Nutrition in diabetic people with cancer

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Abstract

Introduction
Diabetes and cancer are prevalent diseases whose incidence is globally increasing. Type 2 diabetes mellitus is an independent risk factor for the development of several different types of cancer, including that of the colon and pancreas both in men and women, breast cancer in women and cancer of the liver and bladder in men. Nutritional assessment is an essential step in the global management of diabetic cancer patients. Malnutrition occurs due to a variety of mechanisms, involving the tumour, the host response to the tumour and anticancer therapies (surgery, radiotherapy and chemotherapy). In diabetic patients with cancer, malnutrition is a significant cause of morbidity, with high rate of toxicities during chemotherapy and radiotherapy, increased hospital length of stay, increased treatment costs and altered quality of life. Further, in diabetic cancer people, anorexia and cachexia can co-exist to determine the ‘anorexia–cachexia syndrome’, which acts synergistically to impact patients’ morbidity and mortality. Indeed, the concurrence of diabetes and cancer results in profound changes in the protein, lipid and glucose metabolism, in turn causing inefficient use of the energy and plastic substrates. The aim of this paper was to discuss nutrition in diabetic people with cancer.

Conclusion
The best way to treat cancer cachexia is to cure the cancer, although unfortunately this remains an infrequent achievement among adults with advanced solid tumours.

Introduction
Diabetes and cancer are prevalent diseases whose incidence is globally increasing. Epidemiologic evidence suggests that type 2 diabetes mellitus (T2DM) is an independent risk factor for the development of several different types of cancer including that of the colon and pancreas both in men and women, breast cancer in women and cancer of the liver and bladder in men. The link between T2DM and certain types of cancer was first postulated many years ago and it was believed that the relationship could be entirely attributable to the direct effects of diabetes, such as hyperglycemia. Current thinking suggests that diabetes is a possible marker of altered cancer risk due to changes in underlying metabolic conditions, including insulin resistance, hyperinsulinaemia and hyperglycaemia, via their influence on neoplastic processes.

Nutritional assessment is an essential step in the global management of diabetic cancer patients, in order to distinguish malnourished and non-malnourished patients. The American Society for Parenteral and Enteral Nutrition guidelines defined malnutrition as an involuntary loss or gain of >10% of usual body weight in 6 months or >5% in one month. Malnutrition occurs due to a variety of mechanisms, involving the tumour, the host response to the tumour and anticancer therapies (surgery, radiotherapy, chemotherapy). In diabetic patients with cancer, malnutrition is a significant cause of morbidity, with high rate toxicities during chemotherapy and radiotherapy, increased hospital length of stay, increased treatment costs, decreased performance status and altered quality of life.

Cachexia is more common in elderly patients and becomes more pronounced as the disease progresses. The prevalence of cachexia increases from 50% to more than 80% before death and in more than 20% of patients, cachexia is the main cause of death.

In diabetic cancer patients, anorexia and cachexia can co-exist to determine the ‘anorexia–cachexia syndrome’ that acts synergistically to impact patients’ morbidity, mortality and quality of life. The presence and severity of anorexia-cachexia syndrome reduce overall survival, contribute to the occurrence of post-operative complications, increase the toxicity induced by radio-chemotherapy, while reducing the sensitivity of tumour cells to antineoplastic treatment. In addition, it lowers the immune response and ultimately becomes the source of psychological stress for the patient and family. This paper discusses the management of diabetic cancer patients including the attempt to address and possibly solve typical diabetes and tumour metabolic changes, reduced caloric intake secondary to the presence of cancer anorexia and specific nutritional requirements by the tumour itself.

Discussion
The ‘anorexia–cachexia syndrome’ in diabetic cancer patients
For a long time, the nutritional problems of diabetic cancer patients

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Critical review

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was addressed late, often when the presence of cancer cachexia made it difficult to continue with the pharmacological treatment. Since the pathophysiological mechanisms leading to clinical cachexia do work early in the clinical history of the neoplastic disease, a modern approach to diabetic people with cancer should be based on an early and effective prevention of the anorexia–cachexia syndrome. For prevention of malnutrition in cancer patients, further in diabetics, a continuous interchange of clinical information between oncologists and nutritionists is mandatory, thus avoiding the patient from going to the nutritional consultant when the anorexia–cachexia becomes florid, severe and disabling. Possibly, this way, we can succeed in stretching the time between the diagnosis of cancer and the cachexia onset as much as possible.

While anorexia is defined as the loss of the desire to eat, which frequently leads to reduced food intake, cachexia is a multi-organ syndrome characterised by weight loss (at least 5%), muscle plus adipose tissue wasting and inflammation. The underlying metabolic abnormalities include alterations in carbohydrate, lipid and protein metabolism, sustained both by humoral inflammatory substances (such as cytokines) as well as by mediators of tumour origin. The main features of the anorexia–cachexia syndrome are the profound alterations of brain neurochemistry, responsible for the development of anorexia and reduced food intake and the significant changes occurring in the metabolism of carbohydrates, lipids and proteins in peripheral tissues leading to insulin resistance, increased lipolysis and accelerated muscle proteolysis leading to cachexia.

Alterations in energy and substrate metabolism

The concurrence of diabetes and cancer results in profound changes in the protein, lipid and glucose metabolism, causing in turn the inefficient use of the energy and plastic substrates. This contributes to the onset of cachexia, the ‘theft’ of nutrients by tumour cells in active replication at the expense of the tissues of the host organism. While they control the food intake, the metabolic disturbances associated with tumour burden contribute most significantly to the appearance of cachexia.

Most solid tumours produce a variety of changes in the energy and nutrients metabolism, regardless of their place of origin.

Carbohydrate and lipid metabolism

The carbohydrate metabolism is widely altered in T2DM during the tumour growth. The key changes are glucose intolerance, insulin resistance, increased gluconeogenesis from amino-acids and lactate (Cori cycle), since many solid tumours produce a large amount of lactate. Hepatic gluconeogenesis from lactate and amino acids is markedly increased in the course of cancer remaining insensitive to physiological stimuli inhibitors such as the administration of glucose. Gluconeogenesis from lactate uses adenosin tri phosphate (ATP) molecules and it is very energy inefficient for the host; so, this cycle may be considered one of the main determinants of the increased energy expenditure observed in cancer patients.

The lipid metabolism is also affected by diabetes as by tumour itself. The reduction of exogenous lipolysis by lipoprotein lipase is relevant; however, the fat deposits are mainly consumed as a result of increased lipid mobilisation and oxidation. Unlike what happens in simple malnutrition, fatty acid oxidation is not interrupted by the glucose administration, this contributes to an increase in the energy resting expenditure. Increased lipid mobilisation in cancer cachexia can be attributed to a tumour catabolic factor named lipid mobilising factor (LMF) which acts directly on adipose tissue with the release of free fatty acids (FFA) and glycerol through an elevation of the intracellular mediator cyclic AMP similar to that produced by the natural lipolytic hormones. LMF has recently been isolated from a cachexia-inducing murine tumour and from the urine of weight-losing cancer patients. The LMF showed an apparent molecular weight of 43 kDa and was homologous with the plasma protein Zn-α2-glycoprotein in an amino-acid sequence. Studies in animal models suggested that production of LMF by cachexia-inducing tumours might account for the loss of body fat and the increase in energy expenditure, but not for anorexia. These alterations in fat metabolism lead to decreased fat storage and severe cachexia in animal models and humans, especially when combined with decreased food intake.

Amino-acid (AA) metabolism

Alterations of the AA metabolism leading to a change of the plasma amino–acid profile contribute significantly to the trouble in the intermediary metabolism, typical of diabetes, similar to that induced by the cancer. These changes are partly a direct consequence of the energy metabolism disorder as well as of the altered liver and muscle protein turnover. In diabetic patients with cancer, several reports did show a reduction in plasma concentrations of gluconeogenic amino-acids due to an increased liver gluconeogenesis. In contrast, the branched chain amino acids, which are quickly consumed in case of simple malnutrition, show physiological levels in diabetic cancer patients, thus confirming the relevant pathophysiological differences between the simple malnutrition and the cancer cachexia.

During starvation, glucose utilisation by the brain is normally replaced by ketone bodies derived from fat, leading to decreased...
glucogeneogenesis from amino acids by the liver with the preservation of muscle mass\textsuperscript{15}. On the contrary, in diabetic cancer patients with cachexia, amino-acids are not spared and there is depletion of lean body mass. This feature can play a role in reducing the survival time of cachectic diabetic people with cancer\textsuperscript{17,18}. The body protein turnover is augmented as a consequence of the increased hepatic synthesis and the raised degradation of the muscle tissue, while the protein synthesis is normal or slightly reduced. Both reduced rates of protein synthesis and increased rates of protein degradation have been observed in biopsies of skeletal muscle from cachectic diabetic cancer subjects\textsuperscript{17}. Anyway, the whole body protein turnover is significantly increased in weight-lossing diabetic cancer individuals because of the re-prioritisation of liver protein synthesis, commonly known as the acute-phase reactant response\textsuperscript{15}. Loss of skeletal muscle mass in both cachectic mice and diabetic cancer patients did correlate with the serum proteolytic activator (PIF), capable of inducing catabolism in skeletal muscle\textsuperscript{17}. PIF was shown to be excreted in the urine of patients with diabetes and cancer cachexia, not in those with similar tumors without cachexia\textsuperscript{18}. The major mechanism through which PIF is believed to induce catabolism in skeletal muscle is the upregulation of the ATP-ubiquitin-dependent proteolytic pathway, an intracellular system for protein degradation in physiological conditions, as demonstrated in mice with cachexia exposed to PIF\textsuperscript{19}. A complex system of mediators including cytokines, humoral factors like TNF, IL-1, IL-6, catabolic factors tumor-specific, such as PIF, play a key role in the ATP-ubiquitin-dependent proteolytic pathways activation, thus contributing to development of hypotrophy mediated by activation of this proteolytic system.

**Nutritional intervention**

The management of diabetic cancer patients includes the attempt to address and possibly counteract the typical diabetes and neoplasia metabolic changes irrespective of the tumour type and location, the reduced caloric intake secondary to the presence of cancer anorexia and the specific nutritional requirements by the tumour itself.

**Preventing and/or reversing malnutrition**

The nutritional intervention must be done before the patient’s nutritional status becomes dramatically compromised (as, unfortunately, it happens too often) because cancer cachexia responds slightly to the nutritional treatment once developed\textsuperscript{2}. The ideal feeding intervention starts with the evaluation of the patient’s nutritional status and, based on this preliminary assessment, it may include dietary counseling\textsuperscript{21}, oral nutriment supplementation\textsuperscript{22}, enteral\textsuperscript{23} or total parenteral nutrition (TPN)\textsuperscript{24}. Regularly scheduled evaluations are needed to monitor the efficacy and/or reconsider the type of intervention, until a normal nutritional status has been conceivably restored.

Accurate feeding intervention is essential to prevent and/or reverse malnutrition\textsuperscript{21} by maintaining neutral or positive energy and protein balance as well as adequate vitamin, mineral, trace-element and electrolyte levels. Although nourishment intervention is not a primary part of the specific cancer treatment, it is fundamental at all stages of the disease and its role becomes central to the therapeutic strategy\textsuperscript{21}. A good nourishment procedure allows controlling diabetes-cancer-related symptoms, reduces postoperative complications\textsuperscript{25}, and infection rate, shortens the hospital stay, improves tolerance to treatment and enhances immunometabolic host response\textsuperscript{25–27}. Finally, timely nourishing support is associated with improved Quality of Life (QoL).

In diabetic patients with cancer, there is an imbalance between energy intake and expenditure, with food intake being relatively inadequate to meet the body’s current requirements. Total energy expenditure includes the resting energy expense (approximately 70%), the voluntary energy charge (25%) and finally, energy waste due to digestion (5%). Voluntary energy loss may be reduced in cachexia, which may manifest clinically as apathy, fatigue and depression. The imbalance between energy intake and expenditure in diabetic cancer patients is such that it might disclose reasons and mechanisms of the weight loss, resulting in a possible guide to nutritional requirements.

If the patient is fed orally and is able to satisfy his nutritional need, the development of a personalised diet possibly in accordance with the patient preferences is recommended. The nutritional regime should provide 30–35 kcal/kg/day, 1–1.2 g protein/kg/day, with a share of fat that can cover 30% to 50% of non-protein calories. Food intake can be increased by providing frequent small meals that are energy-dense and easy to eat. Patients should be encouraged to eat in pleasant surroundings and attention should be given to the presentation of food. It is advisable to avoid high-fat food, because fat delays gastric emptying and may exacerbate early satiety, a symptom of anorexia. Since changes in taste and smell occur in anorectic patients, extremes in food temperature and flavour should be avoided\textsuperscript{28}. Because diabetic cancer survivors might be at increased risk for second cancers, they should eat a variety of antioxidant-rich foods each day. Vegetables and fruits are rich in antioxidants that include vitamin C, vitamin E, carotenoids and many phytochemicals (plant-based chemicals). They help prevent damage to cells...
in the body from chemical reactions with oxygen. Some recent studies suggest that a higher intake of vegetables may have a helpful effect on the recurrence or survival for breast, prostate and ovarian cancers. So far, since the studies of antioxidant vitamin or mineral supplements have not found that they can reduce cancer risk, the best advice at this time is to get antioxidants through foods rather than through supplements. During and immediately after cancer treatment, there might be a benefit adopting a standard multiple vitamin and mineral supplement which contains about 100% of the daily values since in these circumstances it may be hard to eat a diet with enough of these nutrients.

Dietary intake of fat should be reduced to no more than 30% of total calories: saturated < 7%, minimal intake of trans-fatty acids, cholesterol intake below 200 mg/day and two or more servings of fish per week. A low fat/high carbohydrate (55%) diet, rich in fibre (25–30 g/day), is advisable. Several studies have looked at the link between fat intake and survival after the diagnosis of breast cancer, with conflicting results. There is little evidence that total fat intake affects cancer outcomes, but diets high in fat tend to be high in calories. This may lead to obesity with further risk of several types of cancer, higher risk of cancer recurrence after treatment, possibly to shorter survival for many types of cancer.

It is better to avoid protein intakes > 15%–20% of total daily energy, although no studies have looked at the effect of processed meat, meat cooked at high temperature or meat in general on cancer surviving. Soy foods may be an excellent source of protein representing a good option for meals without meat. Several components in soy have antioxidant or other helpful properties. For the breast cancer survivors, current research finds no special benefits or harmful effects when no more than three servings of soy are eaten per day as a part of a healthy diet. Higher doses of soy may have oestrogen-like effects and higher levels of oestrogens can cause certain breast cancers to grow and spread. For this reason, it is best for breast cancer survivors to avoid the high doses that are found in more concentrated sources such as soy powders and isoflavone supplements.

Limiting salt (< 6 g per day) and alcohol intake is necessary. In people already diagnosed with cancer, alcohol intake could affect the risk for new cancers in these sites. Alcohol intake can also increase levels of oestrogens in the blood. This could possibly increase the risk of oestrogen receptor-positive breast cancer recurrence after treatment, although studies so far have not addressed questions like this 29.

The use of artificial nutrition (AN) is needed in the following cases: when oral intake of nutrients falls below the 50% of estimated needs, when mechanical obstruction and/or dysphagia, oro-pharyngeal and intestinal mucositis preclude the assumption.

Enteral Nutrition (EN) must be preferred to parenteral nutrition (PN) when the functional integrity of the gastro-intestinal tract is preserved in a partial or total way. Contraindications to the EN as well as the absolute indications for PN are represented by a lack of proper bowel function or an impaired intestinal transit or finally by the denial of consent by the patient or his tutor 22,24,30.

Nutritional support has variable efficacy in patients with cancer disease: the best results occur under conditions of hypofagia or intestinal failure, whereas in cases of cachexia without significant involvement of the digestive tract, the results are very limited 22. To prevent further deterioration of nutritional status and allow a slow partial recovery of some nutritional indices, a realistic option can ensue from treatment with AN. Anyway, the efficacy of this strategy may be largely influenced by the duration of adequate support, the intrinsic biological aggressiveness of the tumour and the availability of an effective cancer treatment.

Conclusion

The best way to treat cancer cachexia is to cure the cancer, although unfortunately this remains an infrequent achievement among adults with advanced solid tumours. The next therapeutic option is increasing nutritional intake, with the aim of inhibiting the wasting of muscle and fat by manipulating the metabolic milieu (reported before) by various pharmacological agents employed for cancer treatment. It is essential to identify the different causes of reduced food intake, such as nausea and vomiting treatment-induced, oral mucositis and gastrointestinal obstruction, as well as to utilise appropriate palliative interventions for relieving these conditions.

Abbreviations list

AN, artificial nutrition; ATP, adenosine triphosphate; EN, Enteral nutrition; FFA, free fatty acids; LMF, lipid mobilising factor; PIF, proteolysis-inducing factor; PN, parenteral nutrition; QoL, Quality of Life; T2DM, type 2 diabetes mellitus; TPN, total parenteral nutrition.

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