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Comparing the effects of transdermal hormone therapy to oral hormone therapy on gallbladder disease, cholecystectomy, and gallbladder cancer

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Abstract

Objective: To determine whether transdermal hormone therapy produces less effects on the development of gallbladder disease and cancer than oral hormone therapy.
Data sources:OVID, PubMed, Medline, and NIH
Study selection: Studies that included women who are 40 -75 years of age who were naive to hormone therapy. Studies chosen had to include both transdermal and oral routes of hormone administration as well as findings related to gallbladder disease, cancer, or markers that affect these conditions. Reviews were not included in our study criteria. The primary outcome was incidence of gallbladder disease and cholecystectomy.
Data synthesis: Of the 98 articles, 5 articles were included in the assessment. 2 studies assessed gallbladder disease/cholecystectomy, 2 assessed biomarkers for gallbladder stone, and 1 assessed gallbladder disease as a risk for gallbladder cancer. Prospective data suggests that transdermal hormone therapy has a lower risk of gallbladder disease and cholecystectomy. Evidence also suggests a positive correlation between gallbladder disease and gallbladder cancer.
Conclusions: The preliminary evidence suggests that transdermal hormone therapy has a lower risk of gallbladder cancer. There is a strong association between gallbladder cancer and cholelithiasis, chronic cholecystitis, and inflammation. Based on the evidence, transdermal therapy may have a lower risk of gallbladder disease and cholecystectomy. In addition, transdermal has a more favorable lipid panel. The evidence also suggests some correlation between hypercholesterolemia and risk of cholecystectomy.

1 Introduction

Menopause symptoms are often time treated with hormone therapy to improve quality of life for many women. Some serious adverse effects of this therapy include the development of certain cancers and disease states. There are multiple dosage forms available for therapeutic use, some may be safer than others. We propose that transdermal delivery of hormones will have decreased risk of gallbladder disease and gallbladder cancer development compared to oral therapy. Currently its understood that any type of oral hormone therapy increases the risk for any gallbladder event. Risk factors for developing gallbladder cancer include female gender, ethnicity, cholelithiasis, age, chronic inflammatory conditions (affecting gallbladder), congenital biliary abnormalities, and diagnostic confusion over gallbladder polyps. There is a strong association between gallbladder cancer and cholelithiasis, chronic cholecystitis, and inflammation (1). Although the benefits and the risks that hormone therapy has on different types of cancers have been shown, the comparison between the effects of oral versus transdermal hormone therapy on gallbladder disease/cancer is not well studied or well understood. Our rationale for this project is to provide deeper insight into hormone therapy as it relates to its potentially cancerous side effects on the gallbladder in perimenopausal and postmenopausal women.

This could help improve patient safety as well as morbidity and mortality.

Key words: Oral Hormone Therapy, Transdermal Hormone Therapy, gallbladder disease, gallbladder cancer

2 Methods

2.1 Search Strategy

We obtained our data from prospective cohort and case studies that lasted eight or more weeks. We utilized scientific databases to search for these trials, such as OVID, PubMed, Medline, and NIH. Strengths of our data sources collected include data from primary literatures that encompass a variety of different study types, validity, and ability to filter content/results. The search strategy is limited to publications in the English language after 1990. Our inclusion criteria are; women who are 40 -75 years and without a history of gallbladder disease. Our exclusion criteria are women with a history of deep vein thromboembolism, steroid use up to 6 months before the study and history of any cancer or myocardial infarction in the last year. The search terms used include HRT, estrogen, gallbladder stones, gallbladder cancer, gallbladder disease, cholelithiasis, chronic cholecystitis, menopause, postmenopausal, perimenopausal, oral and transdermal hormone therapy. The results presented in the paper are from articles that represented statistically significant results with a p value of <0.05. Results that are not statistically significant are also included as it may be considered a potential area of research in the future. Disagreements among the abstractors were resolved based on pro and cons and any significant controversial extraction was documented under a section titled controversial findings. The quality of the study was assessed using center of evidence based medicine criteria to define levels of evidence. Categories will include therapy/prevention aetiology/harm, prognosis, diagnosis, differential diagnosis/symptom prevalence study, and economic aid decision analyses.The primary outcome is the incidence of gallbladder events in women using oral hormone formulations versus transdermal formulations. The studies provided further insight on the risks of gallbladder events and cancer in premenopausal and postmenopausal women taking hormone therapy to reduce symptoms and improve quality of life. The results from this study will establish if there is any statistically significant benefit in rates of gallbladder event development in perimenopausal and postmenopausal women who are on a transdermal formulation versus an oral formulation.

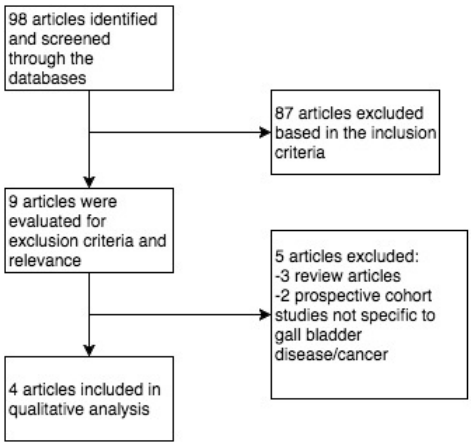

Figure 1: Study section flow diagram

3 Results

Three investigators independently identified four articles that met our inclusion criteria. The studies were divided into 2 criteria, one that analyzed the incidence of gallbladder and/or cholecystectomy and the other analyzed serum markers associated with gallbladder disease. A summary of the studies is listed in the tables below. The exclusion criteria for the studies were similar and also met our inclusion criteria.

3.1 Gallbladder cancer/ cholecystectomy: Prospective studies

The follow-up was carried out through linkage to their medical records, providing unbiased follow-up. The incidence of gallbladder disease and cholecystectomy according to the use of hormone replacement therapy was the primary outcome of both studies. The study method used was self reported through study questionnaires. The questionnaires assessed the use of menopausal hormone therapy, medical history and lifestyle characteristics (3). For the 16 year study and the Million Women study, questionnaires were sent out every 3-5 years. Analysis of risk was determined using the Cox model (2,3). One study used Cox proportional models, with age as time-scale to analyze the risk cholecystectomy associated with use of menopausal hormone therapy (3). Another study used Cox regression to estimate the relative risk of hospital admission for gallbladder disease in relation to use of hormone replacement therapy (2).

3.1.1 Evaluation of clinical outcomes

Two prospective cohort studies evaluated whether transdermal hormone replacement therapy had a different risk of gallbladder disease and cholecystectomy compared to oral in postmenopausal women. One was a 16 year study based on a French E3N cohort and the other was 6 year, multi-center, population-based prospective observational cohort study based on the Million Women Study. Both groups reported no significant difference in the patients at baseline in terms of age, BMI, smoking, alcohol intake, education level, income level, use of oral contraception ever and cardiovascular factors (2,3). However, one group reported a significant difference in the women who had a hysterectomy with the transdermal group having a higher percentage (73.5%) compared to the oral group (32.6%) (2). The incidence rates of hospital admission and cholecystectomy were reported in both studies. One group reported hospital admission rates for gallbladder in patients using transdermal therapy as 2.07% with a relative risk of 1.17, 1.10 to 1.24. The group taking oral therapy reported hospital admission rates of 2.61% with a relative risk of 1.74, 1.68 to 1.80. In this study, many of the women receiving transdermal therapy had gotten a hysterectomy in the past and were using estrogen only therapy (2). In the other study, researchers found that in the transdermal group the percentage of women who developed a cholecystectomy was 3.87% with an age adjusted hazard ratio of 0.97 (0.89-1.04) and the oral group was 3.73% with an age adjusted hazard ratio of 1.10 (1.00-1.20). The researchers also found that the risk of cholecystectomy was significantly increased with oral estrogen versus transdermal estrogen (p=0.03) (3). One group also compared risk based on different factors and none of them were significant except the BMI. The relative risk decreased with an increase in body mass index. The relative risk was 1.88 (1.77 to 2.01) for a body mass index <25 kg/m^2 and 1.47 (1.30 to 1.67) for a body mass index ≥ 35 kg/m^2; P=0.001 for trend (2). The other group found a positive correlation between risk of cholecystectomy and increasing BMI, higher parity, hypercholesterolemia, diabetes, and education level (3).

3.2 Markers associated with gallbladder disease

3.2.1 Prospective Study

In this study blood samples were collected before and after 8 weeks of estrogen administration. The outcome measures included serum FSH, LH, E2, estrone, estrone sulfate, sex hormone-binding globulin, lipid profiles, biliary cholesterol saturation index, cholesterol nucleation time, presence of cholesterol crystals in bile, as well as biliary arachidonate, PGE2, and mucous glycoproteins. A comparison of baseline values between the groups was performed by a two-sample t test. A paired t test was then used to determine whether the

percent change from baseline was significantly different from zero. A two sample t tests or McNemar tests were used for these comparisons. Significance was accepted at P <0.05 (4).

3.2.2 Evaluation of clinical outcomes

The study was carried out to evaluate if there was any significant difference in development of cholesterol gallstones between oral and transdermal estrogen. The study duration was 8 weeks and involved women who had undergone spontaneous menopause more than 1 year or surgical menopause more than 3 months before the start of the study. There was no significant differences in demographics and laboratory values at baseline between the two study groups. The levels measured between the two groups were generally elevated and not significantly different. In terms of lipid profile, the percent changes with oral estrogens were always greater than those with transdermal E2, with the exception of total cholesterol. The percentage changes are indicated in the table below (4).

	Transdermal E2			***Oral conjugated equine estrogens***			***% Change comparison between groups***
	n	***% change***	***p***	***n***	***% change***	***p***	
Total Cholesterol (mg/dL)	48	-4.3±10.7	<0.05	49	-3.7±11.3	<0.05	NS
HDL (mg/dL)	48	-2.0±14.3	NS	49	16.5±16.8	<0.05	<0.05
LDL (mg/dL)	48	-4.0±13.3	<0.05	48	-14.8±16.4	<0.05	<0.05
VLDL (mg/dL)	47	0.5±40.4	NS	48	23.2±42.0	<0.05	<0.05
Triglycerides (mg/dL)	48	-0.5±41.1	NS	49	24.2±41.9	<0.05	<0.05
*Percent change from baseline for lipid profile and percent change comparison between groups Values are the mean ± standard deviation							

Table 1: Comparing percentage change in lipid profiles from baseline between the two groups.

Table 2:Summary of studies comparing the effects of transdermal to oral hormone therapy on gallbladder disease and cancer

Year	Intervention/ study parameters	Study design	Patient population	Results
1992-2008	Cholecystectomy and first diagnosis of gallstones, along with their respective dates self reported. -Concordance between documents and self-report evaluated (99% for cholecystectomy and 67% for gall	Large Prospective cohort study evaluating the risk of cholecystectomy associated with different regimens of menopausal hormone therapy	-70 928 women, -mean age transdermal therapy 53.8yrs and oral therapy 53.2 yrs	Increased risk of cholecystectomy with oral estrogen versus transdermal estrogen (p=0.03) [HR] 1.10, 95% confidence interval [CI] 1.01-1.20.

	stone disease)			
1996-2001	Women received an invitation to a breast cancer center screening in one of the 66 NIH facilities in the UK. A questionnaire was sent along with the invitation that was to be filled out by time of screening. Approx. 70% returned the questionnaire and agreed to partake in the study.	Large Prospective cohort study comparing transdermal and oral use of hormone therapy reduces the risk of gallbladder disease in postmenopausal women.	-1.3 million women -Age range 50-69yrs with mean of 65yrs	Transdermal versus oral hormone therapy had reduction in risk of gallbladder disease and cholecystectomy in women naive to hormone therapy (relative risk [RR] 1.17 v. 1.74; $p < 0.001$).
2008	The serum concentrations of CRP, IL-6, E- and P-selectin, ICAM-1 and VCAM-1, SAA, transferrin, prealbumin, IGF-I, and the hormone-binding globulins SHBG, TBG, and CBG were measured at baseline and at the end of each treatment period.	Randomized, open-label crossover clinical trial	-25 healthy naturally menopausal women -Age range 42–70 yr -currently using combination estrogen-progestin hormone therapy (HT).	During oral CEE, 9 parameters changed significantly CRP (192%; P <0.001); E-selectin (−16.3%; P = 0.003); P-selectin (−15.3%; P = 0.012); ICAM-1 (−5%; P = 0.015); transferrin (5.3%;P = 0.024); IGF-I (−30.5%; P < 0.001); SHBG (113%; P < 0.001); TBG (38%; P < 0.001); and CBG (20%; P < 0.001). With the transdermal only three parameters had a significant change and to a lesser degree: ICAM-1 (−2.1%; P = 0.04); IGF-I (−12.5%; P < 0.001); and SHBG (2.6%; P = 0.042)
1996	Bile samples were obtained by before and after 8 weeks of estrogen administration -measures included serum FSH, LH, E2, estrone, estrone sulfate, sex hormone-binding globulin, lipid profiles, biliary cholesterol saturation index, cholesterol nucleation time, presence of cholesterol crystals in bile, as well as biliary arachidonate, PGE2, and mucous glycoproteins.	Prospective, randomized, double blind, parallel study	- 97 postmenopausal women -40–70 yr of age -women who had undergone spontaneous menopause more than 1 yr or surgical menopause more than 3 months before the start of the study.	The oral estrogens induced greater changes in hepatic markers (levels of SHBG and lipids) than transdermal E2. Both significantly increase biliary cholesterol saturation index, arachidonate, and PGE2 and a significant decrease in the nucleation time Oral estrogen increased cholesterol significantly from baseline compared to transdermal

3.2.3 A randomized open-label crossover study

This study enrolled a total of 27 women and only 25 completed both treatment periods. Subjects were randomized to 12 week treatment to an oral conjugated equine estrogen or transdermal estradiol after a 6 week withdrawal period from prior HT. Baseline measurement of CRP and other parameters were assessed. These parameters were taken for the second time at the end of the treatment. Subjects were then crossed over to 12 weeks of the other treatment. For the oral ET treatment subjects were given 0.625mg tablets of CEE daily for 12 weeks. The transdermal ET subjects received 0.05mg/d twice weekly for 12 weeks. Both groups were given oral micronized progesterone (5).

3.2.4 Evaluation of Clinical Outcome

Investigators measured levels of CRP, IL-6, E- and P-selectin, ICAM-1 and VCAM-1, SAA, transferrin, prealbumin, IGF-I, and the hormone-binding globulins SHBG, TBG, and CBG at baseline and at the end of each treatment period. During the oral CEE 9 parameters changed significantly, CRP (192%; P <0.001); E-selectin (−16.3%; P = 0.003); P-selectin (−15.3%; P = 0.012); ICAM-1 (−5%; P = 0.015); transferrin (5.3%;P = 0.024); IGF-I (−30.5%; P <0.001); SHBG (113%; P <0.001); TBG (38%; P <0.001); and CBG (20%; P <0.001). With the transdermal only three parameters had a significant change and to a lesser degree: ICAM-1 (−2.1%; P = 0.04); IGF-I (12.5%; P <0.001); and SHBG (2.6%; P = 0.042). A log-log relationship between CRP and IL-6 at baseline showed a parallel shift during the oral therapy, indicating a greater sensitivity to Il-6 stimulation.

4 Discussion

An extensive research concluded with four studies that looked at the effects of transdermal hormone therapy products and oral hormone therapy in association with hepatic inflammation, gallstones, gallbladder disease, and/or gallbladder cancer. Majority of this evidence suggests oral hormone therapy increases the risk of developing inflammation or other factors affecting the gallbladder, incidence of gallbladder disease, and cholecystectomy over transdermal administration. Use of transdermal hormone therapy for premenopausal and postmenopausal management may lower the risk of gallbladder disease and cancer.

Although some of the studies were not directly focused on gallbladder disease and cancer, they compared the differences in the levels of markers in the body that are associated with gallbladder disease and cholecystectomy, such as hepatic markers or biliary cholesterol. From these studies, it can be inferred that the downstream effect of increased levels of these markers increases risk of gallbladder disease and cancer. To support this assumption, one study on the epidemiology of gallbladder disease reported that several risk factors for gallstone are implicated in gallbladder cancer (1). A randomized, open-label crossover clinical trial found a significant increase and changes with CRP, inflammatory markers, and hepatic proteins during the oral estrogen hormone treatment compared to transdermal treatment (5). However, a prospective study found no significant difference between transdermal and oral routes in promoting gallstone formation by alteration of biliary lipids (4).

The Million Women Study showed significant risk reduction in gallbladder disease and cholecystectomy. These women were all nave to hormone therapy. Many of the women who received the transdermal formulation had a hysterectomy in the past and were using estrogen only therapy (2). Similar findings were found with the French E3N Study; as in they also showed transdermal estrogen resulted in less cholecystectomies.Transdermal patches were used regardless of whether a woman had as hysterectomy or not. The largest caveat of the E3N Study was that participants self-reported their use of menopausal hormone therapy, medical history, and lifestyle characteristics via a questionnaire (3).

Lower risk associated with transdermal routes may be due to bypassing first pass metabolism, which means estrogens are not getting absorbed via the GI system or traveling through the liver to get extensively metabolized. Therefore, the liver is not increasing biliary cholesterol saturation. Transdermal estrogens are administered in lower doses than oral estrogens and are absorbed through the skin to directly enter systemic

circulation. Avoidance of first pass metabolism means that less estrogen and its metabolites are collecting in the bile, metabolites which may play in part in gallbladder disease development.

Our review also revealed a correlation between hypercholesterolemia and gallbladder disease. One study showed that a rise in total cholesterol increases the possibility of cholesterol crystals in the bile that lead to the development of gallstones (4). Another study reported an association between high cholesterol and a higher risk of cholecystectomy (5). However, both studies did not find a significant difference between transdermal and oral hormone therapy in terms of increasing total cholesterol. One study did however, report an overall better lipid profile with transdermal compared to oral hormone therapy(4). Further studies need to be performed to evaluate the difference in effects of transdermal and oral hormone therapy on cholesterol levels.

The information from our findings can be applied to pharmacy practice by providing patient specific care. For patients with a history of gallbladder disease and patients with high cholesterol, transdermal hormone therapy might be considered over oral therapy to reduce the risk of gallbladder disease and cancer. These findings were obtained from two large prospective studies in different populations, the Million Women Study and the French E3N, as well as smaller studies. This may be an added benefit of transdermal hormone therapy, which has been shown to be as effective as oral hormone therapy, but with a safer profile in terms of preventing osteoporosis, cardiovascular disease, and venous thromboembolism.

Conclusion

Our review of the articles identified four studies that compared transdermal hormone therapy to oral therapy, and their effects on risk of gallbladder disease, cholecystectomy, and markers that increase gallbladder cancer risk. The preliminary evidence suggests that transdermal hormone therapy has a lower risk of gallbladder cancer. There is a strong association between gallbladder cancer and cholelithiasis, chronic cholecystitis, and inflammation. Based on the evidence, transdermal therapy may have a lower risk of gallbladder disease and cholecystectomy. In addition, transdermal therapy has a more favorable lipid panel. The evidence also suggests some correlation between hypercholesterolemia and risk of cholecystectomy. However, further studies may be needed to directly compare the difference in the incidence of gallbladder cancer between transdermal and oral hormone therapy.

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