate the production of ketone bodies, which provide an alternative energy substrate for healthy cells, preserving their function even under conditions of severe metabolic stress. Conversely, cancer cells, which are dependent on glucose and glutamine, find it more difficult to adapt to this metabolic shift, making them more vulnerable.

METABOLIC EFFECTS OF INTERMITTENT FASTING

One of the main effects of intermittent fasting is the reduction in blood glucose levels and insulin production. Insulin is an anabolic hormone with a crucial role in regulating blood glucose levels, but also acts as a growth factor, stimulating cellular signalling pathways that can promote cell proliferation and, in certain contexts, support tumour growth. Chronic high insulin levels, often associated with a diet rich in sugars and refined carbohydrates, can contribute to a state of systemic inflammation and promote insulin resistance, a mechanism that further increases the risk of tumour progression.

Intermittent fasting, by reducing calorie intake and synchronising meals with circadian rhythms, helps lower insulin and blood glucose levels, thereby reducing the proliferative stimulus on cancer cells. Furthermore, in the absence of a constant supply of glucose, the body switches to a metabolism based on ketone bodies, an energy source that does not effectively support the growth of cancer cells, which rely primarily on glucose and glutamine for their proliferation. This metabolic shift also promotes greater mitochondrial efficiency, improving energy production in healthy cells and stimulating cellular repair processes, such as autophagy. Studies have shown that a reduction in insulin levels can inhibit signalling pathways linked to mTOR (*mammalian target of rapamycin)*, a key protein in the regulation of cell growth and protein synthesis, which is often overactive in cancer cells.

Diet plays a decisive role in modulating these effects. Diets rich in simple carbohydrates and ultra-processed foods contribute to blood sugar spikes and hyperinsulinaemia, whilst a balanced diet, based on whole grain foods and low-glycaemic index foods, helps maintain stable blood sugar and insulin levels, amplifying the benefits of intermittent fasting. This integrated approach combining nutrition and fasting represents a promising strategy for supporting cancer treatments and improving patients' quality of life. To reduce carbohydrate and sugar intake and lower insulin secretion, various scientifically evidence-based nutritional strategies can be adopted:

- Refined carbohydrates and simple sugars rapidly raise blood glucose levels and insulin secretion. Replacing them with low-glycaemic-index foods, such as leafy green vegetables, and small amounts of legumes, whole grains and low-sugar fruits (such as berries and citrus fruits), can help maintain stable blood glucose levels.

• Choosing parboiled or brown rice instead of white rice can also reduce the glycaemic impact of meals.

• Fibre slows down the absorption of carbohydrates, reducing blood sugar peaks and insulin levels. Good sources include non-starchy vegetables, seeds and fruit with peel.

• Supplementing with fermentable fibre, such as inulin and galacto-oligosaccharides, can improve insulin sensitivity and reduce inflammation.

• Replacing refined carbohydrates with sources of healthy fats (olive oil, avocado, nuts, oily fish) and lean proteins can reduce the insulin response during meals.

• It is important to choose high-quality protein and limit the consumption of processed meats.

• Artificial sweeteners can also stimulate insulin secretion and alter the intestinal microbiota. Opting for natural sweeteners with a low glycaemic impact, such as erythritol or stevia, may be beneficial.

• Sleep deprivation and chronic stress increase insulin resistance and cortisol levels, promoting greater accumulation of visceral fat.

• Intermittent fasting, particularly the 5:2 protocol or restricted eating windows (such as 16:8), has been shown to lower insulin levels more effectively than simple calorie restriction. During fasting, the body switches from using glucose to burning fat, lowering insulin levels and improving insulin sensitivity.

An innovative aspect linked to intermittent fasting is the concept of **the Intermittent Metabolic Switch (IMS)**, proposed by Mark P. Mattson. This mechanism describes the metabolic alternation between the use of glucose and ketone bodies as primary energy sources. During prolonged fasting, the depletion of liver glycogen reserves triggers a shift to fat metabolism, resulting in the production of ketone bodies. These not only serve as an alternative fuel source for the brain and muscles but also activate signalling pathways that promote cellular resilience, such as autophagy, DNA repair and protection against oxidative stress.

For example, a study of cancer patients showed that intermittent fasting regimens, combined with a balanced diet, improved inflammation markers and reduced the toxicity of chemotherapy. Another practical example is the adoption of the 16:8 protocol, which involves a 16-hour fast followed by an 8-hour window for eating, synchronising this

with circadian rhythms to maximise metabolic benefits and minimise the side effects of treatments. A low-carb diet is an essential complement to intermittent fasting, helping to keep blood sugar and insulin levels stable. By reducing the intake of simple carbohydrates and favouring foods rich in lean protein, healthy fats and low-glycaemic vegetables, glucose intake is limited, promoting metabolic adaptation towards the use of ketone bodies. This approach not only enhances the effects of fasting but also offers an additional tool for modulating inflammation and supporting cancer treatments.

To implement intermittent fasting safely, it is essential that patients consult their doctor and are monitored by a nutritionist. Light regimens such as the 16:8 protocol, which involves a 16-hour fasting window followed by 8 hours of eating, can be adapted to individual needs, taking into account ongoing treatments and general health status. These personalised approaches allow fasting to be integrated into the treatment plan without compromising the patient's energy and nutritional balance.

PRACTICAL EXAMPLES

A practical example of intermittent fasting could be to start the eating window at 10:00 am and end it at 6:00 pm. During the eating window, meals can include nutritious foods such as leafy green vegetables, whole grains, lean proteins and healthy fats such as avocados and nuts. Outside the eating window, it is important to stay hydrated with water, herbal teas or vegetable broth.

Another approach could be to gradually reduce the eating window, starting with a 12:12 regimen (12 hours of eating and 12 hours of fasting) and progressing towards a 16:8 protocol as the body adapts. This allows patients to become accustomed to fasting without feeling an excessive impact on energy levels. Finally, to optimise metabolic benefits and promote an intermittent metabolic switch, meals can be planned that combine protein and healthy, low-glycaemic-index fats, whilst limiting refined carbohydrates. For example, a breakfast rich in eggs, avocado and vegetables or a light dinner with fish and steamed broccoli can help maintain stable blood sugar levels and support the production of ketone bodies. Intermittent fasting, through reduced calorie intake and the synchronisation of meals with circadian rhythms, promotes a reduction in

insulin and blood sugar levels, thereby reducing the proliferative stimulus on cancer cells. Furthermore, in the absence of a constant supply of glucose, the body switches to a metabolism based on ketone bodies, an energy source that does not effectively support the growth of cancer cells, which rely primarily on glucose and glutamine for their proliferation. Prolonged fasting, lasting several days, represents a more intense metabolic approach than intermittent fasting. Prolonged fasting activates profound mechanisms of cellular regeneration and metabolic adaptation. During this period, the body depletes its glycogen reserves and relies entirely on lipolysis, generating ketone bodies as its primary energy source. This state of prolonged ketosis promotes a systemic reduction in inflammation and markedly stimulates autophagy.

KEY BENEFITS OF PROLONGED FASTING

Reduction of inflammation: Prolonged fasting lowers levels of pro-inflammatory cytokines such as IL-6 and TNF-α, creating a microenvironment less conducive to tumour growth.

Immune regeneration: Studies have shown that prolonged fasting supports the regeneration of the immune system, promoting the production of haematopoietic stem cells and enhancing the immune response against tumours.

Enhanced autophagy: The extended duration of fasting allows for more thorough cellular cleansing, eliminating damaged proteins and dysfunctional organelles.

Synergy with cancer therapies: Prolonged fasting increases the sensitivity of cancer cells to chemotherapy and radiotherapy, whilst protecting healthy tissues from collateral damage.

PRACTICAL CONSIDERATIONS

Prolonged fasting must be carried out under strict medical supervision or that of a qualified nutritionist, especially in cancer patients. It is important to closely monitor metabolic parameters and to adapt the protocol to individual clinical conditions. For example, one might begin with a three-day fast, followed by a gradual reintroduction diet based on easily digestible, nutrient-rich foods, such as vegetable broths, fresh juices and steamed vegetables. The prolonged fasting approach can be safely integrated into the therapeutic pathway, offering significant benefits within the context of metabolic cancer therapy.

THE CONCEPT OF ORMESIS AND BODY RESILIENCE

Ormesis is a fascinating principle that describes how the human body can become stronger and more resilient through exposure to small, controlled stresses. It is a concept rooted in both modern biology and ancient practices, such as 'Mithridatism'. Mithridates VI of Pontus, a king of Asia Minor, was known for taking small doses of poisons in an attempt to immunise himself against potential poisoning attempts. This strategy, though risky, represents a primitive example of how the body can adapt to difficult conditions, gradually strengthening itself. The idea behind this principle was well summarised by the physician and chemist Paracelsus in his famous phrase: "*Everything is poison, nothing is without poison: only the dose ensures that a thing is not poison*". In modern terms, hormesis describes the body's process of adapting to controlled stresses, which activate repair and protection mechanisms. The sauna is an excellent example of a hormetic stimulus, a moderate factor of stress that induces the body to activate beneficial adaptation mechanisms. Exposure to high heat temporarily raises body temperature, simulating a state of "controlled fever". This process triggers a cascade of biological responses: the production of heat shock proteins (HSPs), which protect cells from stress and promote the correct folding of proteins, and the release of neurotrophic factors, such as BDNF, which support brain plasticity and cognitive function. The sauna also stimulates the cardiovascular system, improving vasodilation and blood circulation, and contributes to detoxification through intense sweating. Furthermore, repeated exposure to heat promotes improved insulin sensitivity and reduces levels of chronic inflammation, key factors in the prevention of metabolic diseases and in support of cancer therapies. This preconditioning effect makes the sauna not just a wellness ritual, but a genuine tool for biological resilience. Furthermore, when the body is subjected to moderate stimuli, such as light physical exercise, a change in diet, or periods of fasting, biological processes such as autophagy are activated a physiological process that allows the body to 'clean itself'. During autophagy, in fact, cells eliminate damaged or dysfunctional components, thereby remaining healthier and more resilient. This process is particularly beneficial for cancer patients, as it can help reduce the side effects of treatments and improve the body's resilience.

HORMESIS AND PHYSICAL ACTIVITY

Physical activity is one of the most powerful tools for harnessing the benefits of hormesis. However, it is essential to strike a balance between moderate and intense exercise. Excessively intense physical activity can cause inflammation and worsen physical well-being, whilst well-measured activity can improve mobility, strengthen joints and stimulate the production of natural antioxidants such as glutathione. For example, moderate-intensity aerobic exercise, such as a walk or a light session on an exercise bike, can activate fat metabolism and promote the production of ketones, molecules that stimulate autophagy and cell regeneration. To maximise these effects, these activities can be performed on an empty stomach, so as to take advantage of the metabolic benefits of fasting itself, such as the shift from carbohydrate to fat metabolism. However, it is important to start gradually: a short walk is sufficient to begin with. As the body adapts, it will be possible to increase the intensity or duration of the physical exertion. Another useful type of activity is resistance training, which includes exercises with weights, resistance bands or free-body exercises. This type of training is particularly important for cancer patients as it helps preserve muscle mass, preventing conditions such as cancer-related cachexia, an uncontrolled loss of muscle mass that can worsen the prognosis. It is essential, however, that exercises are performed using correct technique and at an appropriate intensity to avoid inflammation or injury.

PRACTICAL SUGGESTIONS FOR PHYSICAL ACTIVITY

Start gradually: those who are not used to physical activity, should begin with short walks or light exercises. Even 10–15 minutes a day can make a difference.

Listen to your body: Some days one may feel stronger, others less so. Adjust the intensity of your exercises to your energy levels.

Alternate aerobic and anaerobic activities: Combine walking or yoga with resistance exercises, using resistance bands or small weights.

Exercise outdoors whenever possible: Exposure to sunlight promotes the production of vitamin D, essential for the immune system, and improves ones mood.

Respect your circadian rhythms: Try to exercise during the day, avoiding the evening hours so as not to interfere with sleep.

HORMONES AND NUTRITION

Diet can also be used to activate hormetic mechanisms. Controlled periods during which eating and fasting windows are adjusted throughout the day, for example, can stimulate autophagy, making healthy cells more resilient and cancer cells more vulnerable. This approach, however, must be followed under the guidance of a doctor or an expert nutritionist, especially during cancer treatments. Foods rich in hormetic compounds, such as polyphenols, can support the cellular repair processes. These compounds are found in berries, green tea, turmeric and other spices. Incorporating these foods into daily diet can offer an additional layer of protection against oxidative stress.

PRACTICAL NUTRITION SUGGESTIONS

Plan meals strategically: Coordinate meals with physical activity to maximise metabolic benefits, with the help of a qualified nutritionist.

Include polyphenol-rich foods: Add berries, green tea, turmeric and other anti-inflammatory spices to your diet.

Changes in eating habits: the adjustment of eating windows should be attempted, aiming to extend the fasting periods between meals using time-restricted feeding, always in consultation with a doctor and a nutritionist.

Consume high-quality protein: Carefully balance your protein intake to support muscle mass without promoting metabolic excess.

PHYSICAL ACTIVITY AND NUTRITION IN SYNERGY

To achieve maximum benefit, physical activity and nutrition must work together. For example, a morning aerobic workout on an empty stomach can be followed by a balanced breakfast containing protein and healthy fats, which supports muscle recovery and provides energy for the day. Working on the timing of different meals is essential to help the individual to sustain their training and maximise its effects. Different workouts will require different meals both before and after physical activity. It is essential that the nutritionist, doctor, physiotherapist and trainer have a thorough understanding of the principles of hormesis and how they can be utilised to improve a person's health. Hormesis is a principle that teaches us how controlled stimuli can make the body more resilient. Through moderate physical activity, a targeted diet and a gradual approach, it is possible to activate natural protective and repair mechanisms, improving overall well-being. It is important to remember that, as with everything, if these stimuli are overdone, the body will respond negatively, which may also lead to a deterioration in health. Every patient is unique, and for this reason it is essential to personalise their journey with the support of qualified professionals. With small steps and consistency, the body can be transformed into a strong and resilient ally in the fight against cancer.

STRATEGIES FOR PREVENTION AND MANAGEMENT OF SIDE EFFECTS

EFFECTS OF THERAPIES AND SUPPORTIVE NUTRITION

Cancer treatments, such as chemotherapy and radiotherapy, often cause significant side effects that can affect not only the body but also patients' mental health and daily lives. Nausea and vomiting, for example, can limit food intake, leading to unintentional weight loss and malnutrition. Chronic inflammation, often exacerbated by therapies, can contribute to pain of the joints, fatigue and reduced mobility. Psychologically, the feeling of constant fatigue, combined with loss of appetite and digestive problems, can increase the risk of anxiety and depression. Furthermore, changes to the intestinal microbiome can affect the intestine-brain axis, further exacerbating emotional instability. To alleviate these symptoms, it is essential to adopt targeted nutritional strategies. Small meals, rich in lean protein and small portions of healthy fats, can improve energy levels and help stabilise blood sugar. The use of ginger, in the form of herbal tea or as a supplement, is particularly effective in combating nausea. At the same time, an adequate intake of fluids, such as light broths and herbal teas, can prevent dehydration and support digestion. The importance of personalising the nutritional approach cannot be underestimated: every patient is unique and necessitates a dietary plan tailored to their specific clinical needs and personal preferences. The support of an expert nutritionist can make all the difference in helping patients maintain adequate nutrition during therapy, improving not only their quality of life but also the effectiveness of cancer therapies.

FOODS AND PRACTICES THAT SUPPORT DIGESTION

Alterations to the intestinal microbiome are a common side effect of cancer treatments, with negative consequences for digestion and nutrient absorption. To restore intestinal balance, it is advisable to include probiotics, prebiotics and fermented foods in the diet.

Probiotics: Natural yoghurt, kefir and probiotic supplements containing specific strains such as Lactobacillus and Bifidobacterium can help to repopulate the beneficial intestinal flora.

Prebiotics: Soluble dietary fibre, found in foods such as oats, onions, garlic and bananas, promotes the growth of beneficial bacteria.

Fermented foods: Sauerkraut, miso and kimchi contain live microorganisms and enzymes which contribute in the improvement of microbial diversity in the intestine.

Digestive herbal teas: Herbal teas made from fennel, aniseed, chamomile and ginger can relieve swelling, reduce intestinal spasms and aid digestion.

Healthy fats: Adding small amounts of healthy fats, such as olive oil or avocado, to meals can stimulate the release of bile and aid fat digestion.

Avoid triggers: Limit fried foods, hot spices, alcohol and fizzy drinks, which can irritate the stomach and slow down digestion.

Abdominal massage: A gentle massage of the abdomen, using a clockwise circular motion, can aid peristalsis and relieve feelings of heaviness.

Soluble fibre: Consuming foods rich in soluble fibre, such as carrots, artichokes, apples, chia seeds or psyllium, helps regulate bowel movements without irritating the digestive tract.

Light exercise: Diaphragm-opening exercises before eating or a short 10–15-minute walk after meals can improve bowel motility and reduce swelling.

PRACTICAL CONSIDERATIONS FOR THE FEEDING PHASES

For patients who cannot or do not wish to follow an intermittent fasting regime, the focus shifts to the quality and distribution of meals. An effective strategy involves:

Splitting meals: Dividing the daily calorie intake into 3–4 small meals to improve digestion and reduce feelings of nausea.

Easily digestible foods: Opt for light foods, such as vegetable soups, well-cooked whole grains, white fish and lean meat. Marinades are also excellent (in wine, yoghurt or lemon) to aid digestion.

Constant hydration: Drinking water, herbal teas and light

vegetable or bone broths throughout the day maintains good hydration levels.

In summary, a balanced and personalised diet can be a valuable tool for alleviating the side effects of cancer treatments, improving quality of life and optimising treatment outcomes. In some cases, supplementation may be necessary to compensate for nutritional deficiencies or to support the immune system during treatment. Among the most studied supplements are:

Vitamin D: Essential for the immune system and bone health, supplementation is particularly important in patients with low levels.

Vitamin K2: Works in synergy with vitamin D to improve bone and cardiovascular health. It helps direct calcium to the bones, reducing the risk of arterial calcification.

Omega-3 fatty acids: Found in oily fish such as salmon and mackerel, omega-3s help modulate inflammation and support brain and cardiovascular function.

Selenium: A trace element with antioxidant properties that can modulate the immune response and reduce oxidative stress. It is found in foods such as Brazil nuts, seafood, fish (salmon, tuna, cod) and eggs.

Zinc: essential for the immune system, tissue repair and protection of the intestinal mucosa.

Berberine: may lower blood sugar levels and influence tumour metabolic pathways, inhibiting the proliferation of certain cancer cells.

Carnitine: useful for combating fatigue and improving energy production in cells.

Magnesium and potassium: often deficient in cancer patients, they help combat muscle weakness and electrolyte imbalances.

However, it is essential to consult a doctor or a nutritionist before starting any supplementation, to avoid interactions with ongoing treatments and to ensure a safe and appropriate dosage.

REFLECTIONS ON THE ROLE OF NUTRITION IN QUALITY OF LIFE

NUTRITION AS AN INTEGRAL PART OF LIFESTYLE MEDICINE

Nutrition is a fundamental pillar of Lifestyle Medicine, an integrated approach that views health not merely as the absence of disease, but as a balance between physical, mental and social well-being. A balanced and personalised diet can help prevent complications, improve response to treatments and promote recovery. Adopting healthy eating habits, such as the regular consumption of fresh, whole and seasonal foods, not only supports the body in fighting disease but also helps to develop greater awareness of one's own health. This holistic approach encourages patients to actively participate in their healing journey, making nutrition not only a therapeutic tool but also an opportunity to cultivate a healthier and more fulfilling lifestyle.

THE INTESTINE-BRAIN AXIS AND THE ROLE OF NUTRITION

The gut-brain axis represents a two-way communication system between the central nervous system and the gastrointestinal tract. This connection influences numerous aspects of health, including psychological well-being, the immune system and the stress response. Changes in the intestinal microbiome, such as those caused by cancer therapies, can disrupt this communication, contributing to symptoms such as anxiety, depression and chronic fatigue. A balanced diet can play a key role in supporting the intestinal-brain axis. Foods rich in prebiotic fibre, such as oats, artichokes and bananas, promote the growth of beneficial bacteria, enhancing the production of bioactive metabolites such as short-chain fatty acids (SCFAs). These compounds play a fundamental role in regulating inflammation and protecting the intestinal barrier. Probiotics, found in fermented foods such as yoghurt and kefir, can help restore the balance of the microbiome, whilst

nutrients such as magnesium and omega-3s support nerve function and psychological resilience. Incorporating these strategies into the daily diet, alongside relaxation techniques such as meditation or mindful eating, can significantly improve the quality of life for cancer patients. A healthy, balanced diet not only supports the body during cancer treatment but also has a significant impact on psychological well-being. Numerous studies show that nutrient-rich foods, such as fruit, vegetables and healthy fats, help improve mood and reduce stress levels. Foods rich in magnesium, such as nuts, seeds and spinach, and in omega-3s, such as oily fish and flaxseeds, can help modulate the stress response and improve sleep quality. A diet rich in antioxidants also helps reduce oxidative stress, which can negatively affect the intestinal-brain axis, thereby improving both mental and physical wellbeing. Adopting healthy eating habits, such as avoiding excessive consumption of refined sugars and ultra-processed foods, helps maintain stable energy levels and prevent mood depression.

EATING AS A RITUAL OF SELF-CARE

Turning mealtimes into moments of mindfulness and self-compassion can significantly improve overall wellbeing. The practice of mindful or conscious eating encourages patients to give their full attention to food during eating times. This approach can help develop a positive relationship with food, reduce stress associated with eating, and foster greater gratitude towards the body.

Creating a supportive environment: eating in a quiet place, free from distractions such as the television or smartphones, helps one to focus on the meal and improves digestion.

Savour every bite: chewing slowly and appreciating the flavours and textures of food promotes satiety and connection with the body.

Involve the family: involving family members in preparing and sharing meals can strengthen bonds and create an essential emotional support system during the cancer period. Food, experienced as self-care, can become a powerful tool of resilience. Integrating these practices into daily life helps improve mood, reduce anxiety and foster greater serenity in navigating the cancer period.

THE DIET OF THE HEALTHY AND THE DIET OF THE SICK: A LESSON FROM HIPPOCRATES

Hippocrates, considered the father of medicine, already emphasised the importance of adapting diet and lifestyle to individual conditions, distinguishing between the ‘regime of the healthy’ and the ‘regime of the sick’. For the healthy, food represents prevention, a means of maintaining bodily balance and preventing disease; for the sick, however, diet becomes an essential component of treatment, adapted to support the body in the healing process. This distinction remains relevant today in clinical practice and in the management of cancer patients. For those in good health, the aim is to follow a varied and nutritious diet that strengthens the immune system and prevents the onset of disease. For those facing an illness, such as cancer, the diet must be personalised, taking into account the side effects of cancer treatments, nutritional deficiencies and the body’s specific energy requirements. The Hippocratic approach emphasises the need to listen to one’s body and to view nutrition as a means of restoring balance, a principle that is reflected today in modern theories of integrated nutrition and lifestyle medicine. Eating is not merely a physiological act, but also a moment of self-care, a connection with one’s state of health and a source of strength to face the challenges of illness.

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EtruriaLuceGas S.p.A. Società Benefit

The company is active in the supply of electricity and gas: promotes and supports research. In particular the company has supported the Research titled "Lymphatic Pathologies in Cancer Patients – Strategies for Prevention, Early Diagnosis and Treatment". The attached publication has the objective of transmitting the research findings to the scientific community. This activity of high scientific and social value is aligned with the objectives of common benefit contained in our Corporate mission statement.

EtruriaLuceGas SpA as a Benefit Corporation, renews its commitment to supporting local Voluntary Associations and third-sector entities (ETS).

Renato Pellicioli
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