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REVIEW

Diabetes management in cancer patients. An Italian Association of Medical Oncology, Italian Association of Medical Diabetologists, Italian Society of Diabetology, Italian Society of Endocrinology and Italian Society of Pharmacology multidisciplinary consensus position paper

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Cancer management has significantly evolved in recent years, focusing on a multidisciplinary team approach to provide the best possible patient care and address the various comorbidities, toxicities, and complications that may arise during the patient's treatment journey. The co-occurrence of diabetes and cancer presents a significant challenge for health care professionals worldwide. Management of these conditions requires a holistic approach to improve patients' overall health, treatment outcomes, and quality of life, preventing diabetes complications and cancer treatment side-effects. In this article, a multidisciplinary panel of experts from different Italian scientific societies provide a critical overview of the co-management of cancer and diabetes, with an increasing focus on identifying a novel specialty field, 'diabeto-oncology', and suggest new co-management models of cancer patients with diabetes to improve their care. To better support cancer patients with diabetes and ensure high levels of coordinated care between oncologists and diabetologists, 'diabeto-oncology' could represent a new specialized field that combines specific expertise, skills, and training.

Key words: cancer, diabetes mellitus, diabeto-oncology, multidisciplinary approach

INTRODUCTION

Cancer and diabetes mellitus (DM) are among the two most prevalent and serious health concerns worldwide, and their incidence and prevalence have increased significantly in the last decade.[1] A diagnosis of either cancer or DM can significantly impact an individual's life; even more so, their coexistence can affect the quality of life (QoL), patient care, and survival.

It is estimated that a significant proportion of oncology patients, ranging between 8% and 18%, also suffer from

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DM.[2] Several studies revealed a complex relationship between DM and cancer.[3] Recently, in addition to the common pathogenetic mechanisms usually proposed to explain this relationship (e.g. hyperinsulinaemia, hyperglycaemia, chronic inflammation, pharmacological treatments, surgery outcomes), new biological mechanisms, such as the dysregulation of microRNAs intervening in pathways involved in the pathogenesis of both DM and cancer, have been proposed as possibly responsible for the close correlation between these two pathological conditions.[4] However, more research is needed to better understand the biological links between these two diseases aiming at developing more effective therapeutic strategies and better management.

While the exact relationship between these two diseases is not fully understood, people with DM are at a higher risk of many types of cancer. Epidemiological evidence indicates an increased risk for cancer in individuals with DM, including pancreatic, liver, colorectal, breast, and bladder cancer.[5] Therefore, it is essential to emphasize on primary prevention and healthy lifestyle habits, especially regular exercise, healthy eating, and smoking cessation, to reduce the risk of developing DM and cancer.

Some studies have reported increased cancer-related mortality in patients with DM.[6] Several aspects of the interaction between DM and cancer may determine this trend.

DM-related comorbidities may influence cancer treatment choice, and patients may receive less aggressive treatments, potentially resulting in a suboptimal approach with worse outcomes.

A study has recently confirmed that patients with type 2 DM (T2DM) have a significantly higher risk of cancer mortality than the general population. The risk of death due to cancer was 18% higher for all types combined, 9% higher for breast cancer, and 2.4 times for colorectal cancer.[7] These results could indicate the possible benefits of a breast cancer screening programme for young women with T2DM.

Hyperglycaemia in oncological patients is a frequent issue during cancer treatment and palliation. DM management for cancer patients is crucial to reduce both short- and long-term complications and the incidence of cancer treatment toxicities: a better DM control not only avoids delays in scheduling some diagnostic tests (e.g. [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography scanning) but also increases the adherence to the therapeutic programme, the QoL, and the prognosis.

The metabolic control in cancer patients can be affected by anticancer treatments, such as corticosteroids, widely used in premedication and supportive and palliative care.[8] Moreover, the management of patients with DM may also be overlooked by the tendency of both patients and caregivers to focus mainly on cancer treatment. As a result, these patients are at a higher risk of experiencing poor outcomes.

The role of health care providers is essential in supporting and educating cancer patients with DM on managing their glucose control throughout their entire care plan, from diagnosis to end of life.

Three main scenarios could involve oncologists and diabetologists in the multidisciplinary approach of patients with cancer and diabetes: patients with a history of DM, patients with previously unknown DM, and patients with iatrogenic DM.

The specific characteristics and emerging relevant clinical aspects are summarized in Figure 1.

Cancer management has evolved significantly in recent years, focusing on a multidisciplinary team approach to provide the best possible patient care and to cope with the various comorbidities, toxicities, and complications arising during the patient's treatment journey.

Specialized fields such as cardio-oncology and onco-nephrology have emerged to provide the best possible care for cancer patients based on a comprehensive approach to the management of treatment toxicities, comorbidities, and cancer-related complications.

Emerging trends in 'diabeto-oncology'[9] focus on developing personalized treatment plans for cancer patients with DM, identifying biomarkers predicting cancer risk and prognosis in diabetic patients, and implementing primary prevention strategies. Co-management of cancer and DM requires collaboration between various health care professionals, including endocrinologists and oncologists, and the formation of dedicated specialists for this setting.

'Diabeto-oncology' offers a holistic approach to cancer patient management by considering glucose control and the presence of long-term diabetic complications: this coordinated approach allows not only a personalized treatment plan but also addresses the unique challenges and needs of these patients.

MANAGEMENT OF CANCER PATIENTS WITH DIABETES: THE INTERPLAY BETWEEN DIABETOLOGIST AND ONCOLOGIST

Diabetes management in cancer patients requires a comprehensive and collaborative approach. Collaboration and interaction between oncologists and diabetologists are critical to achieve appropriate levels of care and reduce the risk of complications. Each specialist brings a unique set of skills and knowledge, and their collaboration can help to ensure that patients receive the best possible care. Effective teamwork involves communication, coordination, and cooperation. It requires a shared understanding of the patient's needs, goals, and preferences, as well as a willingness to work together to develop a personalized treatment plan that addresses each patient's unique needs and goals. Collaboration can also help to improve patient outcomes, prevent errors, and reduce costs.

In addition, interaction with patients and their families is crucial for providing high-quality cancer care, improving outcomes, and enhancing their experience.

Patients with DM and cancer often have complex medical and psychosocial needs, and effective communication and support can help them to cope with treatment-related complications.

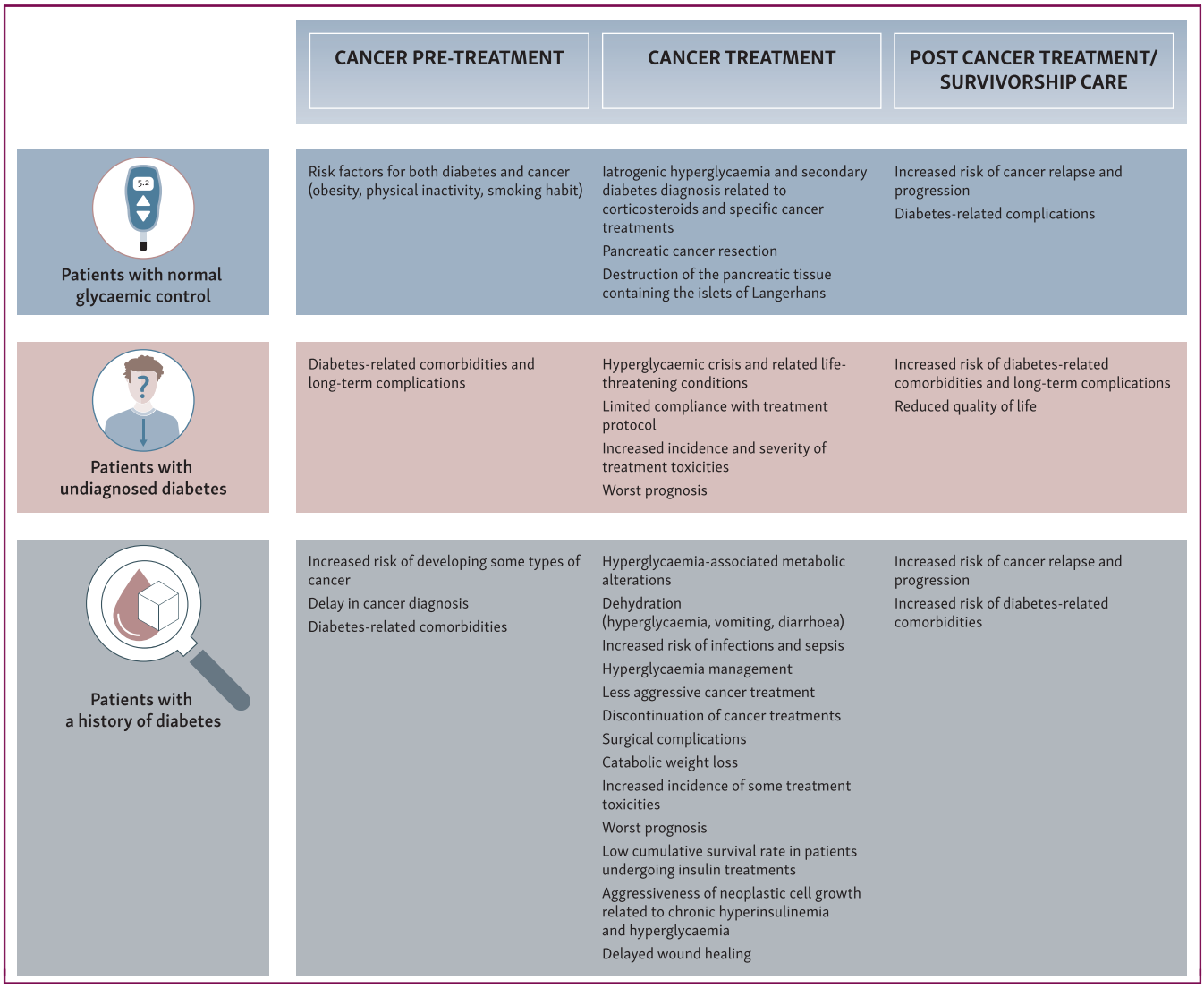

Figure 1. **Diabetes and cancer interplay across the therapeutic cancer patient journey: key points and challenges.**

The fragmentation of care is a major challenge in managing comorbid patients, leading to a lack of coordination between health care professionals.

The Italian Association of Medical Oncology (AIOM) and the Italian Association of Medical Diabetologists (AMD) have been working in strict cooperation for several years to improve the approach towards cancer patients with DM.

This collaboration led to creating and sharing a common road to address the challenges in providing effective care to such patients, particularly cooperating in a dedicated working group on 'Diabetes and Cancer'.

A multidisciplinary panel of oncologists and diabetologists first met in January 2015 in Turin, Italy, to develop a shared understanding of the challenges posed by DM and cancer, evaluate the impact of care pathways on interprofessional teamwork, and create evidence-based shared clinical protocols to treat patients with DM and cancer in different settings (including nurses, nutritionists, psychologists, etc.).[10]

The primary objective of this partnership was to offer patients optimal cancer and diabetes treatment, thus reducing the risk of complications and improving patients' overall QoL.

The collaboration has also been relevant in promoting awareness and education on DM management in cancer patients through several scientific initiatives, such as surveys, consensus papers, reviews, and expert insights.

To further improve the multidisciplinary approach, common working group activities were established with other societies such as the Italian Society of Endocrinology (SIE), the Italian Society of Pharmacology (SIF), the Italian Society of Diabetology (SID), and Italian Association of Nuclear Medicine (AIMN).

A panel of experts from AMD, AIOM, SIE, SIF, and SID provide in this manuscript an overview of the clinical interplay of cancer and DM and new models of shared management of cancer patients with DM to improve their QoL and survival.

Table 1. Recommendations for DM screening before starting cancer therapy

Basal assessment
FPG, PPG, HbA1c,* lipid panel, uric acid, and BP
Follow-up assessment
Patients without previously known diabetes, especially if at increased risk* • FPG every 2 weeks during the first month, then monthly for 6-12 months • BP monitoring at every visit • HbA1c after 3 months (together with lipid panel and uric acid), and then annually if normal • Education for early recognition of symptoms of hyperglycaemia and DKA, if on ICIs
Patients with already known diabetes • FPG, HbA1c, LDL-C, triglycerides, and BP every 3 months • Reinforce SMBG (basal and postprandial); consider FGM/CGM • Revise diabetes self-management education and support • Consider overall CV risk
Patients who develop hyperglycaemia on ICIs • Urine/capillary ketones • ICA, anti-GAD, anti-insulin Ab • Insulin, C-peptide • Pancreatic amylase and lipase

Anaemia, disordered haematopoiesis, and altered red blood cell turnover (e.g. red blood cell transfusions) could affect HbA1c reliability in cancer patients.
Modified from AMD-AIOM position statement.[21]
Anti-GAD, anti-glutamic acid decarboxylase autoantibodies; BP, blood pressure; CGM, continuous glucose monitoring; CV, cardiovascular; DKA, diabetic ketoacidosis; FGM, flash glucose monitoring; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; ICA, anti-islet cell autoantibodies; ICIs, immune checkpoint inhibitors; IFG, impaired fasting glucose; IGT, impaired glucose intolerance; lipid panel, total, high-density lipoprotein, and low-density lipoprotein cholesterol (LDL-C), triglycerides; PPG, postprandial glucose; SMBG, self-monitoring of blood glucose.
*Subjects at higher risk: patients with a family history of diabetes or a history of gestational diabetes, with pre-diabetes (IFG/IGT), with several comorbidities and concomitant treatments, a history of home corticosteroid use, and/or a high BMI.

FROM THE NETWORK MODEL TO THE NEW ROAD OF 'DIABETO-ONCOLOGY'

Diabetes screening before starting anticancer therapy and proactive strategies to manage iatrogenic hyperglycaemia

Patients with previously known DM should be scheduled for a visit at a DM care clinic before starting oncological treatments to evaluate the presence of diabetic complications that could influence the choice of anticancer therapy and to assess current nutritional status and requirements, the overall metabolic control, and the need to proactively modify current glucose-lowering therapy.[10,11]

On the contrary, many patients with normal glucose control can develop new-onset DM or metabolic disorders (dyslipidaemia, hyperuricaemia, hypertension) because of cancer therapies or supportive drugs.[12] Therefore, paraphrasing the quote of a famous Canadian ice-hockey player, it is not important to (only) know where the patient with DM and cancer is but also where he/she will be. This includes careful consideration of how we expect glucose control and clinical condition to change to proactively modify antidiabetic therapy accordingly [e.g. avoiding antidiabetic drugs (ADDs), with specific contraindications and potential adverse events (AEs)].[13]

Early recognition and proactive management of anticancer drug-induced hyperglycaemia allow starting antidiabetic therapy at an early stage, enhancing care, nutritional status, and QoL of cancer patients.

Corticosteroids commonly induce (or exacerbate) hyperglycaemia, hyperlipidaemia, and other metabolic side-effects. Even if it is hard to reliably identify in advance subjects who will develop steroid-induced DM, older patients with specific conditions are at increased risk, especially if a high dose and long duration of steroid treatment are predictable (Table 1).[8,14,15] It is fundamental to remember the predominant effect of corticosteroids on postprandial glucose levels. Indeed, fasting plasma glucose may be normal in these patients, with relevant glucose excursion after lunch.

Over the last two decades, many commonly used targeted therapies [e.g. kinase/multikinase inhibitors, monoclonal antibodies, along with poly (ADP-ribose) polymerase, phosphoinositide 3-kinase (PI3-K), and mammalian target of rapamycin (mTOR) inhibitors] have shown to exert detrimental effects on glucose and lipid metabolism, as well as on blood pressure, and the cardiovascular (CV) system.[13,16] Therefore, every cancer patient starting a targeted therapy, as well as those who are going to be treated with high-dose steroids, should undergo an appropriate screening at baseline to identify those people requiring close monitoring of glucose and lipid metabolism (Table 1).[17,18]

In patients with increased DM risk, we recommend fasting plasma glucose monitoring every 2 weeks during the first month and then monthly after that, together with glycated haemoglobin (HbA1c) at baseline, at 3 months, and annually. Self-monitoring of blood glucose (SMBG) should be proposed or reinforced in patients with already known DM, monitoring fasting and 2-hour postprandial glucose levels. Flash and continuous glucose monitoring can also provide valuable help in enabling patients to avoid severe hyper- and hypoglycaemia.[19]

More recently, a new type of permanent insulin-dependent DM has been recognized in cancer patients treated with immune checkpoint inhibitors (ICIs).[20,22] ICIs may trigger autoimmune diabetes even far beyond 6 months from their introduction. Since severe hyperglycaemia and ketoacidosis may abruptly occur, diabetologists and oncologists should know about this potential risk. In this setting, a proactive approach means that patients should be appropriately trained to recognize signs and symptoms of severe hyperglycaemia. Since ICI-induced autoimmune DM may also affect patients with already known DM, monitoring glucose levels of these patients should be reinforced, too.

Anticancer drug's effect on glucose metabolism

Glucocorticoids. It is widely recognized that glucocorticoid therapy can lead to hyperglycaemia or further worsen a pre-existing condition of DM.[23,24] However, the development of *de novo* DM in patients with normal glucose tolerance is uncommon.[25,26] The effect of glucocorticoids on glucose metabolism is dose-dependent and, although it causes only a mild increase in fasting blood glucose levels, a large

increase in postprandial blood glucose both in patients with and without pre-existing DM,[27] predominantly occurring in the afternoon and evening,[27] and impaired sensitivity to exogenous insulin[28] are frequently observed. Glucocorticoid-induced hyperglycaemia may be due to increased hepatic glucose production and inhibited glucose uptake in adipose tissue and skeletal muscle, as well as due to decreased β-cell insulin production.[26,29] For these reasons, before initiating glucocorticoid therapy and throughout treatment, glycaemia should be closely monitored, and antidiabetic therapy started, or adjustment should be considered if necessary.[23,30] Although risk factors for steroid-induced DM predominantly include older age and higher body mass index,[31] glucose level monitoring should be considered for all patients taking glucocorticoids. Clinicians should aim to the same glycaemic targets in glucocorticoid-induced DM as in those with pre-existing DM.[30] Importantly, hyperglycaemia improves with the reduction in the dose of glucocorticoids and usually reverses when the medication is stopped[25,32]; therefore, patients who are taking ADDs, which increase endogenous insulin availability (insulin or sulfonylureas), and are tapering their glucocorticoid dose should closely monitor their blood glucose level, because of the risk for life-threatening hypoglycaemia.[23,25,30]

Chemotherapy. Patients with both DM and cancer undergoing chemotherapy are at a greater risk of glycaemic issues. Around 10%-30% of cancer patients during chemotherapy may experience hyperglycaemia.[33] Although it is typically a temporary condition during treatment, it can develop into a long-term issue. Several chemotherapy drugs are known to cause hyperglycaemia, even in patients without DM. Cisplatin, 5-fluorouracil, and chemoradiation have been linked to hyperglycaemia.[34,35]

Combining chemotherapy and steroids, frequently used as premedication, can increase the risk of hyperglycaemia and the potential to either cause *de novo* DM or worsen existing DM, which can cause complications during treatment, such as dose reduction or interruption.[36] Poor glycaemic control in cancer patients is associated with more severe cancer courses and AEs such as neutropenia, infections, and even increased mortality.

Receiving chemotherapy can be challenging for patients with pre-existing DM and related health issues, which can lead to CV problems, renal disease, or neuropathy. Chemotherapy drugs can worsen renal function and neuropathic complications. Patients with DM should be well-informed about the risks and benefits of chemotherapy drugs, and preventing dehydration to avoid acute kidney injury should be a top priority.[36]

Chemotherapy drugs like platinum derivatives and taxanes are also known to cause peripheral neuropathy. These drugs are commonly used to treat various types of cancer. Depending on the type of symptoms and the used drugs, patients with DM are more likely to experience neuropathy as a side-effect of chemotherapy. The severity of neuropathy symptoms may increase at higher doses of chemotherapy. Diabetic patients may experience longer-lasting neuropathy after chemotherapy, with symptoms persisting for up to 2 years after treatment.[37]

A meta-analysis was conducted to analyze the effect of DM on the clinical outcome of patients with pancreatic cancer who received adjuvant chemotherapy. The results showed that patients with DM who underwent chemotherapy for pancreatic cancer presented with reduced survival rates and larger tumours. Additionally, pancreatic cancer patients with DM had a higher risk of death after chemotherapy.[38]

Targeted therapy. Targeted therapy with tyrosine kinase inhibitors (TKIs) and mTOR inhibitors has increased the possibility of treatment in various types of cancer. TKIs and mTOR inhibitors interfere with glucose metabolism[39,40] with hypo- or hyperglycaemia, even for the same molecule. TKIs and mTOR inhibitors are associated with a high incidence of hyperglycaemia with a reported rate of 15%-50%,[41,42] depending on the molecules used as anticancer therapies. Hyperglycaemia generally occurs within the first 3-4 weeks of therapy with TKIs. TKIs may impact glucose metabolism by various mechanisms, but the molecular mechanism remains unclear. First- and second-generation TKIs influence glucose metabolism.[18] Prevalence of DM, glucose intolerance, and metabolic syndrome did not differ depending on TKI molecules. However, the most diabetogenic drugs seem to be nilotinib and crizotinib (up to 40% and 49%, respectively), while imatinib and dasatinib have been reported also to cause hypoglycaemia. A possible mechanism could be the increase in insulin resistance and the reduction in β-cell function with impaired insulin secretion. Another proposed mechanism is the potential inhibition of glycogen synthesis and/or activation of glycogenolysis, with inhibition of peripheral glucose uptake. TKIs can have a hypoglycaemic impact in type 1 DM (T1DM) and T2DM, with an improvement in glycaemia. Severe hypoglycaemia has been reported in non-diabetic patients treated with sunitinib or imatinib.[38,43]

Everolimus is an oral mTOR inhibitor. mTOR exists in two distinct large protein complexes: mTORC1 and mTORC2. A relationship has been found between hyperglycaemia and everolimus.[39] The effects of mTOR on glucose homeostasis are complex, depending on the level of mTORC1 activity. mTORC1 promotes insulin resistance and improves insulin secretion. Hyperglycaemia induced by mTOR inhibition may also be due to a decrease in insulin secretion.[44] The risk of hyperglycaemia with everolimus seems to vary by tumour type. The highest has been observed in renal cell carcinoma and the lowest in breast, hepatocellular, and neuroendocrine tumours (NETs).[45]

Somatostatin analogues. Long-acting somatostatin analogues (SSAs) are used to treat NETs, acromegaly, and Cushing's disease.[46] Two first-generation SSAs, octreotide and lanreotide, and one second-generation somatostatin

receptor agonist, pasireotide, are available. SSAs have been shown to decrease growth hormone and insulin-like growth factor-I (IGF-I) levels in patients with acromegaly,[47] and contribute to progression-free survival in patients with NETs.[48] SSAs also inhibit the secretion of prolactin, thyrotropin, cholecystokinin, glucose-dependent insulinotropic polypeptide (GIP), gastrin, motilin, neurotensin, secretin, glucagon, insulin, and pancreatic polypeptide. They also inhibit the exocrine secretion of amylase by salivary glands; hydrochloric acid, pepsinogen, and intrinsic factor by gastrointestinal mucosa; enzymes and bicarbonate by pancreas; and bile in the liver. Furthermore, glucose, fat, and amino acid absorption is inhibited by SSAs.[49]

Among the most frequently reported AEs, SSAs have a negative impact on glucose homeostasis. Pasireotide has shown a good safety profile, as expected for SSAs, except for a higher degree of hyperglycaemia.[50] Octreotide and lanreotide usually induce minor glucose metabolism abnormalities. Hyperglycaemia with a reduction in insulin secretion during an oral glucose tolerance test was reported with octreotide and lanreotide.[51,52]

Mechanistic studies in healthy volunteers suggest that pasireotide-associated hyperglycaemia is due to reduced secretion of glucagon-like peptide (GLP)-1, GIP, and insulin; however, it is associated with intact postprandial glucagon secretion.[53]

AEs such as hyperglycaemia and DM, classified as grade 3 and 4 toxicity (according to the National Cancer Institute Common Terminology for Adverse Events version 5.0[54]), occurred in up to 20% of patients. Glucose and HbA1c levels increased soon after the initiation of pasireotide treatment.

Immunotherapy. ICIs have revolutionized the treatment of various cancers by enhancing the immune system's ability to target cancer cells. However, recent studies suggest that these drugs may also induce DM development.[55,56] Specifically, ICIs, such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors, have been found to induce *de novo* DM in a low percentage of patients (1%-2% across ICI regimens).[57,58] Among these drugs, PD-1 inhibitors, including pembrolizumab and nivolumab, and programmed death-ligand 1 (PD-L1) inhibitors, such as durvalumab, are more likely to precipitate DM than CTLA-4 inhibitors alone, such as ipilimumab. The development of DM induced by ICIs can manifest as new-onset insulin-dependent DM or worsening of pre-existing T2DM. The mechanism behind this phenomenon is not yet fully understood but it is considered immune-related, similarly to T1DM.[59]

The combination therapy with anti-PD-L1 and anti-CTLA-4 has been shown to significantly impact the onset of DM in cancer patients. While the median onset of ICI-induced DM is after 4.5 cycles, in ICI combination therapy it has been found to occur earlier (median 2.7 cycles).[60]

Glucose management during cancer treatments. Given the potential negative effects of hyperglycaemia and uncontrolled DM on cancer patient outcomes, achieving good glycaemic control throughout the care pathway (both in inpatient and outpatient settings, before, during, and after active antineoplastic therapy) is warranted for cancer patients with DM.[13] The management of DM in cancer patients requires a 'paradigm change' as compared to DM patients without cancer. In the last few years, growing evidence has brought to consider an early and proactive multimodal approach towards subjects with DM, to lower diabetes-associated CV risk. Recent international guidelines have endorsed the early use of some classes of ADDs with proven CV benefits, such as sodium-glucose co-transporter inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP1-RAs), in the treatment pathway for DM patients with atherosclerotic CV disease and/or heart failure, in order to reduce CV events and CV-related mortality and hospitalization for heart failure.[58-60]

Moreover, these suggestions are placed alongside the 'classic' recommendation of achieving tight glycaemic control in most non-frail patients with DM to minimize the risk of chronic diabetic complications.[58-60]

Although CV risk and complications should not be underestimated in cancer patients with DM, the choice of therapy and glycaemic targets should be carefully evaluated and individualized. In this setting, the goals of treatment switch from prevention of chronic complications and control of CV risk to maintaining acceptable glycaemic levels, minimizing drug interactions and AEs, and improving nutritional status with the final aim of improving patient's well-being and adherence to cancer therapy.[13]

Various factors contribute to determining the glycaemic targets in the setting of cancer patients with DM. In particular, overall performance status, life expectancy, disease stage, hypoglycaemic risk, comorbidities, and presence of caregiver(s) are pivotal for the evaluation of glycaemic targets and frequency of self-monitoring (SMBG).[13,19] In the case of a good life expectancy, limited and controlled comorbidities, and younger age, a stricter glycaemic target should be aimed for. On the contrary, poor performance status, short life expectancy, significant hypoglycaemic risk, and older age need a substantially less tight target to avoid symptomatic hyper- and hypoglycaemia. In the palliative care and 'end-of-life' settings, glycaemic targets should be further loosened, and SMBG frequency should be reduced to the minimally acceptable.[13,19]

Another difference lies in the methods by which glycaemic status should be evaluated. Given the frequent occurrence of anaemia and the need for blood transfusion (especially in haematologic malignancies), HbA1c measurement could frequently provide an inaccurate result in evaluating glucose control.[13,61] Moreover, short-term glycaemic excursions (albeit significant, like in steroid-induced hyperglycaemia) do not usually affect HbA1c levels. Therefore, in this setting, SMBG represents a valuable option for cancer patients with DM/dysglycaemia.[13] In selected cases, such as in patients with high glycaemic variability/instability (e.g. pancreatectomized patients, immunotherapy-induced autoimmune DM), the use of glucose sensors should be considered, considering patient's characteristics, local

resources, and patient/caregiver suitability to this technology.[19]

The above-mentioned clinical factors should also be evaluated before choosing the type of antidiabetic treatment. Furthermore, the safety profile of the various classes of ADDs, drug interactions, and type of cancer therapy (and its possible contribution to hyperglycaemia/worsening of DM) should be considered, too.[13]

Cancer treatments are usually associated with frequent AEs, especially involving the gastrointestinal tract (e.g. nausea, vomiting, diarrhoea), significantly burdening patients' QoL. Attention should be given when prescribing ADDs with the potential of gastrointestinal AEs, such as metformin, acarbose, and GLP1-RAs.[13] Moreover, although metformin usually represents the first choice of ADD for DM treatment, one should remember to thoroughly evaluate renal function and the risk of its worsening for which cancer patients, through exposure to nephrotoxic antineoplastic drugs and intravenous contrast agents, are more vulnerable. Metformin should also be temporarily held before imaging procedures requiring the administration of iodinated contrast agents.

SGLT2is, while effective in reducing CV risk and treating heart failure, carry the risk of dehydration and urogenital infections that could become clinically significant in a setting of active cancer therapy and subsequent immunosuppression. Their use should therefore be thoroughly evaluated.[13]

The neoplastic disease is often accompanied by a catabolic state that facilitates anorexia, weight loss, and cachexia. The nutritional status of cancer patients with DM should be carefully evaluated, and the use of ADDs with known weight loss effects (e.g. metformin, SGLT2is, GLP1-RA) should be cautiously balanced.[13,62] In this setting, also favoured by its flexibility and efficiency, insulin could represent the treatment of choice producing an anabolic effect.

Nonetheless, the use of insulin, albeit useful in a great percentage of cancer patients with DM and virtually with no contraindications, carries with itself a significant hypoglycaemic risk and the need to adequately educate patients and caregivers about its everyday management and SMBG/sensor use.[13,19]

Some cancer treatments can cause significant metabolic and glycaemic derangement, favouring DM onset or worsening, through the induction of significant insulin resistance or reduced insulin production.[13] Understanding the underlying mechanisms through which hyperglycaemia develops is pivotal for choosing the most appropriate antidiabetic treatment. For instance, ADDs with known insulin-sensitizer effects could be the drugs of choice in managing hyperglycaemia related to some kinase inhibitors (e.g. nilotinib, ponatinib, alpelisib), mTOR inhibitors (e.g. everolimus), or corticosteroid therapy.[13,15,63] On the contrary, in situations of relative or absolute insulin deficiency, such as immunotherapy-induced autoimmune DM, pancreatic cancer-related DM, or post-pancreatitis DM, insulin therapy is mandatory.[13,20]

Given the higher risk of severe complications from various infectious diseases (including coronavirus disease-19) in people with DM and the relative immunosuppression associated with neoplastic disease and treatments, cancer patients with DM should also be offered vaccinations recommended by the International Diabetes Federation (IDF) to reduce mortality and morbidity risk.[64]

Supportive and palliative treatments in cancer patients with diabetes. Supportive and palliative care is essential to the overall care plan for patients with DM and cancer. These conditions can be challenging to manage, and patients often require various supportive services. Health care providers need to work together to develop a plan that addresses the patient's cancer- and DM-related needs.

Supportive care may include training and support on managing blood sugar levels, ADD management, lifestyle changes, and access to a multidisciplinary team of health care professionals who can provide symptom management, nutrition, and emotional support.

Palliative care services may also be necessary for patients experiencing neuropathy, chronic pain, symptoms related to treatment toxicities, or cancer progression, such as pain, nausea, or fatigue. Overall, supportive and palliative care for individuals with DM or cancer aims to improve their QoL and provide them with the resources they need to manage their symptoms and maintain their functional status.

Cancer patients with DM and limited glycaemic control often experience increased pain and asthenia and have a higher incidence of treatment toxicities, such as nausea, vomiting, reduction of appetite, diarrhoea, and weight loss, which can lead to malnutrition and sarcopenia, with skeletal muscle mass loss and a decline in functional status.[65,66]

Nutritional intake is crucial for managing DM and cancer. A well-balanced diet that includes adequate protein and calories can help patients to improve glycaemic control, maintain weight, and improve their overall strength and energy levels, reducing the risk of complications associated with DM.[67]

Also, exercise has been shown to have a protective effect against both DM and cancer, not only in the prevention setting but also in each phase of the patient journey, with an adaptive and personalized approach, maintaining muscle mass and reducing or delaying the risk of neoplastic cachexia.[68]

However, the nutritional needs of cancer patients with DM may differ depending on several factors, such as clinical conditions, comorbidities, cancer site and stage, and age.

These patients need to warrant specialized and personalized nutritional support in the multidisciplinary team and provide specific interventions for oral and parenteral supplementation.

A NEW SUBSPECIALTY APPROACH FOR A CHALLENGING CLINICAL SITUATION IN DIABETIC CANCER PATIENT MANAGEMENT

Metabolic emergencies

Hyperglycaemia and hypoglycaemia are more likely to occur in patients with DM and cancer. Conditions such as fatigue,

Table 2. Diagnostic criteria for euglycaemic diabetic ketoacidosis (EDKA), diabetic ketoacidosis (DKA), and hyperglycaemic hyperosmolar state (HHS)

	EDKA	DKA			HHS
		Mild	Moderate	Severe	
Plasma glucose (mg/dl)	<250	>250	>250	>250	>600
pH	<7.3	7.25-7.30	7.00-7.24	<7	>7.30
Serum bicarbonate (mEq/l)	<18	15-18	10 to <15	<10	>18
Urine ketone	Positive	Positive	Positive	Positive	Low
Serum ketone	Positive	Positive	Positive	Positive	Low
Serum osmolality (mOsm/kg)	Variable	Variable	Variable	Variable	<320
Anion gap	>10	>10	>12	>12	Variable
Mental status	Variable	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Plasma glucose levels <250 mg/dl can be found in EDKA from sodium-glucose co-transporter inhibitors.

dehydration, vomiting and diarrhoea, cachexia, and infections can trigger acute DM complications like surgical and medical procedures.

Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS) are life-threatening conditions accounting for several DM-related deaths (∼0.4% for DKA, reaching 2% in patients >65 years,[69] and up to 20% for HHS).[70]

DKA's main features are hyperglycaemia, ketonaemia, and metabolic acidosis with a high anionic gap, whereas HHS is characterized by hyperglycaemia, hyperosmolarity, and dehydration without significant acidosis (see Table 2).[71] While the former is related to an absolute shortage or lack of insulin, endogenous production of insulin persists in HHS: albeit not sufficient to provide glucose to the insulin-sensitive tissues, it is adequate to prevent lipolysis and consequent ketogenesis (Figure 2).[71] Euglycaemic DKA (EDKA), whose diagnosis can be delayed by the absence of hyperglycaemia and ketonuria, may also develop in specific circumstances.[72] The incidence of EDKA has recently increased due to the introduction of SGLT2is. Since intravascular volume depletion induced by diarrhoea and emesis or by a ketosis-prone status consequent to reduced food intake, hospitalization, and surgery are all precipitating factors for EDKA, oncologic patients treated with these ADDs should be closely monitored.

The clinical presentation of DKA is relatively fast, while it can take days or weeks for HHS. Common symptoms include polyuria, polydipsia, weight loss, and weakness, associated with signs related to intravascular volume depletion. Both in DKA and in HHS, neurologic signs and symptoms may occur. Conversely, polyuria and polydipsia may not be present in the case of EDKA, whereas these patients experience fatigue and malaise. Severe ketoacidosis may also simulate an acute abdomen.[73,74]

In oncology, the sudden onset of DKA may also be the first manifestation of autoimmune DM (much similar to T1DM) induced by ICIs, which are responsible for several immune-related AEs.[75-77] These patients often show normal levels of HbA1c, with a low C-peptide and sometimes positive islet-cell autoantibodies.[78] More commonly, other drugs used in oncology (e.g. glucocorticoids, TKIs, and everolimus) may worsen a pre-existing DM and trigger hyperglycaemic complications due to insulin resistance, reduced insulin secretion, or both.

Therefore, blood glucose should be closely monitored in patients with DM and cancer. Particular attention should be paid to patients treated with ICIs and people with already known DM treated with glucocorticoids in order to take immediate action in case of DKA and/or HHS. Differential diagnosis between the two types of acute complications is based on glucose levels, pH value, the presence/absence of ketones, osmolality, anion gap, and mental status (see Table 2).

Medical treatment of DKA/HHS in cancer patients does not differ from the general population, requiring restoring the circulatory volume and extracellular compartment, reducing blood glucose levels, plasma osmolality, and correction of electrolyte alterations. Intravenous insulin infusion is the treatment of choice for these patients. Identifying and treating precipitating events such as dehydration and infections are mandatory.[59]

Patient education is also fundamental, particularly concerning glucose monitoring and DM management on sick days, especially in case of fever and/or concomitant infection. Ongoing training and education must be provided to the medical staff and caregivers about recognizing and treating symptoms before they escalate to acute, life-threatening conditions.

Chronic diabetes complications influencing cancer treatments

Many data indicate that glycaemic control, adherence to therapy, and self-management of DM worsen after a cancer diagnosis, partially explaining the increased risk of adverse outcomes in diabetic patients with cancer compared to non-diabetics.[79] Moreover, anticancer therapies have a further detrimental effect on metabolic compensation,[80] which affects the onset of long-term micro- and macrovascular complications, and exacerbates already present diabetes-induced organ damage.[81] Consequently, the onset or progression of CV, renal, ocular, and neuropathic injuries should be prevented and monitored in patients with DM and cancer, provided that life expectancy is not too short.

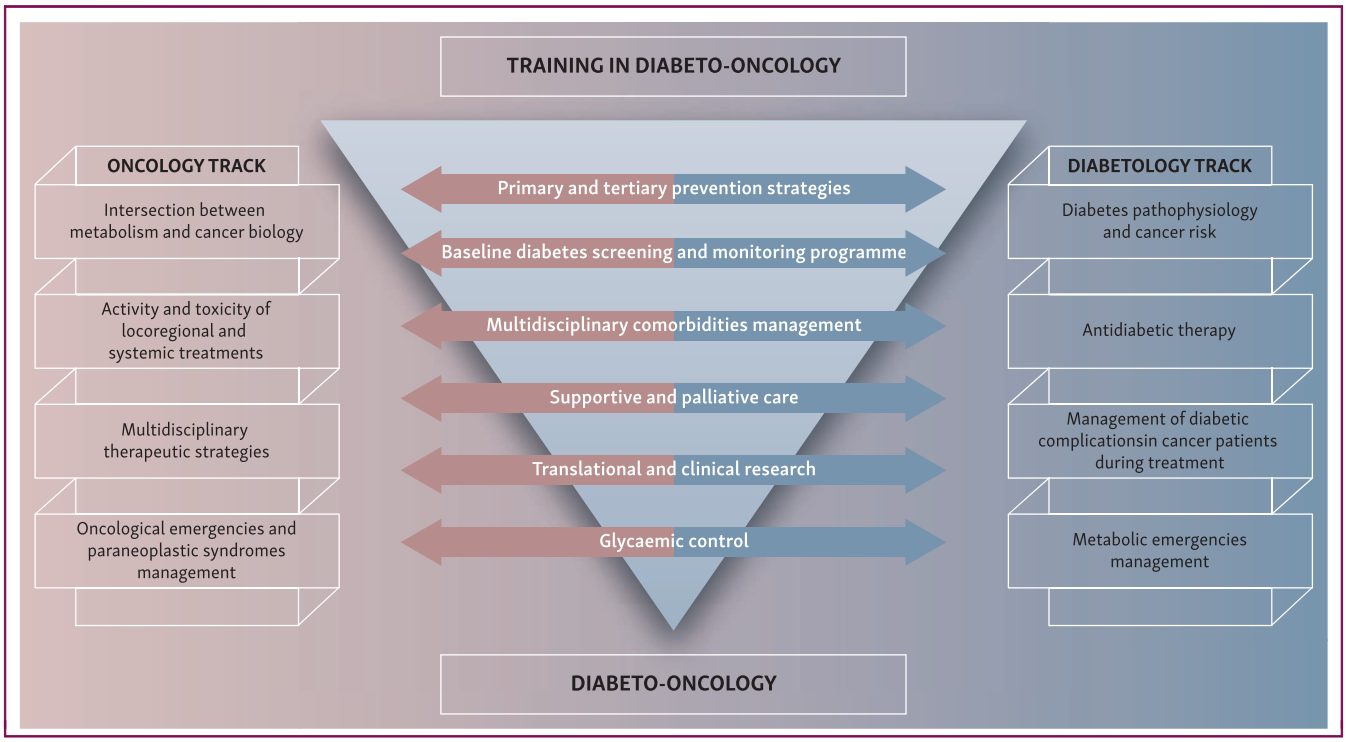

Figure 2. **Specific areas of oncology and diabetology for the training in diabeto-oncology.**

Macrovascular complications (ischaemic heart disease, stroke, and peripheral vascular disease) are a leading cause of mortality among people with T2DM, and the risk of developing heart failure is more than double compared to patients without DM.[82] Conventional anticancer therapies (e.g. anthracyclines, antimetabolites, cyclophosphamide) and novel therapies (e.g. monoclonal antibodies, TKIs, ICIs) are associated with many adverse CV events, including left ventricular dysfunction and heart failure, hypertension, vascular thrombosis and ischaemia, rhythm disturbances and QT prolongation, cardiomyopathy, myocardial fibrosis, and myocarditis, which can contribute to the worsening of CV complications related to DM.[83] The occurrence of cancer treatment-induced CV impairments differs greatly, depending on the patient's age, specific anticancer therapy used, duration of therapy, and the patient's comorbidities. Some anticancer treatments lead to irreversible and progressively worsening CV damage (classical cytolytic cancer therapies). In contrast, others induce only temporary dysfunctions (some novel biological therapies) with no apparent long-term consequence.[84] Furthermore, coronary artery disease, valvular disease, myocardium damage, defects in the conduction system, and diastolic dysfunction constitute the broad spectrum of CV AEs that can occur after radiotherapy.[85] In order to prevent chronic cardiotoxicity of anticancer drugs, early detection using cardiac biomarkers [troponin-I, brain-type natriuretic peptide (BNP), and N-terminal proBNP] and/or imaging techniques (echocardiography, cardiac magnetic resonance) may be extremely useful and required as well as the use of cardioprotective therapy (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin inhibitors, and mineralocorticoid receptor antagonists), even if cardioprotective effects of most of these agents have not been clearly proven in the setting of cancer treatment-related CV damage.[86]

Diabetic nephropathy (DN) affects ~25%-30% of patients with DM and has become the leading cause of end-stage renal disease.[87] DN is characterized by a progressive increase in proteinuria and/or a gradual decline in estimated glomerular filtration rate (eGFR), which are worsened at a relevant incidence by various anticancer drugs. In particular, mTOR inhibitors (everolimus and temsirolimus), probably as a consequence of their hyperglycaemic effect rather than direct damage on renal cells, showed an increase in creatinine and proteinuria[88]; TKIs (e.g. pazopanib, sunitinib, axitinib, sorafenib, and lapatinib) and monoclonal antibodies (bevacizumab, aflibercept) pointed out an increase in proteinuria.[89,90] Finally, acute inflammatory infiltrates in the renal interstitium have been observed in patients treated with ICIs (ipilimumab) in the short and medium term.[91]

Epidemiological data from developed countries, unconfirmed in low- and middle-income countries, have suggested a downward trend in the prevalence of blindness related to diabetic retinopathy in people with DM.[92] There is limited evidence on the effects of anticancer drugs on diabetic retinopathy. A low percentage of diabetic patients have been reported to have worsening retinopathy, including vascular injuries (e.g. tamoxifen) and retinal ischaemia with neovascularization (e.g. alkylating agents, ICIs), soon after starting cancer therapy.[93]

Considering diabetes-related neuropathy, many new anti-myeloma agents can set off or aggravate any pre-existing

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Table 3. Some examples of the issues to be deepened on

Clinical phase	Competence to be developed by diabeto-oncologists
Before cancer/diabetes development	Pathophysiological basis of the link between diabetes and cancer Real epidemiology of the association between diabetes/metabolic syndrome and cancer How to prevent cancer in patients with diabetes How to prevent diabetes in patients with cancer
During cancer management	How to manage and control hyperglycaemia How to counteract glucocorticoid-induced metabolic side-effects How to manage nutritional problems and prevent cachexia How to manage glucose control in patients on artificial nutrition Diabetes management during palliation
After cancer treatment	How to help prevent cancer recurrence with lifestyle and nutrition How to manage metabolic and cardiovascular late effects of cancer therapies in cancer survivors

sensory (thalidomide, bortezomib), sensorimotor (thalidomide), or autonomic (bortezomib) neuropathy. Combinations of chemotherapeutic drugs with the highest peripheral neurotoxicity rates include those involving platinum salts (cisplatin, carboplatin, and oxaliplatin), vinca alkaloids (vincristine, vinblastine, vinorelbine), bortezomib (proteasome inhibitor), and taxanes (paclitaxel, docetaxel, cabazitaxel).[94,95]

Paraneoplastic hypoglycaemia and hyperglycaemia

NETs are secreting neoplasms frequently associated with hormonal hypersecretion. Up to 30% of pancreatic NETs are associated with functioning endocrine syndromes, which can result in impaired glucose homeostasis. One of the most frequent syndromes is related to insulinoma, an insulin-secreting pancreatic NET with an incidence of 1-3 per million per year.[96] Hypoglycaemia-related symptoms generally guide the diagnosis when the tumour is still localized within the pancreas, as in ∼90% of cases.[97] Insulinomas are malignant but slowly progressing tumours, explaining the gradual development of the syndrome and a kind of adaptation of the patient to hypoglycaemia. However, in the case of advanced unresectable disease, hypoglycaemia could be life-threatening and requires either insulin-lowering drugs (i.e. diazoxide, everolimus, pasireotide) or any potentially active antiproliferative agents (chemotherapy, targeted therapy, radionuclide therapy, liver-directed therapy).[98] Nutritional recommendations are a high-protein diet with a low glycaemic index and complex carbohydrates to minimize hypoglycaemic events and rapidly absorbable carbohydrates during hypoglycaemia.[99]

Very rarely, IGF-II-secreting pancreatic NETs can induce hypoglycaemia by activating insulin receptors. Other IGF-II syndromes arise from mesenchymal, epithelial, or haematopoietic neoplasms.[100]

On the contrary, hyperglycaemic syndromes can also develop in NET patients. Sporadic endocrine syndromes arising from NETs of the duodenum—pancreas include glucagonoma and somatostatinoma. Glucagon and somatostatin exert proglycaemic and inhibitory effects on insulin secretion, resulting in reduced glucose tolerance and DM.[101] More frequent syndromes inducing glucose impairments are Cushing's syndrome and paraganglioma syndromes, both cortisol and catecholamines being proglycaemic hormones counteracting insulin activity. In particular, Cushing's syndrome is frequently associated with hyperglycaemia or overt DM, which is worsened by the metabolic syndromes characterizing these subjects.[102] Metformin is an optimal approach to improve insulin sensitivity to manage these syndromes, while insulin should be rapidly adopted in case of poor glycaemic control. From a nutritional point of view, a Mediterranean-style diet is optimal in these patients since the control of both hyperglycaemia and body weight as well as other metabolic impairments could be of benefit both to avoid DM complications and to obtain antitumour effects. Regardless of DM, malnourished patients, as well as those with Cushing's syndrome, should receive nutritional assessment and support.[99]

INTEGRATED TRAINING COURSES FOR DIABETOLOGISTS AND ONCOLOGISTS: AIMING TO CREATE THE NEW GENERATION OF 'DIABETO-ONCOLOGISTS'

The growing need to care for patients with cancer and DM is a major clinical challenge for oncologists and endocrinologists, as well as for haematologists, radiotherapists, and palliative care clinicians.

Today, the clinical management of cancer patients with DM still relies more on the clinician's experience than guidelines. The time has come for academic centres and scientific societies to train *ad hoc* endocrinologists who practice in the oncology field and oncologists who really want to care for cancer-related metabolic issues. Just like cardio-oncology has recently emerged as a subspecialty of clinicians with a special interest in the detection, monitoring, and management of CV side-effects of chemotherapy, targeted therapy, and radiotherapy, the time has probably come for clinicians with special interest and knowledge in treating DM and metabolic complications in people with cancer.

Several issues should represent the core curriculum of specialists with a special interest in diabeto-oncology (see Table 3). In addition to these, some other specific circumstances regarding the everyday clinical management of patients with both DM and cancer should be accurately discussed and shared among specialists and with patients and caregivers.

The diversity of disease entities and aspects of subspecialties covered by diabeto-oncology could make it an essential component of modern health care.

The diabeto-oncology education programme should be designed to develop specific skills on the biological and clinical intersection of DM and cancer and provide effective care to patients affected by both clinical conditions.

A summary of the main specific areas of oncology and diabetology training has been reported in Figure 2, focusing on common topics to be shared and elaborated according to the main expertise.

CONCLUSIONS

Overall, the coexistence of cancer and DM poses significant challenges for patients and health care providers. The complex relationship between these two diseases highlights the need for a multidisciplinary approach and collaboration between oncologists and diabetologists. The management of cancer patients with DM requires careful screening before starting anticancer therapy to assess diabetic complications, nutritional status, and metabolic control. During cancer treatments, health care providers must proactively manage iatrogenic hyperglycaemia and consider the impact of various therapies on glucose metabolism. Glycaemic control plays a crucial role in improving patient outcomes and QoL. Individualized treatment plans, close monitoring of glucose levels, and appropriate adjustment of antidiabetic therapy are necessary to minimize the risk of complications and optimize patient care. The emerging field of 'diabeto-oncology' focuses on developing personalized strategies, identifying biomarkers, and implementing primary prevention strategies to address the unique challenges of cancer patients with DM. By promoting collaboration, education, and awareness, health care providers can improve clinical management, survival rates, and QoL of patients.

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