Nutrition Interventions and Self-Management in Patients with Comorbid Diabetes and Cancer: A Narrative Review

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Abstract

Diabetes and cancer are two of the most prevalent chronic diseases today. Both of these conditions have implications for metabolism and nutrition management in patients affected. In addition, both of these conditions can be managed or improved via nutrition treatment. What is more difficult is patients who have both conditions as comorbidities. This scenario is common, as cancer increases the risk for diabetes, and vice versa. Additionally, evidence has shown that having both conditions as comorbidities increases the risk of mortality. This narrative review aims to investigate the existing evidence on nutrition management in patients with comorbid cancer and diabetes. Findings indicate that glycemic control is a major outcome of concern, as well as that self-management diabetes behaviors may be decreased in this patient population. Overall, the findings from this review were limited due to a lack of research into this patient population. Future research on glycemic control or diet adherence and cancer outcomes, as well as mental health intervention and outcomes in this patient population are warranted.

Introduction

Diabetes and cancer are among the most prevalent chronic conditions in the United States. In 2015, 12.2% of all U.S. adults and 25% of those over the age of 65 had diabetes[1], while approximately 38.4% of Americans will be diagnosed with cancer in their lifetime[2]. With an aging population and cancer and diabetes prevalence both increasing, the number of adults with comorbid diabetes mellitus and any type of cancer can be estimated to be anywhere between 8 – 18% of cancer patients[3]. This figure is likely to continue to increase as development of patients with diabetes are at increased risk of developing cancer. Diabetes has been shown to increase risk of kidney and colorectal cancer in all adults, breast and endometrial cancer in women, and pancreatic, biliary tract, and esophageal cancer in men[4]. Furthermore, patients with diabetes have greater cancer mortality compared to cancer patients without diabetes[5]. Conversely, the development of cancer may in turn increase the risk of developing diabetes, particularly in the cases of pancreatic and breast cancers[6].

Treatment of patients with comorbid cancer and diabetes mellitus can prove complicated as the treatment protocol for one condition may exacerbate the other. For instance, glucocorticoids used in treatment of many types of cancer are associated with impaired pancreatic beta cell function and hyperglycemia[7]. Additionally, chemotherapy can interfere with nutrition management of diabetes by inducing anorexia, nausea, and vomiting all of which can increase the risk of hypoglycemia[8]. However, while complicated, management of patients with both diabetes and cancer is of paramount importance as prognosis for this patient population is worse than for patients with either diabetes or cancer alone[9]. The risk of all-cause mortality for patients

with comorbid diabetes and cancer has been demonstrated to be higher than for patients with cancer without preexisting diabetes mellitus[10]. Furthermore, increased risk of hypo- or hyperglycemia can negatively impact quality of life in this patient population[11],[12].

While much research exists on diabetes and cancer independently, the body of research on the interplay between these two conditions is still growing. To date, the majority of research on these two conditions as comorbidities focuses on the association between the two, such as the heightened risk of developing cancer in patients with diabetes[13]. Some of the growing body of evidence also looks at possible mechanisms explaining this association[14]. For instance, some studies have observed an increased risk of cancer in patients utilizing insulin treatment (particularly Glargine)[15]. And just as glucocorticoid treatment in cancer patients can make glucose control more difficult for patients with preexisting diabetes, use of glucocorticoid in cancer treatment has been observed to increase diabetes risk in patients without preexisting diabetes[16]. This risk extends beyond cancer treatment into cancer survivorship as well. An increased risk of diabetes has been observed for up to 13 years after cancer diagnosis, but is highest in the first 2 years after diagnosis[17]. The metabolic adaptations caused by tumors have also been proposed as possible mechanisms explaining the association between diabetes and cancer, in addition to some of the most common forms of cancer treatment.

The literature also generally explores clinical treatment recommendations for patients with comorbid diabetes and cancer[18][19][20][21]. However, in general these treatment recommendations focus on medical interventions such as the use of insulin[22] or the use of metformin to treat both diabetes and cancer[23]. Little research has been done to investigate the role of nutrition treatment or medical nutrition therapy in treating this patient population. Nutrition treatment is an important factor in both conditions. A systematic review of nutrition therapy in diabetes

treatment suggested that nutrition therapy can reduce HbA1c 0.3%-1.6% after 6 months of treatment, a reduction in HbA1c similar to that found in treatment via oral-glucose lowering medications[24]. Dietary patterns have also been observed to have an impact not only on cancer incidence, but in mortality in cancer survivors. For example, diets high in vegetables and fish were associated with lower risk of mortality, and diets high in alcohol were associated with higher risk of mortality[25].

Thus, the objective of this narrative review is to describe nutrition interventions that have been evaluated in this patient population as well as this patient population's ability to perform self-management behaviors, such as eating, drinking, monitoring blood glucose, and following the recommended diet for diabetes.

Methods

Search strategy

Electronic searches of PubMed and SCOPUS were performed on September 20, 2018 with no limits on publication date. An initial search of PubMed used the search terms "nutrition" AND "cancer" AND "diabetes." Subsequent searches of PubMed used the search terms "enteral" AND "cancer" AND "diabetes" as well as "parenteral" AND "cancer" AND "diabetes." A second search of SCOPUS using the search terms "Nutrition OR diet OR dietary OR nutritional" AND

"Cancer OR oncology OR neoplasm OR tumor" AND "Diabetes" AND "Intervention OR management OR care OR treatment OR co-managing OR co-management." These search terms

were used to focus the search on nutrition interventions versus non-nutrition interventions such as use of insulin or oral hypoglycemic agent therapies. These searches were limited to clinical trials and reviews. Finally, reference lists from relevant reviews were screened for other articles to include.

From the initial list of titles generated in the search, duplicates were removed and then titles were screened to eliminate irrelevant studies. Then the abstracts were reviewed to eliminate non-peer reviewed articles, and articles that looked at only diabetes or cancer but not both. The remaining abstracts were reviewed for inclusion according to the criteria outlined below.

Inclusion/exclusion criteria

To be eligible for inclusion, articles met the following criteria: written in English, peer-reviewed, include only adults as study participants, included study participants with comorbid cancer (of any type) and diabetes, considered the use of nutrition treatment as opposed to non-nutrition treatment such as medication, and the full-text article was available.

Data extraction

The first author reviewed each article and extracted the following characteristics: study design, study duration, sample size, mean age, male/female ratio, stage of cancer, type of cancer, and outcome measures.

Results

The first author conducted the initial search, yielding 1,014 articles. After removing duplicates, 996 articles remained. The remaining articles were screened by title after which 53 articles remained. The abstracts were reviewed for inclusion/exclusion criteria (language, intervention studied is specific to nutrition, etc.) after which point 30 articles remained. The remaining 30

articles were assessed for eligibility for inclusion in this study. Additionally, 3 articles were found from citations in other systematic reviews; the full text of these 3 articles were also reviewed for eligibility. After reviewing the full text, 11 articles were included in this review.

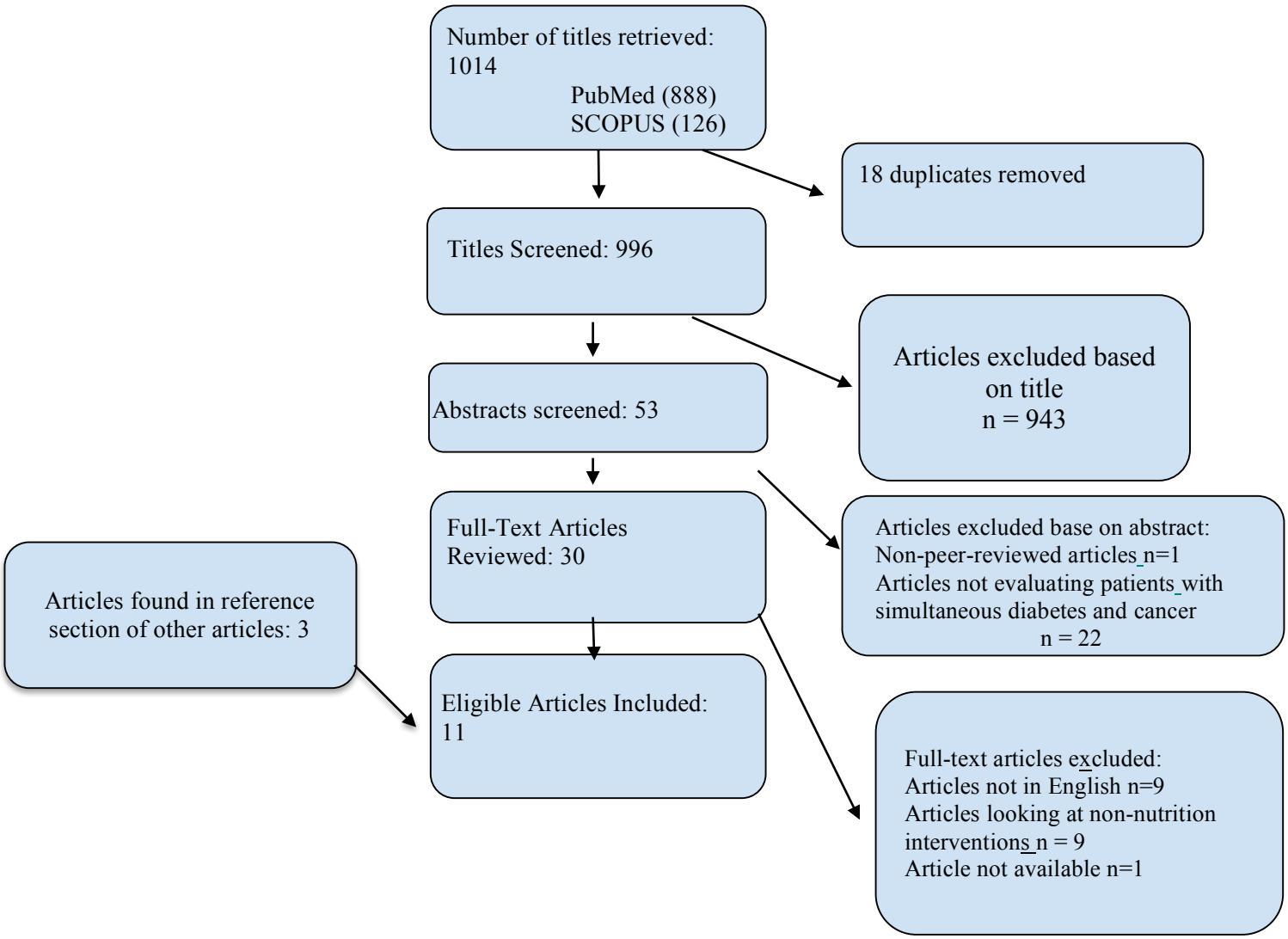

Figure 1: Flowchart of search strategy and results

Study Characteristics

The included studies and their characteristics are included in Table 1. The studies included were published between 2004 and 2018 with the most recently published article dating from May 2018. In the included studies, sample sizes ranged from 42 to 426,129 participants. This wide variation in sample size is due to the wide variety in study designs included.

Of the studies included, a variety of study designs were represented, including: one retrospective case note audit, three retrospective cohort studies, one cross-sectional observational study, two prospective cohort studies, and four clinical trials, two of which were randomized clinical trials and two of which were quasi-experimental (including one evaluation of a proposed a public health intervention).

Exposures

The studies included in this review evaluated nutrition and self-management in patients with cancer and diabetes using a variety of exposures. One of the more common exposures was a cancer diagnosis in patients with diabetes, compared to a control of patients with diabetes but not cancer. One retrospective observational study measured presence of cancer compared to patients with diabetes and no cancer, as well as patients with diabetes and cancer and another chronic condition. Other studies evaluating a cancer diagnosis as an exposure variable include one retrospective observational study, and a cross-sectional observational study. Another retrospective observational study reversed this directionality by using a diabetes diagnosis as the exposure variable in patients with cancer. Other exposures relate to diabetes, either measuring the method of diabetes treatment (insulin, medication, or diet-controlled) as found in the same retrospective observational study that used pre-existing diabetes as a primary exposure. Along

the same lines of treatment type, the two randomized control trials in this review evaluated exposures including glycemic control method during total parenteral nutrition, and use of total parenteral nutrition versus enteral nutrition.

Two prospective cohort studies explored the role of mental health in this patient population. One directly measured post-traumatic stress symptoms in cancer survivors as an exposure. The other measured self-reported symptom severity in patients undergoing chemotherapy and used that as the exposure to measure the association with ability to perform self-management behaviors.

Two quasi-experimental studies were also included. One evaluated tumor patients on TPN and compared blood glucose fluctuations in response to TPN using diabetes diagnosis as an exposure as well as tumor type. The second quasi-experimental study was an evaluation of a public health intervention design. The primary exposure was enrollment in the 4-week or 12-week version of the group class intervention.

Outcomes

Glycemic control: Seven studies used glycemic control and/or hyper- or hypo-glycemic events as an outcome measure as a means of assessing cancer's impact on diabetes management or diabetes outcomes[26 27 28 29 30 31 32]. Studies defined glycemic control differently. Most defined it as a set range of blood sugar or the amount of fluctuation in blood sugar, however HbA1C was also used to define glycemic control in one study[33]. In one case, escalation of T2D treatment was used as a proxy for glycemic control, evaluating if a patient escalated from diet control to oral hypoglycemic agents, or from oral hypoglycemic agents to insulin therapy[34]. A retrospective case note audit looked at the chart notes for 42 patients from one hospital who had died from cancer and also had a diagnosis of diabetes [35], 16 out of 42 patients included reduced or

discontinued blood glucose monitoring altogether. In this same study, two patients experienced hypoglycemic episodes and six experienced hyperglycemic episodes including one instance each of diabetic ketoacidosis and diabetic coma.

In an observational cohort-based study, cancer survivors with diabetes demonstrated poorer glycemic control versus non-cancer survivors with diabetes (31.7% and 34.6% achieving adequate glycemic control) however this difference was not significant. The difference between both these groups and non-cancer non-chronic disease participants was significant, however, with only 17.8% of diabetic patients without cancer or another chronic disease demonstrating adequate glycemic control[36] .

A retrospective observational study evaluating men with prostate cancer measured glycemic control indirectly by looking at escalations in treatment for T2D. This study found men with prostate cancer had 1.75 times the risk of experiencing two consecutive escalations in diabetes treatment versus men without prostate cancer, suggesting prostate cancer may worsen glycemic control[37].

Conversely, one observational study using Korea National Health and Nutrition Examination Survey data showed higher diabetes mellitus control in specific types of cancer. Patients with hepatic, thyroid, and gastric cancers demonstrated 5.50, 10.73, and 16.57 times the odds, respectively, of demonstrating adequate glycemic control compared to other forms of cancer. Compared to non-cancer survivors, cancer survivors of all types were somewhat less likely to achieve adequate glycemic control with only 22.42% of cancer survivors included in the study achieving glycemic control compared to 26.13% of non-cancer survivors[38] .

From a clinical perspective, a randomized controlled trial suggested that total parenteral nutrition ("TPN") was associated with more post-surgical complications and greater fluctuations

in blood glucose versus enteral nutrition ("EN") in patients with diabetes and gastric cancer post-gastrectomy[39].

Another RCT found that in patients receiving enteral nutrition perioperatively, an intensive glycemic control strategy (versus a conventional strategy) resulted in fewer complications from surgery and higher likelihood of achieving blood glucose targets[40].

Similarly, in a retrospective case-control clinical trial, TPN resulted in higher blood glucose values in patients with diabetes versus patients without diabetes within 24 hours of TPN (12.10 and 10.36 mmol/L, respectively) and after 24 hours of TPN (11.01 and 8.36 mmol/L, respectively). This same study also found that in patients with diabetes, certain types of tumors seem to respond with highest variations in blood glucose such as hepatic carcinomas and duodenal carcinomas[41].

Chronic Disease Self-Management Behaviors: Other studies evaluated the impact of chronic disease on self-management behaviors. Two studies used monitoring blood sugar and taking medication as measures of performing self-management behaviors [42] [43]. And one study looked at awareness of having diabetes as a secondary outcome in addition to treatment and control for diabetes[44]. Others looked at adherence to a Diabetes Mellitus diet[45] [46]—although this diet was not defined in the literature—or referral to a dietitian[47]. One evaluation of a public health intervention measured indicators of self-efficacy and health beliefs to measure ability to perform self-management behaviors in the future using a Likert-scale questionnaire[48]. One retrospective observational study evaluated cancer survivors' awareness, treatment, and control of their diabetes compared to two different non-cancer control groups[49]. This study showed that while they demonstrated poorer glycemic control (see previous section), 79.63% of cancer survivors demonstrated awareness of having diabetes versus 69.38% of non-cancer controls. This same

study also evaluated prevalence of treatment of diabetes (defined as use of medical treatment such as insulin or oral hypoglycemic agents) and found 72.22% of cancer survivors reported treatment of diabetes versus 63.23% of non-cancer survivors.

A prospective observational study examined participants' (n = 44) use of diabetes self-management behaviors before and after 8 weeks of chemotherapy, showing that self-management behaviors were significantly decreased after just 8 weeks of treatment, with ability to eat and drink being one of the most affected self-management behaviors along with blood sugar monitoring. This decrease in self-management behaviors coincided with a simultaneous reported increase in symptom burden from cancer treatment. This study also contained a qualitative component in which patients undergoing cancer treatment provided feedback on managing diabetes. Some observations pulled from this data included patients noting that diabetes management became less of a priority for them during cancer treatment, sometimes under the guidance of their medical provider. Patients also reported decreased ability to perform self-management behaviors such as exercise, diet, taking medication, and monitoring blood sugar[50].

In this same vein, one prospective cohort study of cancer survivors' (n = 56) use of diabetes self-management behaviors showed that cancer survivors with higher post-traumatic stress symptoms were 0.08 times as likely to adhere to the recommended diet for diabetes mellitus[51]. In a retrospective case note audit of patients with advanced cancer and diabetes, it was observed that six out of 42 patients with comorbid cancer and diabetes were referred to a dietitian and seven out of 42 used diet interventions to manage diabetes mellitus versus medical intervention such as use of oral hypoglycemic agents or insulin in an inpatient setting[52]. Finally, the last study investigating self-management behaviors in this population evaluated self-management

behaviors before and after implementation of a group-focused public health intervention in the form of weekly group nutrition and physical activity classes designed for cancer survivors. According to this study, a well-planned, culturally appropriate public health intervention can increase cancer survivors' self-efficacy in adhering to a DM management diet, among other self-management behaviors. Participants in the 12 week session of the intervention showed significant improvements in mean waist circumferences compared to participants in the 4 week intervention; and across interventions, over 90% participants reported the intervention motivated them to engage in healthy behaviors and that the nutrition education sessions were relevant to them.

Cancer outcomes: One retrospective observational study evaluated the impact of various types of diabetes mellitus treatment strategies and mortality in patients with comorbid cancer and diabetes (n = 426,129. According to this study, the non-medical intervention (ie management via diet) was associated with lowest mortality rates in this patient population. Men with diabetes and cancer not receiving OHA or insulin treatment had 1.10 times the risk for mortality compared to cancer patients without diabetes. The hazard ratios for patients with diabetes undergoing OHA treatment and insulin treatment were 1.23 and 1.49, in comparison[53]. It is worth noting, however, this association may be due to treatment via OHA or insulin reflecting a further progression of diabetes rather than being a causal factor for mortality.

Discussion

This review aimed to evaluate the current body of evidence surrounding nutrition care in patients with comorbid diabetes and cancer. Little research has been done on specific nutrition interventions in this patient population. The research that currently exists has established a

poorer prognosis in this patient population versus patients with just one chronic condition, as well as higher risk of developing the other condition once diagnosed with either. The prevalence of coexisting cancer and diabetes is expected to grow, and management of patients with both conditions warrants unique considerations. The presence of cancer can worsen a patient's ability to manage their diabetes due to both the metabolic adaptations present in cancer and also due to the mental health effects of a cancer diagnosis and subsequent cancer treatment. This leads to a cycle in which a patient has more difficulty caring for one condition which then exacerbates the other condition. The findings from this review on the impact of cancer on glycemic control are inconclusive, but there is some suggestion that glycemic control may be poorer in patients with cancer. Further research is needed in this area.

Additionally, the findings from this review suggest that while nutrition support may be necessary in advanced stages of cancer, careful consideration must be taken when choosing a method of nutrition support as certain forms such as TPN can worsen glycemic control leading to both hyper- and hypoglycemic episodes. Dietitians in a clinical setting would do well to prioritize oral feeding for as long as possible, keeping in mind traditional nutrition strategies for glycemic control. Once that is no longer an option, a possible best practice would be to use as much of the gastrointestinal tract as possible, leaving TPN as the last resort to prevent protein energy malnutrition.

One of the most interesting findings from this review is the connection between mental health, cancer survivorship, and ability to self-manage diabetes. This review demonstrated that cancer treatment has negative impacts on self-management behaviors in patients with diabetes, and that these effects are higher in patients with higher levels of post-traumatic stress symptoms. Furthermore, these effects last beyond cancer treatment and extend into cancer survivorship. This

connection suggests one of the key variables in the association between poor glycemic control and cancer mortality is mental health. What is promising, however, is the suggestion that this population can experience increased self-efficacy in managing diabetes through well-planned public health interventions. Clinicians treating patients with comorbid diabetes and cancer can address this by referring patients to mental health treatment and emphasizing the importance of continued diabetes self-management, and connecting patients to resources for assistance. Long-term, including mental health care in the coordinated care plan of patients with diabetes and cancer alongside oncology, endocrinology, and nutrition may be beneficial.

While some trends and recommendations can be drawn from this review, the findings of this review were somewhat limited by the narrow scope of research in this area. There are few clinical trials assessing different feeding methods or diet interventions in this patient population. Additionally, the clinical trials that do exist are limited by small sample sizes. The wide variation in sample size across studies included leads to some difficulty in making comparisons. However, this is due to the variation in types of studies included. By its nature, an observational study using publicly available survey data will have a much wider sample size than an intervention which requires participants to actively participate in the study.

Several of the studies investigated this patient population's ability to maintain a diabetes-friendly diet, however, none of the studies included defined this eating pattern so it is difficult to draw comparisons. Future investigators may wish to look into defining a set diabetes-diet and looking at an association between adherence to this diet and cancer outcomes.

This review does carry several strengths. Most research has looked at the impact of cancer or the impact of diabetes but few studies have looked at the impact of both conditions simultaneously. This is a new area of study, and one that has real clinical implications as the

patient population with both conditions is large. Finally, the systematic search method used in this review is an advantage.

Because of the importance of nutrition in managing diabetes, and the importance of maintaining glycemic control to improve cancer outcomes in this patient population, further research into how to improve nutrition care in this population is warranted. Within this patient population, research should be done investigating the level of glycemic control and mortality risk in patients with diabetes and cancer, as well as how specific diet interventions or feeding methods affect cancer outcomes and/or mortality in this population. Finally, further research on mental health interventions or treatment and mortality risk is needed.

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