Message from the Chair

Welcome to another exciting year of ON DPG membership! I am honored to serve as your 2019-2020 Chair, and I am grateful for the knowledge and support of each member of this amazing group of passionate and devoted oncology dietitians. While Chair, I will collaborate with members, including the Executive Committee (EC), to provide new member resources, while continuing to enhance the resources that you know and love.

Please feel confident that the EC listens and acts on member feedback. The recent addition of our diversity committee is a perfect example. This group will lead us to provide more culturally-focused resources for patients and practitioners alike. Other new updates will include exciting improvements to our mentorship program and Speaker’s Bureau, as well as a more user-friendly format to our beloved EML.

There are two great opportunities approaching to connect with oncology nutrition colleagues in person! FNCE® 2019 will take place in Philadelphia, October 26-29. Join us for an ON member reception scheduled for Sunday evening at MANNA. Stay for the ON Spotlight Session, “Sarcopenia in Cancer: Strategies for Diagnosis and Treatment”. In the spring, don’t miss the 2020 Oncology Nutrition Symposium. Here we will learn about cutting edge oncology nutrition from leading experts, while networking with oncology dietitians representing clinics, hospitals, cancer centers, research and academic institutes from across the country. The symposium will also offer a pre-conference course, Oncology Nutrition Fundamentals. This course is designed for (Continued on next page)
The Commission on Cancer Recognizes Nutrition Services as Standard of Care

By Jennifer Lafferty, MS, RDN, LD, FAND

The American College of Surgeon’s Commission on Cancer (CoC) has a new Standard – Oncology Nutrition Services. The CoC’s annual meeting was held July 18-20, 2019 in Washington, DC. Upon the recommendation of the Accreditation Committee, the CoC’s Executive Committee voted to add the nutrition standard, which states that nutrition services must be provided by a Registered Dietitian Nutritionist (RDN).

The CoC standards guide patient-centered care at the over 1,500 accredited cancer centers across the country. Of note, over 70% of the patients diagnosed with cancer in the United States are cared for in cancer centers accredited by the CoC. The new standards will go into effect on January 1, 2020. Please look for the new standards on the CoC’s website this fall.

Thank You!
This standard is the successful result of a six-year effort on behalf of RDNs in oncology practice. Our thanks and appreciation go out to the Commission on Dietetic Registration and the Academy’s Quality Management Committee.

We are so grateful, and bursting with pride, for ON DPG members Kathryn Hamilton, MA, RDN, CSO, CDN, FAND and Barbara Grant, MS, RDN, LD, CSO, FAND. They were appointed to serve on the American College of Surgeon’s CoC as the Academy’s Liaison Representatives - Kathryn (2009 – 2015) and Barbara (2016 – 2022). In addition, they were appointed by the CoC to sit on their Accreditation Committee (the governing body responsible for their standards). These ON DPG members ensured that our profession had a seat at the table and that RDNs are recognized as critical members of the oncology care team. Of note, Barbara was appointed by the CoC to be one of the five workgroup Chairs (the only non-physician) with responsibility for developing the newly revised standards.

Last but not least, ON DPG members like you have made a difference! Thank you for submitting your comments to the CoC and encouraging your colleagues to do so. This is a major victory for optimizing oncology care through expert nutrition intervention.
Flavonoids in the Prevention and Treatment of Ovarian Cancer

By Mridul Datta, PhD, RD, LD, FAND and Andrew Dittman, BS

Abstract

Ovarian cancer is the most fatal of all gynecological cancers and the fifth leading cause of cancer related mortality in women. Diets rich in fruits and vegetables offer some protection against ovarian cancer. Here we review flavonoids, one of the largest constituents found in plant foods, and explore their role in the prevention and treatment of ovarian cancer.

(Continued on next page)
Introduction

Ovarian cancer is the fifth leading cause of cancer-related mortality among women, with approximately 13,980 women projected to die from ovarian cancer in 2019 (1). Ovarian cancer is the most fatal of any gynecologic cancers, with a 47% overall 5-year survival rate and only 29% survival rate in women with metastasized disease, which accounts for about 59% of all women diagnosed with ovarian cancer. The survival rate in women < 65 years of age is twice (60% vs. 30%) that of women > 65 years of age (1). Risk factors for ovarian cancer include personal history of breast cancer, pelvic inflammatory disease, reproductive and hormonal factors (hormone replacement therapy, nulliparity), genetic factors (family history of breast and ovarian cancer, DNA repair gene mutations (Breast Cancer Gene or BRCA)) and environmental factors such as obesity and smoking (1). Genital talcum powder’s role in ovarian cancer remains unclear (1), despite a correlation exploited in lawsuits.

In addition to increased body weight, some dietary constituents have also been implicated in increased ovarian cancer risk. In a systematic review of dietary intake and ovarian cancer risk, Crane et al. (2) observed a higher risk for ovarian cancer from higher total, animal, and dairy fat intake as well as total nitrate and possibly total vitamin C intake. No association was observed between red meat, fiber, vitamin A, vitamin E, β-carotene, or folate intake and ovarian cancer in this study. However, McCann et al. found a lower risk of ovarian cancer in women who consumed higher fiber (odds ratio (OR)=0.43, 95% confidence interval (CI): 0.20-0.94), total carotenoids (OR=0.33, 95% CI, 0.16-0.68), stigmasterol (OR=0.42, 95% CI, 0.20-0.87), total lignans (OR=0.43, 95% CI, 0.21-0.85), vegetables (OR=0.47, 95% CI, 0.23-0.97) and poultry (OR=0.45, 95% CI, 0.22-0.92) (3). In the California Teachers Study cohort (n=97,275), lower risk of ovarian cancer was observed with higher intake of isoflavones but not isothiocyanates, antioxidants vitamins and other macro- or micronutrients. Compared with women consuming < 1 mg of total isoflavones daily, women consuming > 3 mg of total isoflavones daily had a 44% lower risk of ovarian cancer (4). Thus, it appears that some plant compounds such as flavonoids may offer protection against ovarian cancer. Consequently, we explore the role of flavonoids in the prevention and treatment of ovarian cancer.

Flavonoids

Flavonoids are the most common and the largest group of dietary polyphenols and exist as either glycosidic conjugates or free aglycones (5, 6). The basic structure of flavonoids is comprised of two phenyl rings joined by a heterocyclic 4H-pyran ring. Modification of this pyrane ring leads to the different flavonoid classes (7). Flavonoids are categorized into anthocyanin, flavanol, flavanone, flavone, flavonol, isoflavone and chalcones (8, 9). Some classifications of flavonoids categories place flavones and...
flavonoids under anthocyanins (7). The subgroup, subclasses and food sources of flavonoids are listed in Figure 1. Over 10,000 flavonoids have been identified in plants (10).

Food storage and processing can have a significant impact on either the loss or transformation of the flavonoids. Also, plant distribution and variety, seasonal variations, light exposure, climate, and degree of ripeness contribute to variations in the flavonoid content in foods (8, 11). Flavonoids are absorbed in the small intestinal mucosa with only a small amount of the total flavonoids consumed enter the blood circulation (12). Some of the flavonoid remnants that reach the colon are metabolized by resident microbes into byproducts such as butyrate and acetate, which fuel the mucosa (12). Depending on the flavonoid, absorbed amounts may vary considerably from 0.2% to 20% (7).

The biological effects of flavonoids are dependent not only on their structure and chemical properties, but also on the rate of absorption, pharmacokinetics, and the activity of its metabolites (13). Biological properties ascribed to flavonoids include: antioxidant, anticarcinogenic, antiangiogenic, antimutagenic, antiproliferative, immune-stimulating, antibacterial and anti-viral (6, 14, 15). However, the biological activity of metabolites may be higher or lower than the parent compound, which has significant implications in their preventive and therapeutic abilities (13). Flavonoids have a significant potential as chemopreventive agents. Flavonoids neutralize free radical damage by directly scavenging reactive oxygen species, inhibiting oxidases, activating antioxidant enzymes and increasing the antioxidant potential of low molecular weight antioxidants, etc. (16). Flavonoids have also shown a significant potential as modulators of drug resistance (6, 17-20).

Flavonoid intake in the United States varies considerably. Data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 indicate that daily flavonoid intake among participants over 19 years of age was 189.7±11.2 mg (5). Flavanols (82.5%) were the most common, whereas isoflavones (0.6%) were the least likely flavonoids consumed (5). Estimation of total dietary flavonoid content has historically been based on the content of three flavonols (quercetin, myricetin, and kaempferol) and two flavones (apigenin and luteolin), grossly underestimating flavonoid intake and dietary content (11). Key characteristics of the flavonoid subclasses are briefly reviewed below.

**Anthocyanins** are oxonium compounds that are positively charged and exist primarily as glucosides and are not hydrolyzed easily to their aglycones (21). **Flavanols** are strong antioxidants and possess anti-inflammatory benefits (10, 22). Tea is a key source of flavonoids in the US diet, contributing about 157 mg flavonoids daily (23). Flavonol content of teas may vary based on blends, variety and area of production. Either as a result of processing or by the plant themselves, some flavonoids are polymerized into larger molecules called tannins (8). Common tannin subclasses include condensed tannins (or proanthocyanidins), derived tannins (found in oolong and black teas, red wine and coffee) and hydrolysable tannins (8). Flavanol-derived tannins such as theaflavins and thearubigins are found in oolong and black teas and may be responsible for the therapeutic properties of these teas (8). However, decaffeination and the manufacture of instant and ready-to-drink teas decreases flavanol and/or thearubigin levels (8). Additionally, since the amount of catechins and tannins in tea (white, green, black, oolong, etc.) vary considerably and have different bioavailability, it is imperative to identify the type of tea consumed when evaluating therapeutic effects (23).

**Flavanones** have anticancer, antitumor, antibacterial and antioxidant capabilities (24). **Flavones** possess antioxidant, anti-inflammatory and anti-tumor capabilities (25). **Flavonols** are the most highly consumed flavonoid in the Western diet (10, 26, 27), with quercetin being the most common flavonol in the diet (28). **Isoflavonoids** are strong antioxidants and are consumed in high quantities in Asian diets (10, 29). **Chalcones** are an open chain flavonoid, where the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system (9). Licorice and kava-kava are two better known examples of chalcones (9). We examine the role of flavonoids specifically in the prevention and treatment of ovarian cancer.

### Role of Flavonoids in the Prevention of Ovarian Cancer

Increased flavonol and flavone consumption have shown to significantly lower risk of ovarian cancer (30-32). Table 1 summarizes different epidemiologic studies investigating the role of dietary flavonoids and the risk of developing ovarian cancer. Although many of the flavonoids and their subclasses have shown an ability to reduce the risk of ovarian cancer (32-35), several long-term cohort studies showed a null response (36-38) of the flavonoids evaluated (phytoestrogens, flavonols, flavones, tea and coffee). Other studies demonstrated a protective trend with intake of several flavonoid subclasses but failed to reach statistical significance (32, 39). However, caution must be used when interpreting these results. Correlation and not causation can be inferred since most of these studies were case-control/cohort studies.

### Role of Flavonoids in the Treatment of Ovarian Cancer

Table 2 provides a summary of cell and animal studies investigating various flavonoids and their impact on ovarian cancer during treatment. Most research studies have been limited to EGCG, genistein and quercetin. Study end points varied from antiproliferative and apoptotic effects to improved effectiveness of chemotherapeutic drugs in drug-resistant cell lines (17-20, 40-43). The chemo and radiation sensitizer role of flavonoids is critically significant since a high majority of women who have recurrence tend to be resistant to chemotherapeutic drugs (44). Additive effects (43), circumventing chemoresistance (45) or even reversing drug resistance (17) offer significant potential in improving treatment outcomes and potentially survival in this deadly disease.

Some clinical trials evaluating the effectiveness of both synthetic and natural

(Continued on next page)
flavonoids in the treatment of ovarian cancer have been conducted. Trudel et al. conducted a single-arm, phase II study to evaluate the effectiveness and safety of an EGCG-enriched tea drink as a maintenance therapy in 16 women with advanced stage ovarian cancer (46). Participants consumed 500 mL of double-brewed green tea daily until either recurrence or during follow-up of 18 months. The study was terminated early since only 5 of the 16 women remained disease free at 18 months (46).

Diamond et al. conducted a multicenter, open-label, phase I/II study to assess the safety, pharmacokinetics and efficacy of a synthetic isoflavone ME-344 in patients with previously treated, locally advanced or metastatic small cell lung, ovarian and cervical cancers (47). Patients received ME-344 (10 mg/kg) intravenously weekly along with topotecan (4 mg/m2) until disease progression or severe toxicity. Although no dose-limiting toxicities were observed, the researchers did not see any significant anti-cancer activity and did not recommend any further investigation of this combination in patients with small cell lung, ovarian and cervical cancers (47).

As a follow-up to promising preclinical and phase I trials, Bible et al. conducted a phase II trial of flavopiridol (100 mg/m2 IV, 24 hour infusion; 21 day cycles) and Cisplatin (60 mg/m2 IV) in patients (n = 45) with cisplatin resistant (n = 40 (only 26 women with ovarian cancer)) or sensitive (n = 5) ovarian and peritoneal cancers (48). Flavopiridol (Alvocidib) is a synthetic flavone (49). In the cisplatin resistant group seven patients (17.5%) achieved a complete response and 10 patients (25%) maintained stable disease. Overall survival in this group was 16.1 months, with a median time to progression of 4.3 months. Despite positive response in 4 out of 5 patients, the cisplatin sensitive group was closed early due to poor accrual. The median time to progression and survival were 10.8 months and 20.6 months respectively, in this group. The survival time in this study was slightly higher than previously reported (9-15 months) in other drug trials in similar populations. The authors concluded that the combination of flavopiridol and cisplatin was clinically effective and should be evaluated further (48).

Blagden et al. conducted a randomized, double-blind placebo-controlled phase III multicenter trial in 142 women with platinum-resistant ovarian cancer, to evaluate the therapeutic potential of phenoxodiol compared with carboplatin (50). Phenoxodiol (Idronoxil) is a synthetic equol (51). Group 1 received phenoxodiol+carboplatin and group 2 received placebo+carboplatin. The primary and secondary end points were progression-free-survival and overall survival. Response rates, duration of response and quality of life were additional secondary outcomes that were measured. The progression-free-survival was 15.4 vs 20.1 weeks between the groups. The response rate and median survival was 0% vs. 1% and 38.3 vs. 45.7 weeks respectively. None of these results or quality of life differences between groups were statistically significant. Phenoxodiol was well tolerated in this study (50).

Kelly et al. conducted a randomized phase II study to determine the safety and efficacy of phenoxodiol in combination with cisplatin or paclitaxel in women (n = 32) with platinum/taxane-refractory/resistant ovarian cancers (52). Women were randomized to two groups with phenoxodiol (3 mg/kg) weekly and either cisplatin (40 mg/m2 intravenous) or paclitaxel (80 mg/m2 IV) weekly. In cisplatin+phenoxodiol group, three women reached partial responses, and nine women (56%) achieved stable disease, whereas four women (25%) had disease progression. In the paclitaxel + phenoxodiol group one woman had complete and two women had partial responses, eight women (53%) achieved stable disease, and four women (27%) had disease progression. Phenoxodiol with cisplatin or paclitaxel was well tolerated in this study and the researchers concluded that its use should be explored further in this population (52).

**Summary**

Flavonoids have considerable health benefits; chief among them are their chemopreventive and chemotherapeutic effects. Epidemiological and basic research support the role of flavonoids in preventing and treating ovarian cancer. Although the significant variation in absorption and availability of different flavonoids makes the task of diet recommendations extremely difficult, the impact of their sustained intake on the microbiota and its potential health implications cannot be ignored. Basic researchers are exploring the chemotherapeutic potential of several different individual flavonoids. Additionally, some clinical trials have investigated the efficacy of some synthetic and natural flavonoids in chemo-resistant women with ovarian cancer with some encouraging results. Although it may be premature to make diet recommendations for specific flavonoids but consuming an abundant variety of fruits and vegetables in the diet will ensure intake of a considerable diversity of flavonoids and other nutrients and phytochemicals for maximum health benefits.

**References**

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<th>Authors</th>
<th>Year</th>
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<th>N</th>
<th>Follow up duration</th>
<th>Compounds</th>
<th>Conclusion</th>
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<td>Hua et al. (33)</td>
<td>2016</td>
<td>Metanalysis</td>
<td>6275 cases/ 393776 controls</td>
<td>NA</td>
<td>Dietary flavonoids, flavonoid subclasses</td>
<td>↑ flavonoid intake (Isoflavones &amp; flavanols) ↓ ovarian cancer risk</td>
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<td>Cassidy et al. (32)</td>
<td>2014</td>
<td>Prospective</td>
<td>171,940</td>
<td>16-22 years</td>
<td>Total flavonoids, flavonol, flavone, flavanone, flavan-3-ol, flavonoid polymers, proanthocyanidin, anthocyanin</td>
<td>↑ flavonols &amp; flavanones intake may ↓ ovarian cancer risk</td>
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<td>Lee et al. (54)</td>
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<td>Neill et al. (55)</td>
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<td>2780</td>
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<td>Isoflavones (daidzein, genistein, glycitein, biochanin A &amp; formononetin), enterolignans (enterolactone, enterodiol &amp; equol), coumestrol &amp; lignans (matairesinol, pinoresinol, lariciresinol &amp; secoisolariciresinol)</td>
<td>↑ intakes of total phytoestrogens, isoﬂavones &amp; enterolignans ↓ ovarian cancer risk</td>
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<td>Lee et al (56)</td>
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<td>Case-control</td>
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<td>Braem et al. (37)</td>
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<td>Prospective cohort</td>
<td>33,0849</td>
<td>11.7 years</td>
<td>Tea &amp; coffee</td>
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<td>Bandera et al. (39)</td>
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<td>205 cases, 390 controls</td>
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<td>total phytoestrogens, isoﬂavones (daidzein, genistein, formononetin, &amp; glycitein), lignans (matairesinol, pinoresinol, lariciresinol, pinostilbene &amp; secoisolariciresinol), &amp; coumestrol</td>
<td>Although not statistically significant total phytoestrogen intake may ↓ ovarian cancer risk</td>
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<td>Hedelin et al. (36)</td>
<td>2011</td>
<td>Cohort</td>
<td>47140</td>
<td>16 years</td>
<td>phytoestrogens</td>
<td>no association between phytoestrogen intake &amp; overall ovarian cancer risk</td>
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<td>Rossi et al. (34)</td>
<td>2010</td>
<td>Case-control</td>
<td>9622 cancer cases, 16050 controls</td>
<td>NA</td>
<td>flavonoids &amp; proanthocyanidins</td>
<td>↑ flavonols &amp; isoﬂavones intake, ↓ ovarian cancer risk</td>
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<td>Wang et al. (38)</td>
<td>2009</td>
<td>Cohort</td>
<td>38408</td>
<td>11.5 years</td>
<td>Flavonols (myricetin, kaempferol, queretin) &amp; flavones (luteolin, &amp; apigenin)</td>
<td>No association between flavonoid intake &amp; total cancer or ovarian cancer risk</td>
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<td>Myung et al. (57)</td>
<td>2009</td>
<td>Metanalysis</td>
<td>165434 ovarian cancer cases &amp; controls</td>
<td>NA</td>
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<td>Gates et al (58)</td>
<td>2009</td>
<td>Case-control</td>
<td>2324</td>
<td>5 years</td>
<td>myricetin, kaempferol, queretin, luteolin, &amp; apigenin</td>
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<td>Rossi et al. (59)</td>
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<td>7 years</td>
<td>flavan-3-ols, flavanones, flavonols, flavones, anthocyanidins &amp; isoﬂavone</td>
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<td>Gates et al. (35)</td>
<td>2007</td>
<td>Prospective</td>
<td>66940</td>
<td>18 years</td>
<td>myricetin, kaempferol, queretin, luteolin &amp; apigenin</td>
<td>↑ kaemppferol &amp; luteolin intake ↓ ovarian cancer risk</td>
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<td>Chang et al (4)</td>
<td>2007</td>
<td>Prospective</td>
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<td>Isoflavones</td>
<td>↑ isoﬂavones intake ↓ risk of ovarian cancer</td>
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<td>Zhang et al. (60)</td>
<td>2004</td>
<td>Case-control</td>
<td>906</td>
<td>1 years</td>
<td>Soy &amp; soybean products, isoﬂavones (daidzein, genistein, glycitein)</td>
<td>↑ soy &amp; isoﬂavones (daidzein, genistein, glycitein) intake ↓ risk of ovarian cancer</td>
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<td>McCann et al. (3)</td>
<td>2003</td>
<td>Case-control</td>
<td>820</td>
<td>NA</td>
<td>Several dietary components &amp; phytochemicals (β-sitosterol, campesterol, stigmasterol, total phytosterols, total lignan precursors (secoisolariciresinol, matairesinol, quercetin &amp; kaempferol)</td>
<td>↑ stigmasterol, total lignans, vegetables, dietary fiber &amp; total carotenoid intake ↓ risk of ovarian cancer</td>
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<td>Zhang et al. (61)</td>
<td>2002</td>
<td>Case-control</td>
<td>906</td>
<td>1 years</td>
<td>Flavanols (catechins)</td>
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### Table 2. Research studies on dietary flavonoids and treatment of ovarian cancer

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<td>Yan et al. (64)</td>
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<td>Rao &amp; Pagidas (66)</td>
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<td>Ravindranath et al. (68)</td>
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<td>Epicatechin, epigallocatechin, epicatechin 3-gallate &amp; EGCG</td>
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<td>Chan et al. (42)</td>
<td>2006</td>
<td>EGCG</td>
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<td><strong>Genistein and other Isoflavones</strong></td>
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<td>Thasni et al. (69)</td>
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<td>Gossner et al. (45)</td>
<td>2007</td>
<td>Genistein</td>
<td>can induce both apoptotic &amp; autophagic cell death, consequently, may circumvent chemoresistance related to changes in apoptotic signaling</td>
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<td>Gercel-Taylor et al. (43)</td>
<td>2004</td>
<td>Genistein &amp; daidzein</td>
<td>Genistein had an inhibitory effect on the growth of ovarian cancer cells &amp; had an additive effect when combined with cisplatin, topotecan &amp; paclitaxel</td>
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<td>Chen &amp; Anderson (70)</td>
<td>2001</td>
<td>Genistein &amp; daidzein</td>
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<td>Roomi (74)</td>
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<td>significantly suppresses ovarian cancer incidence, growth &amp; lung metastasis</td>
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<td>induces apoptosis &amp; reverses multi-drug resistance to paclitaxel &amp; doxorubicin in resistant ovarian cancer cells</td>
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<tr>
<td>Yang et al. (40)</td>
<td>2015</td>
<td>Quercetin</td>
<td>pretreatment with quercetin significantly enhanced cisplatin toxicity while protecting kidney damage</td>
</tr>
<tr>
<td>Cantanzaro et al. (41)</td>
<td>2015</td>
<td>Quercetin</td>
<td>10-50 µM concentration caused cell cycle changes &amp; exceeded resistance to cisplatin in ovarian cell line</td>
</tr>
<tr>
<td>Wang et al. (76)</td>
<td>2015</td>
<td>Cranberry flavonols (quercetin aglycone &amp; PAC DP-9)</td>
<td>↑ cytotoxic &amp; anti-proliferative effect on ovarian cancer cells</td>
</tr>
<tr>
<td>Yi et al. (77)</td>
<td>2014</td>
<td>Quercetin</td>
<td>↑ apoptosis of ovarian cancer cells</td>
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<tr>
<td>Li et al. (20)*</td>
<td>2014</td>
<td>Quercetin</td>
<td>at low concentrations attenuates the therapeutic effects of cisplatin taxol, Pirarubicin &amp; 5-Fluorouracil in ovarian cancer cells, but in mice, led to ↓ of the therapeutic efficacy of cisplatin</td>
</tr>
<tr>
<td>Maciejczyk &amp; Surowiak (18)</td>
<td>2013</td>
<td>Quercetin</td>
<td>↑ chemosensitivity of ovarian cancer cells to cisplatin &amp; paclitaxel</td>
</tr>
<tr>
<td>Gao et al. (78)*</td>
<td>2012</td>
<td>Encapsulated quercetin</td>
<td>suppressed growth of established ovarian tumors by ↑ apoptosis &amp; ↓ angiogenesis</td>
</tr>
<tr>
<td><strong>Flavones</strong></td>
<td></td>
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<tr>
<td>Tang et al. (31)</td>
<td>2015</td>
<td>Apigenin</td>
<td>apigenin inhibited the self renewal capacity of ovarian cancer cells</td>
</tr>
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</table>

EGCG = Epigallocatechin-3-gallate; 34’7TMQ = 3,4’,7-O-trimethylquercetin; *cell/animal study, all other studies were conducted in ovarian cancer cell lines.


(Continued on next page)
Pediatric Acute Lymphocytic Leukemia and the Effect of a Dietary Intervention on Glucocorticoid-Induced Metabolic Syndrome

By LeAnna Allyson Beech, MS, RDN, LDN, Karen Ringwald-Smith, MS, RDN, LDN, FAND, Jodie Greear, MS, RD, CSO, LDN and Marie van der Merwe, PhD

Abstract
This study investigated whether a dietary intervention of fish oil could reduce the risk of metabolic syndrome phenotype associated with glucocorticoids (GC), typically given as part of acute lymphocytic leukemia (ALL) treatment. Weaned C57BL/6 male mice were assigned to either a standard rodent chow or a Western-type diet providing 45% calories from fat consisting of lard (high omega-6/low omega-3 fatty acids). These diets were consumed until mice were six weeks old, when mice receiving the Western-type diet were further randomized to either the same high omega-6/low omega-3 fatty acid diet or an isocaloric diet providing 45% fat from fish oil (high omega-3/low omega-6 fatty acids). Also beginning at six weeks of age, GC treatment was given daily for 28 days to 50% of the mice in each of the three diet groups. Data showed that the fish oil diet (high omega-3/low omega-6 fatty acids) reduced body mass gain, incidence of fatty liver, and prevalence of glucose intolerance when used in combination with high dose GC therapy. This suggests that consuming a diet high in omega-3 fatty acids and low in omega-6 fatty acids during ALL treatment with GCs may reduce the risk of metabolic syndrome phenotype associated with ALL treatment.

Introduction
The pediatric oncology population has shown an increase in survival rate due to highly effective pharmacological therapies. However, these treatments have triggered long-term, detrimental metabolic changes that can be difficult to reverse. The role of the Registered Dietitian Nutritionist (RDN) in the care of this population is to provide optimal nutrition intervention, including medical nutrition therapy (MNT) that may reduce the risk of harmful side effects of ALL treatments. The study discussed in this article provides evidence for using a diet high in omega-3 and low in omega-6 fatty acids as MNT to counteract the usual metabolic effects of high dose GC treatment. (Continued on next page)
Background

Pediatric ALL constitutes 30% of all childhood malignancies in the United States, making it the most common form of childhood cancer (1). This cancer originates with abnormal white blood cell (lymphoblast) accumulation in the bone marrow and blood (1, 2). The current event-free survival rate for pediatric ALL is increasing and is now 75%-85% (2, 3).

However, despite successful cancer treatment, these survivors have multiple long-term negative health consequences that include and are associated with an increase in body mass. These consequences are consistent with metabolic syndrome and include abdominal obesity, impaired glucose tolerance, high blood pressure, elevated triglyceride levels, low levels of high-density lipoproteins (HDL), and recently added, non-alcoholic fatty liver disease (NAFLD).

The standard treatment protocol for ALL includes multiple chemotherapeutic agents and high dose GCs. During the induction phase (first 28 days of therapy) patients receive Vincristine, Daunorubicin, PEG-Asparaginase, Cyclophosphamide, Cytarabine, and Mercaptopurine along with approximately 40 mg/m²/day of synthetic GCs, specifically Prednisone (5).

It is well known that chronic GC treatment alters metabolism and favors weight gain (6). During ALL treatment most weight gain occurs during the induction phase of treatment, when high doses of the synthetic GC, Prednisone/Prednisolone, are administered. This suggests that GC treatment contributes to the metabolic syndrome phenotype associated with ALL therapy (7).

GCs are stress hormones naturally secreted by the adrenal cortex to help decrease inflammation and control energy metabolism. As stated above, certain GCs such as Prednisone/Prednisolone are part of the chemotherapy treatment protocol of pediatric ALL (8). Prednisone/Prednisolone is typically used for its anti-inflammatory and cytolytic effect on thymocytes, and therefore is essential in treatment because of the dramatic increase in immature thymocytes as well as chemotherapy-induced inflammation seen in pediatric ALL (9). Synthetic GCs are shown to cause massive cell death, or apoptosis, in lymphoid malignant cells by transcriptionally regulating and altering a variety of different genes (10). GCs bind to ligand-activated zinc finger transcription factors called glucocorticoid receptors (GR) found in the cytosol of the cell. After binding to GRs, GCs move to the nucleus and function as a DNA sequence-specific transcriptional regulator of certain GC-responsive target genes (11). These target genes are shown to help control hepatic energy metabolism, especially protein and sugar homeostasis (6).

Sugar homeostasis is the balance of insulin and glucagon to maintain normal ranges of blood glucose levels. When blood glucose is high, insulin is secreted by the pancreatic beta cells to facilitate the transport of glucose into the cells for energy, thus reducing blood glucose levels to the normal range. During a fasted state or prolonged exercise, glucagon from the alpha cells of the pancreas and natural GCs are released to simulate catabolic reactions in the body by antagonizing anabolic insulin actions (6). However, a chronic increase of natural or synthetic GCs can alter certain processes, causing an increase in anti-inflammatory molecules and gluconeogenic enzyme levels such as phosphoenolpyruvate carboxykinase (PEPCK). Consequently, an increase in these gluconeogenic enzyme levels causes the body to use non-carbohydrate precursors to make glucose, leading to a rise in blood glucose levels. Additionally, GCs inhibit glucose uptake into muscle and adipose tissue, which increases the rate of adipose tissue lipolysis and generates fatty acids as an energy source for muscles. These alterations promote a further rise in blood glucose levels, eventually leading to insulin resistance or type 2 Diabetes Mellitus. In obese individuals, enlarged adipose tissue inhibits the anti-lipolytic action of insulin, which results in higher levels of circulating free fatty acids (6). An increase in free fatty acids also can increase the secretion of glucagon, resulting in gluconeogenesis and hyperglycemia (12).

Although acute exposure of GCs increases lipolysis in adipose tissue, chronic use of GCs can lead to an increase in total mass of adipose tissue, especially in conjunction with a high fat diet (HFD) that is low in omega-3 polyunsaturated fatty acids (n-3) (13).

Increases in adipose tissue may be caused by the redistribution of fat from peripheral to central and visceral depots, leading to further deregulation of metabolism. Most pediatric patients with ALL, as well as patients with Cushing’s syndrome, have fat redistribution as a common phenotype. The shared feature between these two types of patients is chronically increased GCs of either natural or synthetic origin, with naturally increased GC levels occurring due to irregular hormonal and metabolic processes and stress responses (6, 14, 15).

Changes in fat distribution and blood sugar are not the only issues with chronic exposure to GCs. Although GCs are known for their anti-inflammatory activity, long-term use tends to promote inflammation by stimulating steatosis of the liver (16). Chronically elevated GC levels alter the regulation of liver processes and increase triglyceride synthesis, decrease fatty acid oxidation, and increase accumulation of lipids, leading to fatty liver (17).

Long-term deregulation of hepatic processes is detrimental as the liver is responsible for the control of glucose and lipid homeostasis. Untreated liver disease can result in liver failure and even death (18). Non-alcoholic fatty liver disease (NAFLD) is a chronic inflammatory condition that can range from simple steatosis, also called simple fatty liver, to nonalcoholic steatohepatitis (NASH). NASH can later progress into more advanced inflammatory stages such as fibrosis, cirrhosis, hepatic apoptosis, and hepatocellular carcinoma (19). Fatty liver results from the accumulation of triglycerides in the liver cells due to an increased uptake of free fatty acids and de novo lipogenesis in the hepatocytes while also exhibiting a decreased secretion of very low-density lipoprotein cholesterol (VLDL-C) out of the liver (20). GCs alter the transcriptional regulation of many different metabolic genes and enzymes such as glucose-6-phosphatase (G6Pase) and PEPCK. These alterations have an immense effect on how macronutrients are metabolized and stored in the body. However, the entire effect of GC treatment in concurrence with an HFD on hepatic inflammation and fibrosis...
remains unclear. There is some evidence that an HFD, providing about 60% of calories as fat, in conjunction with GCs rapidly induces the development of fatty liver disease. In addition to the production of fatty liver disease, there is lipid spillover from central adipose tissue, which rapidly promotes insulin deregulation leading to the diabetic phenotype and hepatic insulin resistance (21).

Conversely, studies have found that an HFD that is high in n-3 fatty acids may improve liver outcomes by decreasing hepatic steatosis, inflammation and necrosis. Omega-3 fatty acids have been shown to be safe and effective for the treatment of fatty liver disease by improving hypertriglyceridemia, down regulating leptin and resistin levels and upregulating adiponectin expression (22). In turn, increased adiponectin levels are associated with decreased liver inflammation and fibrosis as well as decreased hepatic and systemic insulin resistance (23).

Insulin resistance, also known as type 2 diabetes mellitus, can be a consequence of chronic liver disease, especially in the presence of hyperlipidemia. Insulin lowers blood glucose and inhibits lipolysis. Therefore, hyperlipidemia in combination with insulin resistance favors an increase in fat mass and lipolysis, causing elevated levels of free fatty acids and therefore a disruption of insulin signals. Reduced insulin signaling causes hyperglycemia, which leads to elevated hepatic glucose, up regulation of de novo liponeogenesis, and a further increase in free fatty acids (24). The rise of free fatty acids causes an escalation of oxidative stress, fatty liver disease, and increase in adipose tissue. Insulin resistance and the accumulation of adipokines, such as leptin and the pro-inflammatory cytokines, Tumor Necrosis Factor alpha (TNF-α) and Interleukin 6 (IL-6), exacerbate the oxidative stress and perpetuate the liver inflammation leading to further liver damage (25).

TNF-α is released by adipose tissue associated macrophages (ATMs) (26). Previous work demonstrated that an increase in GCs cause adipocyte hypertrophy and thereby stimulates pro-inflammatory TNF-α secretion (27). TNF-α is an inhibitor of the GLUT4 insulin signal through its influence on the tyrosine kinase activity of the insulin receptor, thus preventing glucose uptake in cells (28). Therefore, GCs may cause insulin resistance as a result of the increased release of TNF-α from hypertrophied adipocytes. This accounts for increased TNF-α serum levels that are seen in obesity and hyperinsulinemia (27).

Another component of weight management is the hormone leptin. This hormone helps regulate energy balance by suppressing appetite in order to reduce food intake (29). Increased leptin, together with decreased adiponectin, has been shown to amplify the severity of steatosis and fibrosis of the liver while increasing the occurrence of insulin resistance (30). Previous animal studies have shown that diet high in n-3 can cause a decrease in leptin and resistin levels in serum and adipose tissue, while increasing the adipokine, adiponectin, over time (31). Adiponectin expression can be inhibited by both GCs and the pro-inflammatory cytokine TNF-α (22). Excess TNF-α and leptin have also been shown to impair insulin response by inducing insulin resistance in pancreatic β cells by stimulating the release of mediators that are toxic for these cells (28).

Factors that cause insulin resistance and NAFLD promote signs and symptoms of NAFLD such as malaise, fatigue, right upper quadrant pain, abdominal discomfort, hepatomegaly, jaundice, ascites, and indications of metabolic syndrome. However, most cases of NAFLD are asymptomatic, and therefore biomarkers are useful to assess liver status, including aspartate- and alanine aminotransferase levels (ALT), total and direct bilirubin, fasting serum glucose, and lipid panel (32, 33).

While the liver and the pancreas are key regulatory organs of metabolism, other important and less studied organs that influence metabolism are the small and large intestines. Studies have shown that GCs may play a role in the increased intestinal uptake of glucose, which may contribute to the development of hyperglycemia in patients on chronic GC therapy (17). There are a variety of sugar transporters in the intestine including GLUT2, GLUT5, GLUT7, GLUT9, and sodium-dependent glucose co-transporter (SGLT1) (34). The variety is indicative of adaptation of the intestinal sugar transport system, depending on the different dietary proportions of macronutrients consumed (35). Although there is limited evidence on how these transporters function during digestion, carbohydrates in the intestine require absorption by a two-step, two-membrane-transport process. The SGLT1 and the facilitative fructose transporter, GLUT5, found in the brush border membrane lining the intestinal lumen absorb monosaccharides (36). GLUT2 is a facilitative transporter of both glucose and fructose in the basolateral membrane of the small intestine and is activated by glucose transport through SGLT1 (37, 38).

During postnatal small intestinal development, specific GCs have been shown to regulate cytokine gene expression. This suggests that cytokines may alter sugar absorption (39). One study suggests that Prednisone increases glucose absorption while other studies show no effect (40). An increase in glucose transport to the liver could promote fat accumulation in the liver, which can be another determinant of NAFLD.

Current research is limited but shows that the ratio of omega-6 fatty acids (n-6) to n-3 fatty acids may be important in preventing or reducing the metabolic syndrome phenotypes such as obesity, NAFLD, dyslipidemia, and insulin resistance observed in these pediatric patients (41, 42).

Omega-3 fatty acids help reduce pro-inflammatory cytokines such as TNF-α and IL-8, reducing the risk of liver disease and insulin resistance (42-45). Omega-3 fatty acids may increase anti-inflammatory cytokines by incorporating n-3 fatty acids into cell membrane phospholipids, which interferes with the metabolism of linoleic acid (LA), the n-6 precursor to arachidonic acid (AA). Omega-3 and n-6 fatty acids are competitively metabolized by the same enzyme system, therefore, the polyunsaturated fatty acid (PUFA) that is most abundant will be preferentially metabolized. When n-3 fatty acids are most abundant, they will replace AA (Continued on next page)
in the cell membrane and decrease the pro-inflammatory derivatives of AA. If more n-6 fatty acids are present, then the pro-inflammatory AA-derived eicosanoids will dominate over the anti-inflammatory n-3 derived eicosanoids (46). When dietary intake of n-3 fatty acids is greater, there is an increase in anti-inflammatory mediators and a decrease in the pro-inflammatory mediators, which will reduce inflammation and oxidative stress (47).

Although considerable research has been devoted to proving the beneficial effects of GCs as part of the treatment therapy for ALL, few studies have addressed the role of nutrition, specifically fatty acids, in the reduction of detrimental side effects caused by chronic GC use.

Certain PUFAs have been advertised as a beneficial component of an anti-inflammatory diet as well as a potential deterrent to atherosclerosis, obesity, and diabetes (48). The two major types of essential PUFAs are n-3 and n-6 fatty acids (22). Dietary n-3 fatty acids are commonly found in essential α-linolenic acid (ALA) as well as in eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Food sources include fish, flaxseed oil, and seeds (49). These specific forms of n-3 fats have been shown to decrease inflammation by reducing eicosanoids and other mediators derived from AA (50-51). Eicosanoid products such as prostaglandins are derived from n-6 fatty acids. Therefore, the appropriate ratio between n-6 and n-3 fatty acids is critical to produce positive health effects (52). Common types of dietary n-6 fatty acids are LA and AA, which are found in nutritional sources such as liquid corn, sunflower, olive, and safflower oils. The Western-type diet characteristically contains low levels of PUFAs and higher amounts of n-6 fatty acids than n-3 fatty acids. This high ratio of n-6 fatty acids to n-3 fatty acids leads to an increase in inflammation and related problems with weight and metabolism (42, 53).

Incidences of obesity and metabolic disorders have increased over the past decade due to the increased consumption of a Western-type diet, which is high in calories, saturated fat, and sugar and low in n-3 fatty acids. Pediatric patients undergoing treatment for ALL often consume those same Western foods that are high in saturated fat, n-6 fatty acids, and sugar before, during, and after treatment. Increased consumption of these types of foods contributes to the increase in visceral adipose tissue, NAFLD, insulin resistance, and glucose transporter deregulation, which are also phenotypes that ALL patients develop (54). Increasing consumption of n-3 fatty acids may decrease GC induced health consequences including the redistribution and increase of adipose tissue, as well as the increase in the occurrence of inflammation, hypertension, hyperlipidemia, and liver disease (14, 17, 55).

These observations have led to the hypothesis that a Western-type diet containing high amounts of fat and carbohydrates will exacerbate the risk of developing metabolic syndrome induced by GC treatment. A secondary hypothesis is that the replacement of lard (higher in n-6 fatty acids) with fish-derived fat (higher in n-3 fatty acids) will reduce the metabolic disorder phenotypes induced by chronic, long-term exposure to GC and ultimately reduce the risk of developing obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, and glucose intolerance.

Materials and Methods

Experimental Animals

Newly weaned C57BL/6j male mice were obtained from breeder pairs (purchased from Harlan Laboratories, Inc., Indianapolis, IN) and housed in a USDA approved animal facility at the University of Memphis. Mice were weaned to a standard rodent chow diet (Chow) (6% kcal from fat) or a Western-type diet composed of 41% carbohydrate, 20% sucrose, 9% corn starch, and 12% Maltodextrin 10; Research Diets, Inc., New Brunswick, NJ). At six weeks of age, mice were separated into individual cages. Mice on the chow diet remained on the chow diet for the duration of the study, while mice on the HFL diet were randomly divided with half remaining on the original HFL n-6 and the remainder switched to a diet containing 45% kcal fat from Menhaden (fish) oil (HFO n-3) for an additional four weeks (Table 1A) (Research Diets, Inc.). All animals received food and water ad libitum and were maintained in individual cages with a 12-hour dark/12-hour light cycle. The HFL n-6 diet contains a greater ratio of n-6 to n-3 fatty acids (13:1) than the HFO n-3 diet (Table 1B). The HFL n-6 diet also contains a greater amount of Stearic, Oleic, and Linoleic fatty acids than the HFO n-3 diet. The HFO n-3 diet contains a greater composition of myristic, palmitoleic, stearidonic, eicosapentaenoic (EPA), docosapentaenoic, and docosagexaenoic (DHA). EPA and DHA have been shown to have anti-inflammatory effects and to decrease the risk of cardiovascular and other metabolic issues (56). Due to the increase in the n-3 fatty acid components compared to the n-6 fatty acid components in the HFO n-3 diet, the n-6 to n-3 fatty acid ratio is lower in the HFO n-3 diet. (Tables 1 A and B).

Mice further received daily doses of the GC Prednisolone or vehicle only for the final four weeks. Prednisolone was administered at 0.003 grams/mouse/day (40 mg/m2/day) in a vehicle of 0.25g sweet potato. Control mice received 0.25g sweet potato only. The prednisolone dose given is based on the amount given to pediatric ALL patients during the induction phase of their therapy. This dose is sufficient to have immunomodulatory effects, but not to see major weight loss seen with glucocorticoid therapy the rodents. Food intake and body mass were monitored twice weekly. All experiments were conducted in accordance with the National Institutes of Health Guidelines for the Care and Use of Experimental animals and were approved by the University of Memphis Institutional Animal Care and Use Committee.

Histology

Small intestines were harvested, and length measured. Liver were harvested and weighed. A portion of each tissue was fixed in formalin Fisher Scientific Co. LLC) embedded in paraffin and 4um sections were stained with hematoxylin and eosin.

In vitro Glucose Uptake

Glucose uptake was measured in vitro using the everted sleeve method (57). Briefly, small intestines were harvested and immediately transferred into cold mammalian 290 mOsM Ringer solution (117 mmol NaCl, 4.7 mmol KCl, 1.2 mmol KH2PO4, 1.2 mmol MgSO4, and 20
mmol NaHCO₃). Segments 1.5 cm long were cut, starting at the most proximal region of the intestine. The 1.5 cm segments were everted and secured onto the ends of four mm-diameter stainless steel rods using surgical thread to secure the ends. Mounted tissues were immediately placed in ice-cold 290 mOsm aerated (95% oxygen and 5% CO₂) Ringer solution. Mounted tissue samples were incubated for five minutes in 37°C aerated Ringers solution before being positioned for two minutes over a stir bar rotating at ~1,200 rpm in a solution of aerated mammalian Ringers solution containing 50 mmol/L D-glucose and a tracer concentration of radiolabeled (¹⁴C) D-glucose to determine D-glucose uptake by the tissues. Radiolabeled (³H) L-glucose was added to the incubation solution to correct for D-glucose that is associated with the adherent fluid and passively absorbed (55). At the end of two minutes, tissues were rinsed for 20 seconds in cold mammalian Ringers solution, removed from the rods, and weight was determined. The tissues were solubilized (Solvable, Perkin Elmer, Waltham, MA) at 55°C for four hours, scintillation fluid was added (Ultima Gold, Perkin Elmer, Waltham, MA), and disintegrations per minute were measured. (Tri-Carb 2900TR, Perkin Elmer, Waltham, MA). Calculated rates of glucose absorption were expressed as nmoles of D-glucose transported per minute per mg of tissue.

Glucose Tolerance Test

The ability for glucose clearance were determined at the end of the study. using a glucose tolerance test. Fasting Blood glucose levels were measured after a six hour fast. Glucose was administered at a concentration of 1g/kg of animal weight via an intraperitoneal injection. Blood samples were collected from the tail vein every 30 minutes for a 90-minute period. Glucose concentration was determined using a glucose meter (Onetouch Ultra 2 Meter).

Lymphoid Parameters

To determine Prednisolone efficacy, spleens were harvested and weighed. Splenocytes were isolated and counted using a hemacytometer and trypan blue was used for dead cell exclusion.

(Continued on next page)

**Table 1. Composition of Experimental Diets.** HFL n-6 with 45% kcal/g from lard; HFO n-3 with 45% kcals/g from menhaden oil. (A) ingredients in HFL-n-6 and HFO-n-3 diets; (B) fatty acid composition of HFL n-6 and HFO n-3 diets.

(A) Ingredients | HFL n-6 | HFO n-3 |
--- | --- | --- |
Casein, 80 Mesh | 200 | 200 |
L-Cystine | 12 | 12 |
Sucrose | 172.8 | 172.8 |

(B) Ingredients (g) | HFL n-6 | HFO n-3 |
--- | --- | --- |
Lard | 177.5 | 0 |
Menhaden Oil, ARBP-F | 0 | 177.5 |
Soybean Oil | 25 | 25 |
Total | 202.5 | 202.5 |
C14, Myristic | 2.1 | 14.0 |
C16:1, Palmitoleic | 2.5 | 17.7 |
C18, Stearic | 19.8 | 6.6 |
C18:2, Linoleic, n3 | 56.2 | 16.1 |
C18:3, Linolenic, n3 | 4.2 | 4.3 |
C18:4, Stearidonic, n3 | 0 | 6.0 |
C20, Arachidic | 0.4 | 0.3 |
C20:4, Arachidonic, n6 | 0.5 | 0 |
C20:4, n3 | 0 | 3.1 |
C22:5, Docosapentaenoic, n3 | 0.2 | 4.1 |
C22:5, n6 | 0 | 0.6 |
C22:6, Docosahexaenoic, n3 | 0 | 29.0 |
Total | 190.7 | 189.6 |
Saturated (g) | 60.2 | 59.8 |
Saturated (%) | 31.6 | 31.5 |
Monounsaturated (g) | 67.7 | 41.3 |
Monounsaturated (%) | 35.5 | 21.8 |
Polyunsaturated (g) | 62.8 | 88.5 |
Polyunsaturated (%) | 32.9 | 46.7 |
n6 (g) | 57.0 | 17.9 |
n3 (g) | 4.4 | 66.6 |
n6/n3 ratio | 13.1 | 0.3 |

*BHQ: tertbutylhydroquinone*
Liver enzymes were measured using an Alanine Transaminase (ALT) Activity Assay kit (Abcam ab105134). Activity was determined according to manufacturer's instructions. Samples were diluted 1:5 in the assay buffer and colorimetric change was determined after 60-minute incubation and read at 570nm using a microplate reader (Synergy 2, BioTek).

Statistical Analyses
All data are presented as means ± SEMs. Statistical analyses were performed with GraphPad Prism version 7 software, and statistical significance was established at P < 0.05. Significance between two experimental groups was determined by using the Mann-Whitney test due to small sample size.

Results
Diet containing fat from menhaden oil reduced body mass gain and adiposity independent of glucocorticoid treatment. Mice given a diet containing 45% fat from fish oil (Menhaden oil; major fatty acids EPA and DHA) had reduced body mass gain over a 28-day period as compared with mice fed an isocaloric diet containing 45% fat from lard, resulting in a significantly reduced body mass at the end of the experimental period (Figures 1 and 2). The GC treatment (Prednisolone) did not significantly increase body mass gain, regardless of diet treatment.

Mice consuming the diet containing lard averaged an 18% increase in food consumed in the presence of the GCs as compared with the fish oil diet (Figure 3). Weight gained per gram of food consumed demonstrated that mice on a fish oil diet gained 30% less weight (without GCs) and 32% less weight (with GCs) compared to mice consuming the lard diet (Figure 4).

Glucocorticoid Treatment Reduced Spleen Size Independent of Diet
GCs have become part of the standard treatment for childhood ALL due to its cytokytic effects on thymocytes. Concomitantly with this decrease in immune cells is a reduction in the size of immune organs such as spleen (9). To confirm GC efficacy, spleen weight and splenocyte number were determined. There was a reduction in spleen size compared to normal spleen sizes for the chow diet (22% reduction), lard diet (24% reduction) and fish oil diet (15% reduction; Figure 5). This was also true for splenocyte number, although not significant (Figure 6). Interestingly, there was a significant difference in spleen sizes with the fish oil diet as compared with the chow or lard diet, where the HFO n-3 diets demonstrated larger spleen sizes, while the HFL n-6 diet showed increased cell death independent of GCs.

No Difference in Intestinal Glucose Uptake was Observed
One successful experiment using the sleeve method to measure intestinal glucose absorption showed no difference in intestinal glucose uptake between mice on the lard and fish oil diet (data not shown). However, the small intestine lengths of mice fed the HFL n-6 diet were significantly shorter than those of the chow and HFO n-3 groups (Figure 7).

Liver Histology
Figure 8A demonstrates a significant decrease in liver weight with GC treatment when the animals were on a standard chow diet (P = 0.05). No differences were observed in liver weight between untreated chow diet and the two high fat diets. Despite the fact that mice on the high fat diets have similar liver weight independent of GC treatment, there is a dramatic fat deposition in the liver tissue of mice on the lard diet by histologic examination. (Hematoxylin-eosin staining; Figure 8B.) This fat accumulation is completely absent among mice on the fish oil diet.

Plasma Analysis of Liver Parameters was Not Significant
Plasma Alanine Aminotransferase (ALT) activity was higher in the GC groups for both the HFL n-6 and HFO n-3 diets with a high degree of variability. However, the differences in plasma ALT activity were not significant between groups. (Figure 9).

Plasma Blood Glucose Levels were Higher in HFL n-6 Diet Mice than HFO n-3 Diet Mice. The impact of 40 mg/m2/day of GC administration on glucose tolerance in correlation with the two different HFDs was assessed with an intraperitoneal glucose tolerance test (GTT). Our results show that an HFL n-6 diet caused a greater increase in blood glucose levels as compared with the mice on an HFO n-3 diet. (Figure 10 A and B.) The blood glucose levels of the HFL n-6 group with GC administration was found to be higher compared with the HFL n-6 groups without GCs. Figures 10 A and B demonstrate that the HFO n-3 diets showed similar blood glucose uptake throughout the course of the GTT regardless of the presence or absence of a GC. Glucose uptake of the HFO n-3 diet group had similar levels to the chow diet group (data not shown).

Discussion
Patients undergoing ALL treatment (which includes high dose GCs) have an increased risk of developing metabolic syndrome later in life (16, 58, 59). Pediatric survivors typically demonstrate signs of obesity, insulin resistance, dyslipidemia, and hypertension while in remission from ALL, indicating that GCs may have long-term side effects after therapy (16, 59). These effects may be due to the main role of GCs in decreasing inflammation by suppressing the immune system and controlling energy metabolism, especially hepatic energy metabolism.

GCs have a role in ALL treatment due to their anti-inflammatory and cytolytic effects (10). As GCs reduce the number of immune cells, there is a concomitant reduction in the mass of immune organs. The significant decrease in spleen weights and spleen cells confirmed that GCs had a similar effect on immune cells and associated organs during the 28-day treatment.

Due to the potential influence of dietary intervention on human health, we focused our efforts on the effects of a diet high in n-6 fatty acids from lard compared with a diet high in n-3 fatty acids from fish oil. Our results mirrored data from a previous study reporting that animals consuming a diet high in n-3 fatty acids had less total adipose tissue and intra-abdominal fat while also experiencing reduced insulin resistance than animals consuming a high fat lard diet high in n-6 fatty acids (60). The mice receiving the HFL n-6 diet in the present study experienced greater...
In the presence of GC there is not a significant difference in food consumption, but the consumption of HFL n-6 diet did lead to a significant difference. (P=0.05, n=7-9 mice per group).

Weight gained did not differ significantly between the Chow and the HFO n-3 diets, but there is a significant difference in the amount of weight gained per volume of food consumed (p=0.02, n=7-9 mice per group) in mice on HFL n-6 or HFO n-3 diets with and without GCs.

**Figure 1. Weight Gain over 28 days.** Weight (grams) was monitored weekly over a 28-day period that mice were treated with GCs while on a Chow, HFL n-6, and HFO n-3 diet (n= 5-6 mice for each group).

**Figure 3. Total Food Consumption.** Total food consumption was determined weekly. In the presence of GC there is not a significant difference in food consumption, but the consumption of HFL n-6 diet did lead to a significant difference. (P=0.05, n=7-9 mice per group).

**Figure 2. Total Weight Gain.** Total weight gained was determined at the end of 28 days for each group. Total weight gained did not differ significantly between the Chow and the HFO n-3 diet, but there is a significant increase in total weight gain between the HFL n-6 diet and the HFO n-3 diet (P=0.01 in the absence of GC and P=0.03, in the presence GC) (n=6-9 mice per group).

**Figure 4. Weight Gained per Gram.** GC treatment did not increase the weight gained per volume of food. There is a significant difference in the amount of weight gained per volume of food consumed (p=0.02, n=7-9 mice per group) in mice on HFL n-6 or HFO n-3 diets with and without GCs.
acids from lard induce the expression of transcription factors that n-3 fatty acids in fish oil increase fatty acid oxidation while the n-6 fatty acids be protective against adipose tissue gain. It is now well established that published work demonstrating that a diet high in EPA and DHA intake than the mice on the HFO n-3 diet. This is consistent with overall weight gain and weight gain per gram of food, and greater food intake than the mice on the HFO n-3 diet. This is consistent with published work demonstrating that a diet high in EPA and DHA upregulates fatty acid oxidation, suggesting that the n-3 fatty acids may be protective against adipose tissue gain. It is now well established that n-3 fatty acids in fish oil increase fatty acid oxidation while the n-6 fatty acids from lard induce the expression of transcription factors that regulate lipid homeostasis such as Sterol Regulatory Element Binding Protein (SREBP), which promotes fatty acid synthesis (61). Relative weight gained by the mice provides evidence that the type of diet consumed has a greater effect on weight gain than the use of GCs.

Long-term use of GCs can cause NAFLD due to alterations in hepatic metabolism. NAFLD results from a combination of insulin resistance and an increase in the uptake of free fatty acids and de novo liponeogeneisis in the hepatocytes leading to an accumulation of stored fat in the liver (6). Although there were no histological differences in fatty deposition in the liver between the HFL n-6 with and without GCs, ALT enzymes were increased in the HFD groups with GCs, albeit not significantly. This may indicate that the GCs could be causing liver damage, however, liver damage indicated by elevated plasma ALT levels and fibrosis typically does not develop with less than four weeks of high fat feeding (62-64). A longer time on the HFD may be needed to see more true liver damage as indicated by increased ALT enzymes. The histological results of the livers show that the HFL n-6 diet resulted in greater fat accumulation than the chow or HFO n-3 diets, which could further develop into more extensive liver damage with a longer study period on the HFD, as suggested by high ALT enzyme levels and liver fibrosis. Therefore, the HFO n-3 diet may be protective and decrease the risk of NAFLD. Similar to other findings where hyperglycemia was seen in an HFD in conjunction with GCs, the data from the GTTs throughout our study demonstrates that the HFL n-6 diet rapidly induced a type 2 diabetic phenotype after four weeks on the diet (17). This was characterized by glucose intolerance as measured by an intraperitoneal glucose tolerance test over 90 minutes. Due to the research that shows that insulin resistance could lead to NAFLD, a longer study period could show more data that demonstrates the development of NAFLD (65).

Fatty acids in the liver can alter glucose metabolism, therefore we evaluated possible alterations in intestinal uptake of glucose by the inverted sleeve method to determine if there is an alteration in glucose uptake in the presence of different dietary fatty acid compositions (66). Due to controversial research regarding the fluctuation of glucose
groups have similar glucose absorption rates, indicating that the number of transporters was most likely the same in the proximal areas of the intestines. However, differences in the intestinal lengths could possibly indicate that chow and HFO n-3 diet mice may have greater glucose uptake capacity than HFL n-6 diet mice. Further understanding of why a diet high in n-6 fatty acids could cause a decrease in intestinal size, and yet still advance to obesity and insulin resistance, will need to be rendered.

**Conclusion**

This study demonstrates that a high fat diet higher in n-6 fatty acids can lead to detrimental side effects, especially in combination with GC therapy. Here we show that a diet high in n-6 fatty acids increases total body and adipose tissue weight per volume of food consumed. In addition, the data shows that an HFL n-6 diet in the presence of 40 mg/m²/day prednisolone increases fatty liver development and insulin resistance. However, the replacement of an HFL n-6 diet with an HFO n-3 diet will reduce the metabolic disorder phenotypes, specifically hyperglycemia, obesity, and liver disease, to similar phenotypes of animals consuming a chow diet during GC treatment.

The results suggest that a diet high in n-3 fatty acids may be beneficial for pediatric ALL patients undergoing GC treatment by decreasing the risk of developing symptoms associated with metabolism after their treatment. RDNs can use this information, along with other evidence, to incorporate more n-3 into their patients’ diets to help decrease the risk of developing metabolic syndrome symptoms as well as alleviate current side effects of high dose GC therapy.

**References**


(Continued on next page)
Figure 10. Glucose Tolerance Test. (A) Blood glucose concentration (mg/dl) was measured over 90 minutes. (B) At 90 minutes after glucose (1g/kg) administration, glucose levels increased with the HFL n-6 diet and trended towards glucose intolerance (p=0.06) (n=3-5 mice per group)


Gastrostomy Tube Feeding Education and the Effect on Nutrition-Related Complications: Implications for the Oncology Population

By Mariah Long, MS, RD, LDN, Sharon Foley, PhD, RD, and Marisa Mozer, MS, RD, CSO, LDN, CNSC

Abstract
Enteral nutrition support using gastrostomy feeding tubes (G-tube) is indicated when patients are unable to meet nutritional needs orally. Complications may occur when patients are not properly educated on feeding tube management post-placement. The purpose of this study was to assess the frequency in which inadequate education was provided to patients after outpatient G-tube placement in a large urban academic medical center, and to improve the process to reduce nutrition-related side-effects. Outpatient G-tube education can vary between institutions, but collaboration among health professionals to standardize processes is essential for patient safety and satisfaction.

Between January 2015 and December 2018, a list of 52 medical records was retrieved after searching the electronic medical record by Current Procedures Terminology (CPT) codes for outpatient G-tube placement. Initial data collected to determine the extent of the problem revealed that only 86.5% of patients received education on care of their feeding tube, resulting in nutrition related complications necessitating emergency room visits and hospital readmissions.

Using an interdisciplinary approach, deficiencies in the process and role delineation amongst practitioners were identified. A work queue that automatically notifies the Registered Dietitian Nutritionist (RDN) of scheduled feeding tube placements was created, and a nursing competency checklist was developed. Upon implementing changes, results show improvement in educational provision by nurses, and 100% of patients were seen by an RDN post-tube placement.

Introduction
Patients with chronic dysphagia, head and neck cancer, neurological diseases, and abnormal gut function may not be able to meet their nutritional needs by oral intake alone (1). Poor oral intake increases the risk for malnutrition which further jeopardizes the patient’s health (2). Therefore, long-term enteral nutrition support by means of tube feeding may be warranted to provide adequate nutrition and hydration and to ensure the best quality of life possible (3). Although placement of a feeding tube is considered a minor procedure, lack of proper education and instruction on feeding tube management and administration can result in poor outcomes (4). Education should be provided to patients or caregivers in a timely manner to reduce risk for inadequate intake, dehydration, and admission or re-admission to the hospital. When a patient receives a feeding tube, it is the responsibility of the health care team to provide appropriate education on proper tube care and administration prior to discharge (1). However, the education provided to a patient after feeding tube placement is not always comprehensive or consistent (5).

Additional factors associated with poor quality education are lack of care coordination and time spent on the education. Ultimately, patient safety is jeopardized and avoidable financial losses to the health care system may occur (5). Thus, the study sought to investigate the frequency in which tube feeding education was provided shortly after outpatient placement, and to identify the outcomes associated with that education. Data gathered would be used to improve the feeding tube care and management education offered to patients and caregivers.

Methods
To develop a better understanding regarding the outpatient feeding tube placement process, a multi-disciplinary team consisting of an RDN, Nurse Coordinator (RN), and a physician (MD) responsible for managing a majority of the patients with G-tubes, created a flowchart to map the current process (see Figure 1). The team collaborated to discuss potential breakdowns in the process and identify areas to collect pre-measures. The team decided frequency of documented education and outcomes of inadequate education should be assessed as pre-measures.

In order to collect these pre-measures, a data request was sent to Information Services (IS) to obtain a list of patients who had received an outpatient G-tube placement using CPT codes (EGD: 43246, 43247, 49450, 49440) between January 2015 and December 2018. The list of patients was reviewed for having the G-tube placed as an outpatient procedure as eligibility criteria. Any individual who had a tube placed as an inpatient procedure or was admitted to the hospital for feeding access was excluded.

A review of the medical records was completed by the RDN to collect demographics; indication for tube placement; type of tube placed; health care professional who provided the education; the extent of information provided; hospital readmissions;
and emergency department visits. Statistical methods utilized for analysis included chi-square tests and frequency distributions. After collecting pre-measures, the interdisciplinary team met to discuss potential solutions for improving the process.

**Results**

In the original data set provided by Interventional Radiology on patients who had the CPT codes identified, a total of 52 out of 325 patients met eligibility criteria and were included in the medical record review for pre-measures. Patient demographics and pre-operative related variables are shown in Table 1. The majority of individuals were male (71.2%) with a normal BMI (44.2%). Of the 52 feeding tubes placed, most (98.1%) were placed by the Interventional Radiology department and the majority (53.8%) of the tubes were G-tubes. Head and neck cancer was the most frequent indication for a feeding tube placement (90.4%).

Readmission to the hospital occurred in half of the patients (n=26) and of these readmissions, 13 (50%) were documented as related to nutrition complications (nausea, vomiting, abdominal pain, or any issues with G-tube). Approximately half (n=29), of the patients presented to the emergency department (ED) and of ED visits, 17 (58.6%) were documented as related to nutrition complications (Table 2). A majority of the education on G-tube care was documented by RDNs (86.5%), while minimal documentation of education was provided by extended recovery nurses (13.5%) and no education was documented by the Interventional Radiology department.

Education regarding tube feeding and flushes was documented approximately 85% of the time, however documentation including avoidance of complications or administration of medications through the tube was recorded only twice (Table 3).

During multi-disciplinary collaboration, two opportunities to improve the process were identified and solutions were constructed. The first involved creating an electronic work queue to automatically notify the RDN of a scheduled outpatient G-tube placement to facilitate nutrition services. Second, a nursing competency was developed to ensure that extended recovery nurses were providing consistent, quality education to patients regarding feeding tube administration and care following tube placement.

Each extended recovery nurse was in-serviced by a dietitian to provide training and confirm understanding regarding the competency. The nursing competency comprised of instruction to page the RDN; a checklist of home care education for review with the patient, such as how to empty the drain, vent the tube, flush the tube, administer medications, and properly dress the site; when to call the doctor; equipment list to give the patient; various handouts on feeding administration methods created by the Food and Nutrition department. Extended recovery nurses were required to document education provided in the electronic medical record.

The changes were implemented (Figure 2). A total of eight patients received a G-tube placement after the new process was
implemented, and thus, were included in the post-measures. Of note, it was determined that the Interventional Radiology department would not be responsible for educational provision due to the patient being transported directly back to extended recovery following G-tube placement. Additionally, post-measures related to complications were not collected due to time constraints. The largest improvement in documentation by health professionals was from the extended recovery nurses with 270% improvement (p=.031). Since G-tube placement procedures are not a high-volume outpatient procedure in this institution, the number of post measures obtained were small in comparison to pre-measures at the end of the study period (Table 3). This accounts in part, for the large percent improvement for extended recovery nursing. In addition, 100% of patients were seen by an RDN, indicating a 15.6% improvement, although this was not statistically significant. Post-measures will continue to be collected and analyzed as more G-tubes are placed in the outpatient setting.

**Discussion**
Patients need to be properly educated on how to manage their newly placed G-tubes, or complications may develop. Recovery nurses who support patients with newly placed tubes need to be competent to do so, and a referral for outpatient placement should trigger the RDNs involvement in the patient’s care. It can be inferred that frequent, unplanned return visits to this health care institution may have in part related to the lack of provisional education the patients received post-operatively before release from the hospital.

Various other institutions have also identified complications associated with long term enteral nutrition support and have developed quality improvement initiatives in attempt to decrease and prevent tube feeding complications. Hall et. al. established and implemented an enteral nutrition support clinic (NSC) in which complications and associated costs to the institution were substantially reduced when an RDN or skilled nurse provided education to all surgical and oncology patients after G-tube placement (5). Halstead, implemented a protocol designed to

---

### Table 1. Pre-measure characteristics of patients who received outpatient feeding tubes upon EMR review (n=52)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n=52 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean SD</td>
<td>62 ± 14.2</td>
</tr>
<tr>
<td>Range</td>
<td>27 - 85</td>
</tr>
<tr>
<td>Diagnostic Reason</td>
<td></td>
</tr>
<tr>
<td>Head and Neck cancer</td>
<td>47 (90.4)</td>
</tr>
<tr>
<td>Neurological Defect</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Dept. Placing Tube</td>
<td></td>
</tr>
<tr>
<td>Interventional Radiology</td>
<td>51 (98.1)</td>
</tr>
<tr>
<td>Surgery</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Type of Tube</td>
<td></td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>28 (53.8)</td>
</tr>
<tr>
<td>Percutaneous Endoscopic</td>
<td>24 (46.2)</td>
</tr>
</tbody>
</table>

---

### Table 2. Pre-measure complications related to outpatient feeding tube placement upon Electronic Medical Record review (n=52)

<table>
<thead>
<tr>
<th>Complication Related Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department visits</td>
<td>29 (55.8)</td>
</tr>
<tr>
<td>ED visit related to nutrition*</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>Hospital Readmission</td>
<td>26 (50)</td>
</tr>
<tr>
<td>Hospital Readmission related to nutrition*</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Pain at G-tube site</td>
<td>17 (32.7)</td>
</tr>
<tr>
<td>G-tube replacement</td>
<td>15 (28.8)</td>
</tr>
<tr>
<td>Infection within 90 days of G-tube placement</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

*Nutrition related complications include documentation of nausea, vomiting, abdominal pain, or any issues with G-tube

### Table 3. Comparison of pre-measures vs post-measures of documented education provided to patients who received outpatient feeding tubes upon EMR review

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-measures n=52 (%)</th>
<th>Post-measures n=8 (%)</th>
<th>% improved</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education documented by Registered Dietitian</td>
<td>45 (86.5)</td>
<td>8 (100)</td>
<td>15.6</td>
<td>.578</td>
</tr>
<tr>
<td>Education documented by Extended Recovery Nurse</td>
<td>7 (13.5)</td>
<td>4 (50)</td>
<td>270</td>
<td>.031*</td>
</tr>
<tr>
<td>Education documented by Intervention Radiology</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Documentation included tube feeding and flushes</td>
<td>44 (84.6)</td>
<td>8 (100)</td>
<td>18.2</td>
<td>.582</td>
</tr>
<tr>
<td>Documentation included G-tube site care</td>
<td>22 (42.3)</td>
<td>4 (50)</td>
<td>18.2</td>
<td>.717</td>
</tr>
<tr>
<td>Documentation included avoidance of complications</td>
<td>2 (3.8)</td>
<td>2 (25)</td>
<td>558</td>
<td>.082</td>
</tr>
<tr>
<td>Documentation included administration of meds through tube</td>
<td>2 (3.8)</td>
<td>1 (12.5)</td>
<td>229</td>
<td>.354</td>
</tr>
</tbody>
</table>

*Statistically significant results (p < .05)
One of the limitations of this study was the small number of patients included in the post-measure sample, thus possibly inflating the improvements. Although a majority of the improvements were not statistically significant, all measures were trending upward, indicating initial improvements. Additionally, due to the newly improved process, 90-day complication-related variables were not assessed.

Outpatient placement of G-tubes in a large medical center involves a variety of individuals working across many departments, often in less than full-time capacities. This can contribute to substantial breakdowns in communication, something that needs to be recognized so that sustainability of new processes can remain intact.

**Implications, Conclusions and Applications to Oncology Dietitians**

The results of our study are extremely relevant to oncology RDNs since head and neck cancer was the most common reason (>90%) for G-tube placement. Improper education can have significant nutritional consequences. An effective process for the care of tube fed patients will be different amongst institutions and must be tailored to fit each facility's needs while also efficiently utilizing available resources. Initial results from this study indicated that developing a standardized process was successful in improving the care provided to recipients of a G-tube placement. It is anticipated that a standardized process for providing education to patients with newly inserted G-tubes may reduce nutrition-related complications, unplanned emergency room visits, and hospital readmission. This may ultimately improve patient experience. Efforts to sustain any new process should be included as part of all process improvement initiatives.

**References**

Pledge of Professional Civility and DPG/MIG Online Netiquette Guidelines

ON DPG members are encouraged to review the Pledge of Professional Civility and DPG/MIG Netiquette Guidelines as the 2019-2020 membership year begins.

Consider participating in the Pledge of Professional Civility, a voluntary, public commitment to the civil treatment of professional peers, including those with whom we may not agree on all issues. The pledge asks dietitians to vow to: demonstrate respect to colleagues and others; support productive dialogue and positive engagement; discourage the public criticism of colleagues; and model professional conduct in all public communications and actions. Learn more at FoodandNutrition.org/professionalcivility.

On the same note, the DPG/MIG Netiquette Guidelines remind us to engage within the bounds of professionalism, courtesy and respect when networking and sharing information on the electronic mailing list (EML).

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Any breach of these Guidelines will be grounds for removal from the mailing lists.

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2. The following topics and subject matter are unacceptable, must not appear in messages on the lists, and may in some instances constitute violations of the Academy’s Code of Ethics:
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   D. Inappropriate comments or references with respect to race, gender, religion, sexual orientation or ethnic background;
   E. Religious solicitations;
   F. Profanity;
   G. Illegal or unethical practices; or
   H. Advertising, promotions, or endorsements of commercial products or services.

3. A participant must not send or upload material to the list that is or may be protected by copyright unless written permission from the copyright owner has been obtained. Participants may, however, provide a brief summary or review of a copyrighted article and/or, in most cases, the URL where the material may be found.

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   • The initial decision to act upon any violations, or any complaints about list participants’ conduct, will depend upon the severity of the violation and may be made by the owner of the list or Academy staff.
• Where action beyond a letter of warning to the violator is recommended, such as removal of the participant from the list or referral to the Ethics Committee, the decision will be referred to the Executive Committee of the Board of Directors for consideration and action.

Netiquette
The following are additional points of conduct and protocol that will improve the experience of all participants in the lists. Adherence to these suggested practices is strongly encouraged.

1. Unless responding to a message in which the author has specifically asked for private replies, a participant should send any reply to the list, so the response is shared. Addressing a copy to the sender is usually not required but is acceptable.

2. A participant should include a descriptive subject line in each posting. If using the digest mode and wishing to respond to a post, the participant should be sure to use a subject header that matches the original post. A participant should sign every message with the name, organization, phone number and e-mail address of the sender. Promotional tag lines should be kept to a minimum.

3. Where it is appropriate to reply only to the original sender, as with “me too” or “I agree” messages, the participant should refrain from replying to the entire list unless the message will be of interest to the majority of contributors to the ongoing discussion.

4. The language of a written message can be ambiguous and subject to different interpretations. Each participant should carefully consider the phrasing and choice of language in his or her message to ensure that the intended message is conveyed. Although the list is private and confidential, all participants should also consider the effect of their message if publicly distributed or read by a third party.

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