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OBESITY

ABSTRACT & COMMENTARY

An 'Ounce of Prevention' May Keep Off Pounds

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: Specific self-regulation techniques are shown to be effective at preventing weight gain in young adults.

SOURCE: Wing R, Tate DF, Espeland MA, et al. Innovative self-regulation strategies to reduce weight gain in young adults: The Study of Novel Approaches to Weight Gain Prevention (SNAP) randomized clinical trial. *JAMA Intern Med* 2016;176:755-762.

Although unhealthy weight gain may occur throughout one's lifespan, the greatest incidence of weight gain happens during young adulthood, with an average weight gain of 1 kg/year.[1,2] The Study of Novel Approaches to Weight Gain Prevention (SNAP), funded by The National Heart, Lung, and Blood Institute, was designed to investigate the effectiveness of new approaches to weight gain prevention during this high-risk period.[3] In explaining the thinking behind the study design, Wing et al noted that self-regulation has been a proven successful strategy when looking at prevention of weight regain after weight loss in adults. It was not a long stretch to hypothesize that these same techniques may help prevent primary weight gain in young adults.

Self-regulation is a core intervention in this study but not necessarily a commonly understood concept. The behavioral model of self-regulation developed in the late 1900s by Howard Leventhal and colleagues and since refined is based on a feedback loop. Components include identification of a specific goal (self-monitoring), a concrete method to measure progress or deviation from the goal (self-evaluation), and corrective responses.[4]

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Summary Points

- This is a longitudinal study looking at prevention of weight gain in young adults.
- The authors randomly sorted 599 participants into three groups: control; self-regulation and small daily changes in diet and exercise; and self-regulation and large, periodic changes in diet and exercise.
- Self-regulation included daily self-weighing, submission of results via email or text, and receipt of specific recommendations to change eating patterns or exercise with variation in weight.
- "Small-change" group focused on diet and exercise changes of about 100 kcal/day while "large-change" group incorporated a robust initial weight loss and a more substantial increase in activity level.
- Results after three years showed the "large-change" group had the most success in reducing mean weight gain (vs. control and vs. small-change group) and that both large- and small-change self-regulation groups were more effective at reducing mean weight gain than control.

The SNAP study was designed as a randomized, clinical trial with three arms: a control group and two distinct active intervention groups with specific strategies to monitor and control weight gain. Each of the active groups employed a self-monitoring technique (weighing) but then were instructed in different self-regulation methods: one with small, daily changes known as the "small-change group" and the other with more substantial intermittent interventions known as the "large-change" group.

Adults 18-35 years of age were recruited via mass mailing and emails targeting persons who were concerned about the prospect of weight gain. Among other criteria for inclusion in the study was a body mass index (BMI) between 21-30.9 kg/m^2; at baseline just over half of the participants had BMI > 25.0 kg/m^2, putting them in the "overweight' category.

Although the aim was to include at least 25% males in the study, final numbers fell a bit short (22%). Twenty-seven percent of participants self-identified as a member of a minority group. Retention was notably high in all groups, with more than 80% of all subjects completing at least two full study years.

Participants randomized into the control group attended one educational meeting regarding weight maintenance. Those in either of the other two study arms had more active interventions. Both the small- and large-change groups began with 10 in-person meetings with "interventionists," all of whom had master's level education in nutrition, psychology, or exercise physiology. These meetings occurred face-to-face over four months, with follow-up meetings online. Participants were introduced to the concept of self-regulation with an identified goal of keeping at or below baseline weight. All were encouraged to weigh themselves daily and submit results electronically. Monthly feedback was provided via email with either reinforcement or corrective strategies and/or an option for more personalized assistance if weight had increased above baseline.

The corrective strategies differed between the two active intervention groups. Those in the small-change group were given pedometers and asked to add about 2,000 steps each day, reduce portion sizes, cut down on sugar-filled drinks, and make small incremental changes in physical activity. If weight started to rise above baseline, they were encouraged to implement other small, daily changes.

Those randomized into the large-change

Table 1: Mean Weight Changes				
	Mean weight change over mean of 3 years	Standard error	*P* value relative to control	*P* value relative to small-change group
Control	0.26 kg	0.22		
Small-change	-0.56 kg	0.22	0.02	
Large-change	-2.37 kg	0.22	< 0.001	< 0.001

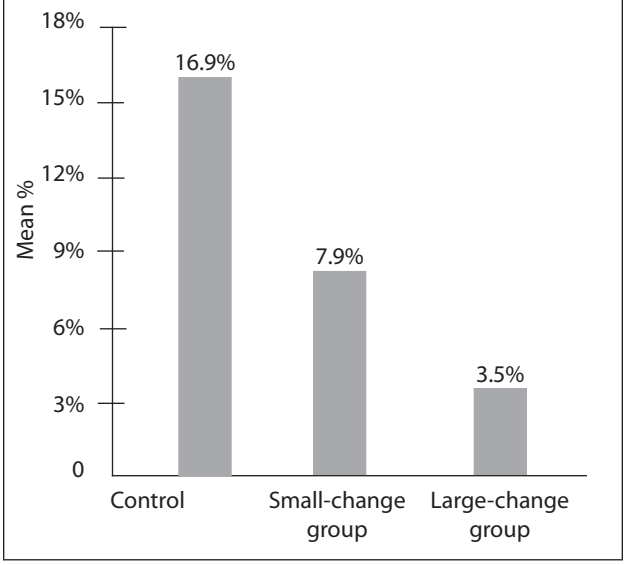
group focused more on large, periodic changes. During the first four months of the study, the authors introduced a goal of creating a weight loss "buffer zone" to protect against the weight gain expected with aging. To achieve this, calorie restriction (500-1,000 kcal from baseline daily) was promoted for the first two months and was prescribed again if weight exceeded baseline later in the study. Moderate-intensity activity to 250 minutes/week was encouraged throughout the entire study.

Assessments were completed at baseline, month 4, month 12, month 24, and, for a portion of the participants (depending on timing of entrance), months 36 and 48.

The primary outcome studied was mean weight change. (*See Table 1.*)

Secondary outcomes were a weight gain of 0.45 kg or more and development of obesity. Although the large-change group was more successful at mean weight loss than either the control or small-change group, both the small- and large-change group participants displayed a reduced incidence of obesity of nearly 50% relative to control. (*See Figure 1.*)

Figure 1: Development of Obesity During Follow-up (%)



■ COMMENTARY

In a recent series of articles, *The New York Times* asked: Why Do Obese Patients Get Worse Care? Their answer: Many Doctors Don't See Past the Fat.[5] Although *The New York Times* may have a valid point, in its exploration of the medical difficulty of treatment for obesity they left out the subject of prevention. This is not a surprise, as the medical field has widely neglected this aspect of obesity treatment as well.

In 2008, the Council of the Obesity Society published a white paper regarding obesity as a disease.[6] The discussion in the paper concluded: "It seems that considering obesity a disease is likely to have far more positive than negative consequences and benefit the greater good by soliciting more resources into **research, prevention, and treatment of obesity**; by encouraging more high-quality caring professionals to view treating the obese patient as a vocation worthy of effort and respect; and by reducing the stigma and discrimination heaped upon many obese persons."

SNAP was designed to look primarily at how to prevent weight gain and, as such, represents a valuable contribution to our knowledge of the field of obesity treatment. Recall that just over 50% of all participants in this study had a BMI > 25 kg/m^2. BMI is a screening tool that may be used to detect obesity and is determined by dividing total body weight in kilograms by height squared in meters.[7] Results of BMI are placed into general categories (some of which may be further subdivided) as follow:

Underweight: < 18.5 kg/m^2
Normal weight: 18.5-24.9 kg/m^2
Overweight: 25-29.9 kg/m^2
Obesity: ≥ 30 kg/m^2

One of the valuable contributions of this study is that both normal weight and overweight participants were involved, making it truly a

prevention rather than a weight loss study. Given the rising medical costs associated with treatment of the obese and growing concerns about an epidemic of obesity,[8] identifying interventions to attack obesity in the arena of prevention (as we do with other chronic disorders) seems a necessary and crucial step in tackling this condition.

Self-monitoring or self-weighing to avoid weight gain is a familiar concept to most adults. Application of specific self-regulation strategies to prevent weight gain is a more nuanced concept akin to the more familiar role of self-regulation in medical disorders, such as diabetes and asthma.

Self-regulation depends on identification and internalization of a goal. In this study, all participants were recruited through mailings looking for young adults with an interest in weight control. All subjects entered the study with a shared goal. This is useful for implementation of self-regulation, but certainly may have led to selection bias. Replicating this study with a more randomized group and with more diverse recruitment tools is essential before applying any conclusions from the results to the population as a whole.

[There is much to be gained and little risk in encouraging patients to adopt a habit of self-monitoring weight and to develop compensatory strategies when needed; these very well may be valuable tools in preventing obesity and may convey lifelong health benefits.]

Bridging the gap from an interesting study to clinical implementation often is challenging. In this case, it is pertinent to wonder if a practitioner has enough solid evidence from this study to encourage young, healthy adults to adopt self-regulation of weight strategies; if so, what would this look like in a clinical setting? The evidence points to the efficacy of self-weighing only when linked with the rest of the feedback loop (reporting of weight and corrective action or reinforcement of success) — there is no evidence or implication from this study that self-weighing divorced from the remainder of the interventions is helpful or if any one step is critical for weight gain prevention. Clearly, this is an area for further research.

Further studies to clarify the sustainability of the interventions over time also are needed. Although a goal of keeping off pounds during young adulthood is significant, continuing this trend throughout a lifetime is the ultimate goal when looking at obesity risks and health.

Likewise, it would be useful to know if any of the participants moved from the overweight to normal weight category (as determined by BMI) during the study period. These statistics were not examined in this paper, but may be helpful to obtain in future investigations to more fully understand the effect of interventions on weight control.

For now, a practitioner is on firm ground in reminding young, healthy patients about the potential for weight gain in early adulthood. There is much to be gained and little risk in encouraging patients to adopt a habit of self-monitoring weight and to develop compensatory strategies when needed; these very well may be valuable tools in preventing obesity and may convey lifelong health benefits. Although this study suggests a role for self-regulation in prevention of weight gain, future studies looking closely at each element of intervention are necessary to give patients definitive answers and strategies to combat weight gain associated with aging. ■

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ABSTRACT & COMMENTARY

Soy Isoflavones on Metabolic Markers in Women with Polycystic Ovary Syndrome

By Priscilla Abercrombie, RN, NP, PhD, AHN-BC

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Dr. Abercrombie reports no financial relationships relevant to this field of study.

SYNOPSIS: This 12-week randomized, double-blind, placebo-controlled trial found that soy isoflavones affected some metabolic parameters but not others in women with polycystic ovary syndrome.
SOURCE: Jamilian M, Asemi Z. The effects of soy isoflavones on metabolic status of patients with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2016;101:3386-3394.

The most common endocrine disorder among reproductive age women is polycystic ovary syndrome (PCOS).[1] Prevalence is 6-10%, depending on the diagnostic criteria utilized.[2] Consensus guidelines developed by the American Association of Clinical Endocrinologists and the Androgen Excess and PCOS Society[1] state the diagnosis of PCOS is made by the existence of two of the following: chronic anovulation, hyperandrogenism (clinical and biological), and polycystic ovaries. These criteria are consistent with the Rotterdam Criteria developed in 2003.[3] All women with PCOS are at increased risk for metabolic syndrome and should be evaluated for impaired glucose intolerance, hypertension, and lipid abnormalities. In addition, women with PCOS are at an increased risk for infertility, endometrial hyperplasia, and gestational diabetes. Goals of treatment vary according to symptomatology, metabolic risk factors, and desire for pregnancy. Typical treatments emphasize weight loss and employ the use of pharmaceuticals such as metformin, combined oral contraceptives, and spironolactone.

The role of adipose tissue and chronic inflammation in the pathophysiology of PCOS is a burgeoning area of research.[4] Current investigations focus on the link between the development of metabolic, endocrine, and reproductive dysfunctions of PCOS and adipose tissue dysfunction and chronic low-grade inflammation.[5] Women with PCOS frequently suffer from abdominal adiposity. Adipose tissue is involved in the release of inflammatory mediators such as cytokines, acute phase proteins, and adipokines that may contribute to insulin resistance and cardiovascular risk factors.

Soy typically contains three isoflavones: genistein, daidzein, and glycitein. Soy isoflavones are being studied for their role as anticancer, antioxidant, and anti-inflammatory agents in the context of metabolic disorders.[6] A recent meta-analysis of randomized, clinical trials suggested that soy improves lipid profiles, especially among those who are hypercholesteremic, but it is more beneficial when eaten as a whole food vs. an isoflavone supplement.[7] Another meta-analysis found that soy improved glucose metabolism in postmenopausal women.[8] These meta-analyses suggest that soy may have a role in improving lipids and glucose metabolism in some populations.

The purpose of the study by Jamilian and Asemi was to determine if supplementation with soy isoflavones had an effect on metabolic status of women with PCOS. Seventy women with PCOS and between ages 18-40 years were recruited from a clinic in Iran during a three-month period

Summary Points

- The investigators undertook a rigorously designed study to understand the impact of soy isoflavones on metabolic status in women with polycystic ovary syndrome (PCOS).
- Seventy women with PCOS were randomized to either receive 50 mg/d of soy isoflavones containing 37.5 mg genistein, 10 mg daidzein, and 2.5 mg glycitein or placebo for 12 weeks.
- Few conclusions can be drawn from this study because the results were mixed for each of the aspects of PCOS studied: metabolic, hormonal, and inflammatory.

ending in February 2016. Participants met the Rotterdam criteria for PCOS. Pregnant women and those with elevated prolactin, thyroid disorder, endocrine diseases including diabetes or impaired glucose tolerance, and gastrointestinal problems were excluded. Participants were matched for age, phenotypes of PCOS, and body mass index (BMI), and then were randomly assigned to receive either soy isoflavone supplements (n = 35) or placebo (n = 35) for 12 weeks. A power analysis determined an adequate sample size of 30 in each group, allowing for five dropouts in each group with testosterone as the primary outcome variable. Computer-generated random numbers were used to assign participants to groups. Both researchers and participants were blinded to randomization. Participants were advised not to change their physical activity or take any nutritional supplements during the trial. All participants completed three-day food records and physical activity records at baseline, three, six, and nine weeks and the end of the trial. Macronutrient and micronutrient intakes were analyzed with nutrition software. Physical activity was determined by metabolic equivalents (METs) in hours per day. Anthropometric measurements were taken and included BMI, waist circumference, and hip circumference. Clinical assessments included documenting hirsutism, acne, and alopecia using a scoring system.

Primary outcomes were markers of insulin resistance and androgens. Secondary outcomes were lipid profiles and biomarkers of inflammation and oxidative stress. The following biochemical assessment was obtained from fasting blood samples at the beginning and end of the study: serum insulin, homeostasis model of assessment-insulin resistance (HOMA-IR), homeostasis model of assessment ß-cell (HOMA-B), quantitative insulin sensitivity check index (QUICKI), total testosterone (T), SHBG, free T, DHEA, free androgen index (FAI), fasting plasma glucose, serum triglycerides, very low-density lipoprotein (VLDL), total LDL, high-density lipoprotein (HDL), high sensitivity C-reactive protein (hs-CRP), nitric oxide (NO), total antioxidant capacity (TAC), total glutathione (GSH), and malondialdehyde (MDA). Detailed testing parameters and types of testing kits can be found in the article.

The intervention group received 50 mg/d of soy isoflavones containing 37.5 mg genistein, 10 mg daidzein, and 2.5 mg glycitein for 12 weeks based on a previous study with PCOS patients. This dosage is equivalent to consuming 500 mL of soy milk daily or two servings of soy. Placebo capsules were of similar shape and size. Supplements were distributed every four weeks and included an extra three-day supply to last until the next scheduled visit. Participants were instructed to return unused pills at each two-week visit. All participants received reminders on their cell phones daily to increase compliance.

All statistical methods employed to evaluate the study appear to be appropriate for the type of variables studied.

All 70 participants completed the trial with a > 90% compliance rate of capsules taken. No side effects were reported. There were no significant differences in anthropometric measurements, METs, or nutrition intake from baseline to the end of the trial between the two groups.

The results are displayed in Table 1. Alopecia significantly decreased in the soy supplement group (31.6 vs. 4.3%; $P = 0.01$) and the modified Ferriman-Gallwey (mFG) score for hirsutism significantly improved. Neither group had a change in acne. Serum levels of insulin, HOMA-IR, and HOMA-B decreased, and QUICKI increased. There were significant reductions in total T, FAI, mFG scores, triglycerides, and VLDL compared to the placebo group. In addition, there were significant increases in SHBG and plasma GSH and a decrease in MDA in the treatment group. There was no significant effect of the intervention on other lipids or inflammatory and oxidative stress markers. In summary, there were some changes in metabolic and hormonal biomarkers but no changes in most markers of inflammation or oxidative stress.

■ COMMENTARY

These researchers attempted to investigate the effect of a soy isoflavone supplement on multiple aspects (metabolic, hormonal, inflammatory) of a complex syndrome called PCOS. This small study had a rigorous double-blind, randomized, placebo-controlled design but there are a few methodological issues that could have affected the study results. Although the participants were advised not to change their physical activity or take nutritional supplements, soy intake was not assessed or monitored in the study.

Conditions such as impaired glucose tolerance and diabetes were in the exclusion criteria but hyperlipidemia was not. Medication use also was not discussed, but oral contraceptives frequently used to treat PCOS as well as other medications could affect biomarkers under study. In addition, the use of complementary approaches to health, such as acupuncture or Ayurveda, could affect study outcomes. All of these flaws in the study

Table 1: Comparing Baseline and Intervention Groups After 12 Weeks in Women with PCOS

	Placebo Group (n = 35)			Intervention Group (n = 35)			
Lab Test	**Change in mean**	**SD**	***P* value***	**Change in mean**	**SD**	***P* value***	***P* value** ANOVA**
FPG, mg/dL	-0.02	±4.5	0.73	1.5	±6.7	0.18	0.19
Insulin, µIU/mL	2.8	±4.7	0.002	-1.2	±4.0	0.08	<0.001
HOMA-IR	0.6	±1.1	0.002	-0.3	±1.0	0.08	<0.001
HOMA-B	10.7	±18.2	0.001	-4.4	±15.0	0.09	<0.001
QUICKI	-0.01	±0.03	0.01	0.00009	±0.01	0.83	0.01
Total T, ng/mL	0.1	±0.3	0.03	-0.2	±0.4	0.19	0.01
SHBG, nmol/L	-1.3	±3.5	0.03	3.9	±6.2	0.001	<0.001
FAI	0.02	±0.03	0.004	-0.03	±0.04	0.001	<0.001
mFG scores	-0.2	±0.8	0.08	-1.1	±0.9	<0.001	<0.001
Free T, pg/mL	-0.4	±1.9	0.19	-0.7	±2.3	0.06	0.54
DHEAS, µg/mL	-0.1	±1.4	0.49	-0.7	±2.3	<0.001	0.96
Triglycerides, mg/dL	10.3	±24.5	0.01	-13.3	±62.2	0.21	0.04
VLDL, mg/dL	2.0	±4.9	0.01	-2.7	±12.4	0.21	0.04
Total cholesterol, mg/dL	-0.2	±14.8	0.93	3.4	±19.4	0.30	0.38
LDL, mg/dL	-2.4	±12.8	0.27	4.9	±24.5	0.24	0.12
HDL, mg/dL	0.2	±4.0	0.81	1.2	±5.3	0.21	0.38
Total/HDL ratio	-0.01	±0.3	0.80	0.005	±0.5	0.94	0.86
hs-CRP, mg/mL	0.2	±2.9	0.82	-0.2	±3.6	0.82	0.75
NO, µmol/L	2.7	±20.2	0.44	3.0	±5.1	0.001	0.93
TAC, mmol/L	33.4	±251.6	0.43	30.0	±68.0	0.01	0.93
GSH, µmol/L	22.7	±157.8	0.75	96.0	±102.2	<0.001	0.04
MDA, µmol/L	0.8	±2.3	0.05	-0.7	±0.8	<0.001	0.001

*Paired-samples t test; ** Time x group interaction (one way repeated measures ANOVA)
FPG: fasting plasma glucose; HOMA-IR: homeostasis model of assessment-insulin resistance; HOMA-B: homeostasis model of assessment ß-cell; QUICKI: quantitative insulin sensitivity check index; Total T; total testosterone; SHBG: sex hormone-binding globulin; FAI: free androgen index; mFG: modified Ferriman-Gallwey score; DHEAS: dehydroepiandrosterone sulfate; VLDL: very low-density lipoprotein; HDL: high-density lipoprotein; hs-CRP: high sensitivity C-reactive protein; NO: nitric oxide; TAC: total antioxidant capacity; GSH: total glutathione; and MDA: malondialdehyde.

design could have affected the study results. Previous studies investigating the effect of soy isoflavones on the metabolic and hormonal health of women with PCOS have shown mixed results. A pilot study with 12 obese hyperinsulinemic and dyslipidemic women with PCOS found that giving 36 mg/d of genistein for six months resulted in significant changes in total cholesterol, LDL, and LD-HDL ratios, but there were no significant changes in other lipids, anthropometric features, hormonal milieu, or menstrual regularity.[9] A quasi-randomized trial (n = 146) found that 18 mg of genistein given to women with PCOS twice a day for three months improved luteinizing hormone (LH), triglycerides, LDL, DHEAS, and testosterone but not HDL and FSH.[10] The results from the Jamilian and Asemi study also were mixed. For instance, when evaluating the effect of the soy supplement on lipids, only triglycerides and VLDL showed improvement while other lipids did not. This also was the case for biomarkers related to insulin resistance and hormonal status. The flaws in study design or the small sample size may account for these mixed results. Soy supplementation may have more of an effect on women with hyperlipidemia and insulin resistance. In addition,

whole soy foods could have more beneficial health effects than soy isoflavone supplements, as other studies suggest.

It may be helpful to look at the results in the context of clinical care and their usefulness in caring for women with PCOS. The hormonal milieu of PCOS usually is monitored using free T, ideally performed with an equilibrium dialysis technique, progesterone, serum 17-hydroxyprogesterone, anti-Müllerian hormone; in some cases DHEAS is assessed.[1] In this study, free T levels did not show improvement, but DHEAS improved significantly and the other laboratory tests were not obtained. The other hormonal tests performed in this study were not recommended in the 2015 clinical guidelines. The oral glucose tolerance test or fasting glucose to insulin ratio commonly is used to screen for impaired glucose tolerance in the clinical setting.[11] The HOMA-IR has had questionable accuracy in studies, so it probably is not a useful marker. In this study, fasting glucose did not improve but insulin and HOMA-IR did improve. In a double-blind, placebo-controlled trial (n = 165), soy isoflavone supplements failed to improve insulin sensitivity among Chinese women with impaired glucose regulation.[12] The results from this study and others make it difficult to determine if supplementation with soy isoflavones improves insulin resistance or the hormonal milieu of women with PCOS.

The underlying role of inflammation in the pathophysiology of PCOS is not completely understood, and consequently which biomarkers should be studied has not been determined. In a study that explored the relationship between chronic low-grade inflammation and PCOS, the inflammatory mediators investigated were CRP, IL6, other IL, TNFα, MCP1, sE-selectin, and sICAM.[13] Many of the same biomarkers for inflammation also were used in large studies, such as Framingham, to determine risk of diabetes.[14] In the Jamilian and Asemi study, there was no significant improvement in CRP, a marker of inflammation, but there was improvement in the antioxidant GSH and a marker of oxidative stress, MDA. Many of the markers of inflammation used in other studies were not included in this study, and these biomarkers are probably most useful within the context of exploratory research.

In summary, this study, which examined the effect of soy isoflavones on the metabolic status of women with PCOS, had mixed results. At this time, supplementation with soy isoflavones does not appear to have a role in the clinical care of women with PCOS. Larger longitudinal studies that include women with PCOS who have metabolic disorders, that examine soy in the diet, and that employ labs recommended for clinical monitoring could shed more light on the effects of soy. Further study of the effect of soy isoflavones on the inflammatory process in PCOS should include replicating the use of biomarkers consistently used in large studies investigating metabolic disorders. This was an ambitious, rigorously designed study that was conducted in a low-resource setting with limited access to costly laboratory tests and research funding. Future studies should build on the efforts of these investigators who have sought to improve our understanding of the effect of soy isoflavones on the health of women with PCOS. ■

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Melatonin and Chemotherapy: A Review

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Recently, melatonin and its potential benefits in cancer and chemotherapy have been discussed in varying publications from the *Lancet Oncology* to the *Huffington Post*.[1,2] Melatonin is best known for its role in the sleep-wake cycle and is a popular supplement used to promote sleep and decrease symptoms of jet lag.[1-3] The National Health Interview Survey (NHIS) conducted in 2012 reported an estimated 1.3% of the U.S. adult population (3.1 million American adults) used melatonin in the last 30 days.[3] The NHIS survey also concluded that the use of melatonin has more than doubled since 2007.[3] Unfortunately, the reason for the use of natural supplements was beyond the scope of this survey.[3] With the increased use of melatonin in the adult population, it is unclear how many individuals may be using it to promote sleep or for other health reasons such as an adjunctive therapy in cancer treatment.

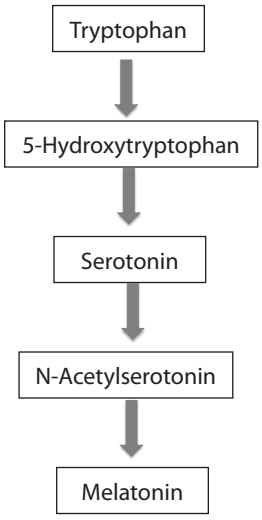
Summary Points

- Melatonin is a popular supplement, with 3.1 million adults in the United States reporting use.
- Melatonin produces pleiotropic effects throughout the body that are not fully elucidated, and its role in cancer prevention or as an adjunctive treatment in oncology patients is not well defined.
- Melatonin used in research may be difficult to extrapolate to clinical use.

BACKGROUND

Melatonin (N-acetyl-5-methoxytryptamine) is an indolic compound that is synthesized from the amino acid tryptophan in the pineal gland; it was identified first in 1958 by Aaron Lerner's group.[4,5,6] (*See Figure 1.*) The pineal gland is the major producer of melatonin; however, other tissues, such as the gastrointestinal tract, retina, and bone marrow,[5] have been shown to produce melatonin. The pineal gland secretes melatonin in response to the suprachiasmatic nucleus (SCN), which is synchronized to the light-dark cycle in the environment by detection of light by the retina. The SCN is described as acting as the master clock in the body that sets all of the peripheral tissue clocks. The pineal gland produces and secretes melatonin at night, which is reflected in the higher concentration of melatonin in the blood stream during the night and early morning hours and lower levels during the day.[5] There is individual variation in the synthesis and secretion of melatonin, with low secretors having peak serum levels at night ranging from 18-40 pg/mL and high secretors from 54-75 pg/mL.[5,6]

Figure 1: Biosynthesis of Melatonin



Adapted from: Vijayalaxmi, Thomas CR Jr, Reiter RJ, Herman TS. Melatonin: From basic research to cancer treatment clinics. *J Clin Oncol* 2002;20:2575-2601.

The sleep-enhancing effects and circadian rhythm regulation are attributed to the signaling pathways that are activated with the binding of melatonin to the melatonin receptors. The melatonin receptors are the MT1 (Mel 1a) and MT2 (Mel 1b) receptors, which are expressed in the central nervous system and in the peripheral tissues.[7] Melatonin also binds to nuclear and cytoplasmic receptors and intracellular proteins that are involved in cytoskeletal rearrangement and estrogen signaling

pathways.[7] In addition to the downstream effects from melatonin binding to the receptors, it is also a powerful antioxidant that scavenges both reactive oxygen and nitrogen species.[8,9]

ANTICANCER EFFECTS

The anticancer effects of melatonin have yet to be fully elucidated in humans.[5,6] In vitro studies have demonstrated that melatonin has many effects on the cell cycle, including inducing apoptosis and up-regulating p53 and p21 (tumor proteins) in cancer cell lines.[8,9] Melatonin also has demonstrated inhibition of VEGF and HiF1α expression in cell lines supporting an antiangiogenic effect.[5,6,8,9] In advanced cancer patients, melatonin supplementation decreased VEGF serum concentrations.[9]

Numerous immune-enhancing effects, including increased activity of natural killer cells, T cells, and B cells, and increased cytokine production, have been reported.[5-9] In breast cancer cell lines, melatonin has demonstrated antiestrogenic effects, which occur through the MT1 receptor.[7-9]

ANTIOXIDANT EFFECTS

As a free radical scavenger, melatonin may be able to decrease chemotherapy-induced toxicity. However, alkylating and platinum-based chemotherapeutic drugs exert anticancer effects through increasing free radicals in the body; antioxidants potentially could decrease the efficacy of these drugs.[10,11] Yasueda et al conducted a recent systematic review (though no meta-analysis) investigating the efficacy and interactions of antioxidant supplements, including melatonin, as adjuvant therapy in cancer treatment.[11] They concluded that more research is needed to further understand the effects of antioxidants in cancer patients and to determine the risks and benefits associated with use.[11]

CLINICAL EVIDENCE

Two recent meta-analyses investigating the efficacy and safety of melatonin use in cancer patients undergoing chemotherapy demonstrated benefit.[12,13] These two meta-analyses overlapped in the clinical trials they investigated. Seely et al included 21 clinical trials in 19 studies and Wang et al included eight of those same studies.[12,13] The 11 studies (13 clinical trials) not included by Wang et al did not meet the selection criteria defined in the methods.[12] The majority of the studies included in both meta-analyses were conducted by Lissoni et al. Wang et al included eight randomized, controlled trials, six of which were performed by Lissoni et al. In the Seely et al meta-analysis, 18 of the 21 studies were conducted by Lissoni et al. Both authors concluded that the general quality of the studies was poor overall, as many of the studies were not blinded, the randomization method was unclear, and there was often a lack of placebo arms.[12,13]

In the Wang et al meta-analysis, data from the eight randomized, controlled trials were pooled, comparing participants receiving 20 mg of melatonin with chemotherapy and/or radiotherapy to participants receiving conventional therapy alone.[12] Complete and partial remission rates were 32.6% in the melatonin group compared to 16.5% in the conventional therapy alone group ($P < 0.00001$).[12] Wang et al also reported a one-year survival rate of 52.2% in the melatonin group vs. 28.4% in the control group ($P < 0.001$).[12] The relative risk (RR) reported was 1.90 (95% confidence interval [CI], 1.28-2.83; $P = 0.001$; $I^2 = 61.9\%$).[12]

Seely et al pooled data comparing conventional treatment with and without adjuvant melatonin and reported an RR for one-year mortality of 0.63 (95% CI, 0.53-0.74; $P \leq 0.001$; $I^2 = 78\%$).[13]

In 2005, Mills et al published a systematic review and meta-analysis investigating the use of melatonin (ranging 20-40 mg) in participants with various solid tumor cancers from 10 research studies performed by Lissoni et al.[14] The melatonin treatment group demonstrated reduced mortality risk at one year with a pooled RR of 0.66 (95% CI, 0.59-0.73; $P \leq 0.0001$; $I^2 = 0\%$).[14] There were no reports of serious adverse events mentioned in any of the studies.[11-14]

In summary, the majority of the studies used in the above meta-analyses were conducted by Lissoni et al and have not been replicated in double-blind, placebo-controlled, randomized, controlled trials performed by other research groups.[1,11-14]

MELATONIN PURITY, SOURCING, AND PHARMACODYNAMICS

Many of the studies included in the above meta-analysis were conducted in Europe, where melatonin is a prescribed medication rather than a supplement. It is unclear from the studies which melatonin product was used and whether it was analyzed for purity prior to its use in the studies. In the United States, melatonin is sold as an over-the-counter supplement and made synthetically.

Labdoor, a company that tests supplements for label accuracy, product purity, nutritional value, ingredient safety, and projected efficacy, tested 30 melatonin supplements.[15] Labdoor found that nine out of the 30 melatonin products deviated off

label claims by at least 20%.[15] One product tested contained < 1% of the label claim for melatonin and another product tested contained 47.4% more than the product's label claimed.[15] Fifteen of the 30 melatonin products were within 10% of their label claims.[15] Two of the products' arsenic levels were higher than California Proposition 65 levels of 0.1 mcg/day of inorganic arsenic levels.[15]

Oral melatonin reaches its peak plasma levels in the human body in 60-150 minutes and has a serum half-life of approximately 20-30 minutes. The bioavailability of oral melatonin ranges from 10-56%. Serum melatonin undergoes extensive first-pass metabolism, with 90% being cleared by the liver through the cytochrome p450 enzymes. The metabolites of melatonin are excreted into the urine.[5,6]

A wide range of melatonin dosages are recommended for sleep. A research group at Massachusetts Institute for Technology found that 0.3 mg of melatonin was the optimal dose for sleep in adults.[16] The researchers found that adults who took more melatonin reported feeling drowsy during the day, which they attributed to melatonin being present in the blood at higher levels than normal during the daylight hours.[5,16] There is no recommended dose for melatonin in cancer patients; however, research studies have used a dosage of 20-40 mg of melatonin once daily in the evening.[11-13]

SIDE EFFECTS/INTERACTIONS

No serious side effects were reported in the above meta-analysis studies. Melatonin is considered safe; however, there have been documented cases of small decreases in body temperature with oral administration.[5] Drowsiness is a common side effect of melatonin that may occur the following day after administration and may be due to doses in the higher ranges.[5,16-19]

INTERACTIONS

Since melatonin is processed by the CYP450 pathway (isoenzymes CYP1A2, CYP1A1, and CYP1B1) in the liver, it is reasonable to assume that melatonin may interfere with the blood concentration of other drugs that use the same pathway. For example, caution is warranted with the coadministration of warfarin, which also uses the CYP1A2 isoenzyme.[5,6,16]

CONCLUSION

Melatonin is best known for its role in regulation of sleep and the circadian rhythm.[1-6] Melatonin has demonstrated anticancer activities in basic science and animal studies that are promising for future studies.[5-14] Although the RR improvements reported by the meta-analyses and the original research investigators are promising, other research groups have not verified them independently, and the study methodologies also are not of high quality. The mechanisms of action of melatonin also need to be fully elucidated so that research investigating safety, efficacy, and drug interactions can be further determined.

Individual cancer types that have demonstrated benefit with melatonin supplementation include breast cancer and non-small cell lung cancer.[8,11-14] Malignant tumors of the same cancer type are heterogeneous in their protein expression and are under investigation.[20] Melatonin produces pleiotropic effects that appear to be the result of numerous interactions with different receptors and proteins that need to be better defined to predict which cancer types and treatments would benefit. Further research with human participants that is both methodologically sound and conducted by more than one research group is required to be able to recommend high doses of melatonin to oncology patients. Another important issue to address to effectively use melatonin in clinical practice in the United States is to have available a standardized melatonin supplement that is free of heavy metals. Further understanding into the low and high melatonin secretors also is required, as there may be a wide range of dosage depending on individual variation, which could affect efficacy in oncology patients.

Although 20-40 mg doses of melatonin appear safe from the body of research investigating the effects of melatonin in oncology patients, it may not be efficacious. More research is needed to be able to determine whether adjunctive treatment with melatonin is beneficial to oncology patients in high doses. ■

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CME QUESTIONS

1. **The Wing study (SNAP) looking at prevention of weight gain in young adults found that:**
   a. electronic communication and virtual meetings were less effective but more convenient modalities to monitor participants than more traditional face-to-face meetings.
   b. the group that incorporated small, daily changes in diet and exercise along with self-regulating techniques was superior in reducing weight gain than the group instructed in large, periodic changes and self-regulating techniques over a three-year period.
   c. both active groups — the group that initiated large, periodic changes along with self-regulation and the group that initiated small, daily changes along with self-regulation — were better than the control group at reducing weight gain during a mean three-year study period.
   d. utilizing electronic communication to record weights and give feedback to participants was more effective than phone feedback and led to more robust weight gain prevention.

2. **In women with polycystic ovary syndrome, a soy isoflavone supplement was found to:**
   a. improve some metabolic and hormone parameters.
   b. reduce lipids and improve insulin resistance.
   c. affect inflammatory processes involved in the pathophysiology of polycystic ovary syndrome.
   d. reduce infertility.

3. **Which of the following is true regarding melatonin?**
   a. 20-40 mg of melatonin is a safe and effective treatment in oncology patients.
   b. 0.3 mg of melatonin is a safe and efficacious treatment in promoting sleep in adults.
   c. Melatonin blood levels are higher during the day and lower at night.
   d. There is no variability in the concentration of melatonin in supplements sold in the United States.

[IN FUTURE ISSUES]

Vitamin D and type 2 diabetes

The effect of stress on the inflammatory response of food

Extra-virgin olive oil and type 1 diabetes

Beetroot juice and endurance

Integrative Medicine [ALERT]

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