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RESEARCH ARTICLE

Cancer cachexia - A review.

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Abstract

Cachexia is considered as a complex interplay of metabolic and behavioral parameters leading to deteriorated quality of life. In recent years many efforts by researchers and clinicians were made to improve our knowledge of cachexia. Cancer and many other chronic or end-stage diseases like AIDS, chronic obstructive pulmonary disease, rheumatoid arthritis, tuberculosis are associated with cachexia, a condition associated with weight loss and alteration in body composition. Cachexia in cancer is generally neglected and contributes to the poor prognosis. A more meticulous understanding of cachexia is needed that probably will lead to combination therapies being developed. Although its prevalence is less, it is a growing problem in Asia. This review is based on the computer-aided Pubmed database and general search for the term "cancer cachexia". Available free articles related to the pathophysiology, diagnosis and possible treatment modalities in cancer cachexia were downloaded for the review.

Introduction:-

Cachexia is a complex interplay of metabolic and behavioral variables leading to continuous deterioration of health and compromised quality of life. The word "cachexia" is derived from the Greek "kakos" meaning "bad" and "hexis" meaning "condition". Cachexia is a debilitating state of involuntary weight loss complicating malignant, infectious, and inflammatory diseases and contributing significantly to mortality. Anorexia, also a frequent complication of these diseases, is a major contributor to the development of cachexia; although the pattern of weight loss in cachexia differs from that seen with pure nutrient deprivation.[1] The anorexia-cachexia syndrome continues to be a very difficult problem in the management of cancer patients. Despite the vast literature that exists on the subject, the etiology of this syndrome is not clearly established. Reduced food intake and abnormal host metabolism are thought to be major factors leading to cachexia. However, the extent to which either of these factors are present in any one group of patients is unknown as are the mechanisms whereby anorexia or abnormal host metabolism develop. The aim of future clinical research must be to build on the limited benefits of conventional nutritional support through a greater understanding of the mechanisms of wasting in the cancer host.[2]

Cachexia is infrequently identified or diagnosed and rarely treated and there is no universally agreed upon definition. It was essential to have a specific definition so that clinicians can recognize the problem and institute corrective measures to treat cachexia. On December 13th and 14th, 2006, scientists and clinicians met in

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Washington DC, to reach a consensus on the definition of the constellation of abnormalities that have been grouped under the name cachexia.[3]

Search strategy:-

The search for the review was based on the key word "cancer cachexia". Pubmed search displayed total 3002 articles including 764 reviews and 586 free full text articles. In MeSH (Medical Subject Heading) search no items were found. Selected free articles were downloaded for the review. Other articles were selected from general web search. The decision to include the article was made by reading the title and the abstract. Articles related to animal studies and genetic studies were excluded while those related to pathophysiology, serum markers, treatment and nutrition were chosen for the review. The review discusses the pathophysiology, studies on diagnosis and treatment of cancer cachexia.

Cancer cachexia:-

About half of all cancer patients show a syndrome of cachexia, characterized by anorexia and loss of adipose tissue and skeletal muscle mass.[4] Although the etiology of cachexia is not well understood, several hypotheses like cytokines, circulating hormones, neuropeptides, neurotransmitters and tumor-derived factors are put forward. Decreased caloric intake and increased metabolic rate have been shown to be present in some cancer patients with pathological weight loss; however, the specific mechanisms by which these changes occur remain to be elucidated.[5] An emerging view is that the anorexia in cachexia is caused mainly by the cytokines produced by the cancer or released by the immune system in response to the presence of malignancy that induce profound lypolysis and protein degradation.[1]

Tumor products that have a direct catabolic effect on host tissues are lipid mobilizing factor (LMF), which acts on adipose tissue, and proteolysis-inducing factor (PIF), which acts on skeletal muscle.[6] Recent evidences suggest that an intricate interplay between multiple hypothalamic effector pathways and afferent hormonal signals of diverse systemic origin e.g. resistin, leptin and adiponectin from adipocytes, ghrelin and polypeptides from the gastrointestinal tract, and insulin from the pancreas are important in the regulation of energy intake and expenditure. Serum levels of these hormones play important role in cancer cachexia.[7]

Numerous cytokines, including Tumor Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interferon-γ (IFN-γ) and leukemia-inhibitory factor (LIF) have been postulated to play a role in the etiology of cancer anorexia-cachexia syndrome. Such cytokines may be produced by tumor or host tissue and are characterized by the induction of anorexia and a decrease in the clearing enzyme lipoprotein lipase. The ability to inhibit lipoprotein lipase varies among the cytokines. High serum levels of TNF- α, IL-I, IL-6 have been found in some, but not all, cancer patients, and the levels of these cytokines seem to correlate with the progression of some tumors. Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and reproducing the different features of the cancer anorexia-cachexia syndrome.[1, 6]

These cytokines exert a variety of behavioral and physiologic effects in addition to their immunologic and nutritional functions resulting in anorexia. The cytokine activity has both central and peripheral elements. The central effect is at the level of hypothalamic nuclei, which control feeding behavior.[8] The cytokines stimulate the expression of leptin and/or mimic the hypothalamic effect of negative feedback from leptin by disarranging the signaling pathway of neuropeptide Y (NPY), resulting in long-term inhibition of food intake. IL-1 antagonizes NPY–induced feeding and disrupts the orexigenic (feeding-stimulatory) pathway of NPY.[9]

As noted, muscle wasting is important in the pathophysiology of cachexia and a major cause of fatigue in patients. Accelerated or exaggerated loss of skeletal muscle mass distinguishes cachexia from the weight loss due solely to reduced energy intake. Several groups of investigators have suggested that actomyosin, actin and myosin are selectively targeted for degradation in clinical conditions associated with cachexia. Selective targeting of skeletal muscle is in part due to the systemic inflammation that frequently accompanies clinical conditions associated with cachexia. The common feature of cachexia, loss of muscle mass, suggests that therapies targeting muscle or inflammatory pathways may be effective in reducing the devastating effects of cachexia.[2]

Loss of skeletal muscle is characterized by a depression in protein synthesis and increased protein breakdown. There are also changes in the concentration of plasma amino acids, and most studies report a decrease in gluconeogenic amino acids, in contrast with severe malnutrition, where the concentration of branched-chain amino acids in plasma is normal or even increased. Protein degradation in muscle results in the release of amino acids, particularly alanine and glutamine. The former is channeled to the liver for gluconeogenesis and ATP synthesis, whereas glutamine is

taken up by the tumor to sustain the energy and nitrogen demands. Leucine oxidation to carbon dioxide is also increased in tumor-bearing animals.[6]

Cancer patients have a high turnover of both glycerol and free fatty acids and the elevated mobilization of lipids is often evident before weight loss becomes established. Loss of fat mass is a key feature of cancer cachexia and has been attributed to increased adipocyte lipolysis. Lipids have a high caloric value, and mobilization of lipids is required to meet the increased energy demands of the cachectic patient. As much as 85% of adipose tissue may be lost during the cachectic process, either through increased lipolysis or decreased lipogenesis. Increased production of lipolytic factors from adipose tissue such as IL-6 and TNF α or by tumor-derived lipolytic factors such as zinc-α_2 glycoprotein (ZAG) could explain increased lipolysis in cancer cachexia. Although some reports suggest reduced plasma levels of lipoprotein lipase (LPL) in cachectic patients, which is important in triglyceride synthesis, others have found no change in the total LPL enzyme activity. One of the characteristics of cytokines TNF- α, IL-6, IL-1α, INF-α, IFN-γ, and LIF is that they inhibit LPL, thus inhibiting lipogenesis in adipose tissue.[6, 10]

Diagnosis:-

The criteria for diagnosis of cachexia were put forward which include weight loss of at least 5% in 12 months or a body mass index (BMI) less than 20.0 kg/m^2 along with decreased muscle strength, fatigue, anorexia and low fat-free mass index. Abnormal biochemistry for increased inflammatory markers (c reactive protein and interleukin-6), anemia and low serum albumin should be evaluated. Diagnosis of cachexia in the presence of weight loss can be done if three of five conditions mentioned above are established.[3]

Discussion:-

Many scientists and researchers have attempted to understand pathophysiology, role of tumor derived factors and cytokines, mechanism of weight loss through lipolysis, and loss of skeletal muscle in cachexia. Estimation of serum levels of various cytokines, tumor derived factors have been done to understand their role in cancer cachexia, anorexia and weight loss. Various treatment modalities in the form of drugs, nutritional supplementation, anti-tumor derivatives and hormones have also been tried for the alleviation of cancer cachexia.

Cachexia is a typical feature of infectious diseases where the invading pathogen may lead to stimulation of the immune system and cytokine production. However, the cachexia of cancer is not normally associated with the presence of infection and while the outward symptoms may look similar, it is unlikely that a single mediator could explain the heterogeneous pattern of changes seen in a wide spectrum of diseases. This raises the possibility that other factors in addition, or instead of the known cytokines, may mediate the changes seen in cancer cachexia. Further structural information of these factors is required for a full understanding of the condition.[11] It is suggested that despite a falling caloric intake, patients with cachexia frequently show elevated resting energy expenditure as a result of increases in Cori cycle (i.e., catalytic conversion of lactic acid to glucose) activity, glucose and triglyceride-fatty acid cycling, and gluconeogenesis. The presence of an acute phase response (APR) has been linked to accelerated weight loss and a shortened survival time. The APR is thought to be initiated by cytokines, the production of which is induced by a tumor factor, proteolysis inducing factor.[4, 6]

It was postulated that those tumors which are only slightly more active than the normal in their ability to concentrate amino-acids will grow slowly and produce only minor metabolic disturbances, while the more active ones will infiltrate faster, cause anorexia, and produce rapid cachexia and eventual death.[12] Anorexia is a common manifestation of cancer and the hypothalamus and probably other parts of the brain produce anorexigenic peptides. It is proposed that peptides, oligonucleotides, and other small metabolites produced by the cancer and by the tumor-bearing host are responsible for the genesis of the anorexia. They produce the anorexia through a peripheral effect on neuroendocrine cells and neuroreceptors and through a direct effect on hypothalamic and other central nervous system sensor and responder cells.[13] There are hypothalamic and extra-hypothalamic control components of feeding. Those control components mediated extra-hypothalamically get deteriorated during tumor growth. Eventually, the accumulated deletion of individual control components destroys the initial redundancy of the feeding control system and the system collapses, with overt cachexia.[14]

In an attempt to understand pathophysiology of cancer cachexia it was suggested that weight loss and failure to gain weight normally in cancer patients are attributable to negative energy balance and altered metabolism. Energy balance is negative because of decreased intake, increased expenditure, or both. Metabolic changes in lipids, proteins and carbohydrates result in muscle wasting in adult cancer patients and growth failure in pediatric cancer

patients.[15] The early appearance of circulating lipolytic activity may represent an early diagnostic marker of certain tumors, and since aberrations in lipid metabolism may be the initial step to generalized anergy (by a decline in all host metabolic pathways) and death, the characterization of the LPF would provide significant insight into the mechanisms of cancer cachexia and the eventual development of studies to reverse this phenomenon.[16] However the effect of recombinant human tumor necrosis factor on inhibition of LPL in adipose tissue was evaluated but the result was negative.[17]

It is proposed that yet unidentified factors among certain cancer patients increase the gene expression and thereby the protein production of hormone sensitive lipase (HSL) in fat cells. This enhances the stimulatory effect of lipolytic hormones and possibly of specific cachexia factors such as ZAG. Because the hormones are always present in the circulation, lipolysis is continuously activated because the action of the major antilipolytic hormone, insulin, is not altered. Therefore, HSL inhibitors may be useful in the treatment or prevention of cancer cachexia.[10]

It is suggested that decreased arginine availability is a specific feature of the presence of cancer and disturbances in arginine metabolism could contribute to the cascade of metabolic events leading to cancer cachexia.[18] Pathways specific to myostatin, nuclear factor nB, and dystrophin glycoprotein complex have been identified and they maintain a link to the proteasome pathway. Further, proteasome remains a preferred choice for therapy and emerging upstream signaling molecules serve as additional promising therapeutic targets for the treatment of tumor-induced muscle wasting.[19] Serotonergic blockade for the treatment of the cancer anorexia-cachexia syndrome was undertaken that apparently improved the ability of patients to enjoy food but failed to prevent weight loss in patients with cancer cachexia or alter laboratory parameters of protein nutrition.[20] It is demonstrated that body fat was lost more rapidly than lean tissue in progressive cancer cachexia, a phenomenon that was related highly to alterations in the levels of circulating classic hormones and food intake, including both caloric amount and diet composition. The results showed importance in the planning of efficient palliative treatment for cancer patients.[21] While defining cancer cachexia, Fearon et al suggested a 3-factor profile i.e. weight loss, reduced food intake and systemic inflammation, which helps to identify the patient with adverse function and prognosis.[22]

The role of Parathyroid hormone-related protein (PTHrP) as a potential target of therapy for cancer-associated morbidity has been studied. It has been observed that PTHrP may cause not only hypercalcemia, but also elevation of the general production of proinflammatory cytokines. Further, PTHrP may be involved in the genesis of paraneoplastic syndrome, not only in terms of hypercalcemia, but also in deterioration of physical and mental activities (food and water intake, depression) and negative metabolic balance, which are frequently seen in patients with cancer, especially in near-terminal stages. He suggested that PTHrP is a promising molecular target for the development of a novel mode of treatment for patients with cancer-associated morbidity.[23]

The acute-phase response and elevated IL-6 are associated with cachexia and it is hypothesized that IL-6 may represent an important therapeutic target for head and neck squamous cell carcinoma patients with cancer cachexia.[24] it was also estimated that active ghrelin levels and the active to total ghrelin ratio were significantly increased in subjects with cancer-induced cachexia, compared with cancer and non-cancer controls.[25] Keram et al investigated the role of the adipocytokines, ghrelin and leptin in gastric cancer cachexia and found the elevated levels of ghrelin and leptin in cachectic patients.[7] The levels of various cytokines viz. serum leptin, IL-1β, IL-2, IL-6 and TNF-α in advanced head and neck cancer before and after the induction chemotherapy followed by concomitant chemoradiation therapy in advanced head and neck cancer were compared. It was found low serum levels of leptin and the high serum levels of proinflammatory cytokines. They also found correlation between lowering levels of leptin and increasing levels of proinflammatory cytokines, particularly IL-6, in patients who had a progressive disease during treatment, wheareas the opposite occurred in patients responded to treatment.[26]

Various treatment modalities have been attempted for medical management of cancer cachexia (table I)[27-32]. Physical symptoms other than pain often contribute to suffering near the end of life. In addition to pain, the most common symptoms in the terminal stages of an illness such as cancer are fatigue, anorexia, cachexia, nausea, vomiting, constipation, delirium and dyspnea.[33] A number of drugs are available for the management of symptoms of cachexia, including corticosteroids and progestational drugs. Prokinetic drugs, either alone or in combination with other agents such as corticosteroids, are highly effective in the treatment of chronic nausea. For patients with asthenia, it should first be determined whether there are any reversible causes; if not, corticosteroids and psychostimulants may diminish the symptoms. Oxygen and opioids are effective in treating dyspnea, whereas there is limited evidence that benzodiazepines provide any relief of this symptom.[34]

The current medical treatment of cancer-related cachexia is been reviewed, in particular focusing on combination therapy and ongoing research. Among the treatments proposed for cancer-related cachexia, some proved to be ineffective, namely, cyproheptadine, hydrazine, metoclopramide, and pentoxifylline. Among effective treatments, progestagens are currently considered the best available treatment option for cancer-related cachexia. Drugs with a strong rationale that have failed or have not shown univocal results in clinical trials so far include eicosapentaenoic acid, cannabinoids, bortezomib, and anti-TNF-alpha MoAb. Several emerging drugs have shown promising results but are still under clinical investigation (thalidomide, selective cox-2 inhibitors, ghrelin mimetics, insulin, oxandrolone, and olanzapine).[35]

Forty years on from its worldwide withdrawal, thalidomide is currently undergoing a remarkable renaissance as a novel and powerful immunomodulatory agent. Over the last decade it has been found to be active in a wide variety of inflammatory and malignant disorders where conventional therapies have failed.[36] It has been demonstrated to suppress TNF-alpha production in monocytes in vitro and to normalize elevated TNF-alpha levels in vivo.[37] Thalidomide, an oral agent with antiangiogenic and immunomodulatory properties, is being investigated extensively in the management of advanced cancer. Multiple studies with large numbers of patients have confirmed that this drug has significant activity in multiple myeloma. The activity of thalidomide in solid tumors is less prominent. Studies in Kaposi's sarcoma, malignant melanoma, renal cell carcinoma and prostate cancer appear more promising especially when thalidomide is combined with biological agents or with chemotherapy.[38] Bruera et al suggest that thalidomide can be expected to be well tolerated and to have at least similar symptomatic effects as Megestrol Acetate.[39]

Eicosapentaenoic acid (an omega-3 fatty acid from fish oils) and the appetite stimulant, Megestrol Acetate have been tried for the management cachexia.[40] N-3 fatty acids in dose of at least 1.5 g/day for a prolonged time to advanced cancer patients with weight loss were associated with an improvement of clinical, biological and functional parameters and with amelioration of quality of life.[41] Gonçalves et al have tried conjugated linoleic acid supplements in patients with cachexia but their result was negative.[42]

It is demonstrated that the synthetic progestogen- medroxyprogesterone acetate has the potential to increase food intake and to concomitantly reverse fat wasting in weight-losing patients with cancer.[43, 44] But as an adverse effect, megestrol acetate may cause symptomatic suppression of the hypothalamic pituitary adrenal axis. In male patients with cancer, treatment with Megestrol Acetate may also suppress the gonadal axis, resulting in symptomatic androgen deficiency. In a study such three cases have highlighted the symptomatic burden of adrenal insufficiency and hypogonadism that warns clinicians about this complication.[45] Couluris et al found cyproheptadine hydrochloride and megestrol acetate very effective appetite stimulant in children with cancer/treatment related cachexia. Oral cyproheptadine hydrochloride was excellent in weight gain and they found elevated serum leptin levels. They recommend use of Megestrol Acetate as second-line therapy due to safety profile.[46]

Malnutrition is common in the cancer patient. The need for nutritional support should be considered in the light of the patient's condition and carefully planned along with specific antitumor therapy. [47] Appropriate clinical judgment is required in proper selection of the total parenteral nutrition candidate. Malnutrition is almost always a prerequisite, as is failure of the gastrointestinal tract**.** When the alimentary tract cannot be used effectively for feeding cancer patients, parenteral nutrition can be lifesaving. Moreover, patients who are poor candidates for any anti-neoplastic therapy because of their debility can be converted to reasonable candidates following a course of intravenous hyperalimentation.[48, 49] Consequently, in upcoming studies, it probably would be more rewarding to focus on improving the effectiveness of nutritional support using additional interventions, such as appetite stimulation and interactive hormonal therapy, perhaps in combination with palliative low dose chemotherapy.[50]
In a study on total parenteral nutrition it is concluded that although it is unable to completely reverse some nutrition-related variables in cachectic patients with cancer, most patients were kept within a normal range and some improved. Therefore, further deterioration of the nutritional state, which is characteristic of this phase of disease, was at least prevented. Health care professionals should focus on physical health-related quality of- life indicators, such as nausea and emesis, dyspnea, and weakness, to gather prognostic clues in patients with terminal cancer.[51, 52] Patients and families as well as the medical community should use a comprehensive approach to improving the caloric and protein intake of patients who are still able to benefit from oral intake and further therapy.[53]

Palliative care is increasingly recognized as an essential component of a cancer patient's care both throughout the course of the disease and regardless of whether that patient's disease is potentially curable. Moreover, clinical application of the principles of palliative care need not and should not be limited to patients suffering from malignant disease. Optimal symptom control and care of the whole person are an integral part of the comprehensive care of any patient and deserve to be considered as such. Recent therapeutic advances in palliative care are exciting and some are controversial. They hold the potential to improve the quality of life of countless patients. To fulfill this role they require rigorous evaluation in properly conducted clinical trials.[54] Care of patients with cancer can be enhanced by continued involvement of the primary care physician. The physician's role may include informing the patient of the diagnosis, helping with decisions about treatment, providing psychological support, treating intercurrent disease, continuing patient-appropriate preventive care, and recognizing and managing or co-managing complications of cancer and cancer therapies.[55]

Table 1: Various treatment modalities in cancer cachexia

Researcher/ scientist (year)	Treatment modality
Daneryd P et al (1998)[27]	recombinant erythropoietin
Trikha M et al (2003)[28]	Targeted anti-interleukin-6 monoclonal antibody
Garcia JM et al (2007)[29]	RC-1291 – an oral ghrelin mimetic and growth hormone (GH) secretagogue
Lundholm K (2007)[30]	Insulin
Strasser F et al (2008)[31]	intravenous Ghrelin
Qi F et al (2010)[32]	Chinese herbal medicines

Conclusion:-

The cancer cachexia is a clinical problem affecting many patients with cancer and other end-stage diseases. Correct identification of treatable, reversible causes must be aggressively sought and, when found, appropriately treated. New research into novel therapies directed at cancer cachexia is continuing, but there is a need of well-structured clinical trials. Professional participation and interventions from scientists and clinicians can have a profound influence on the diagnosis and treatment of patients with cachexia.

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