INCREASE IN GLYCOSYLATED HEMOGLOBIN (HbA_{1c}) IN MENOPAUSAL WOMEN TREATED WITH VAGINAL ESTROGEN CREAM

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Summary: In a group of 20 menopausal women 45-78 years old (mean age 62.4), with typical symptoms such as dryness of the vagina, urinary disturbances, "mental" symptoms, or vasomotor disturbances, treated with topical vaginal estrogen cream, we examined the glucose tolerance, as expressed by Gycohemoglobin (HbA_{1c}) and GTT. Estrogen, well absorbed by the vaginal epithelium, gives rise to the HbA_{1c} from a meanof 6.4% to 14.78% ($P<0.0001$). The GTT too shows a glucose intolerance, but never a frank diabetic picture. In four cases in which the cardinal symptoms were vasomotor disturbances (hot flushes, profuse sweating) the addition of oral clonidine hydrochlorate (Clonirit®) to the vaginal estrogen cream, leads to the relief of symptoms.

The Glycohemoglobin test is fast, inexpensive and easy to perform in every laboratory, giving the possibility of discovering an unknown or borderline diabetes.

Key words: vaginal estrogen cream, glucose intolerance, glycohemoglobin.

Glucose intolerance during estrogen (E) treatment in menopausal women, is a fact that the majority of Authors agree with ([1, 2, 3]). It is also known that vaginal estrogen cream is well absorbed ([4]), influences the lipid metabolism ([5]) and can sometimes cause gynecomastia ([6]) in the sexual partner of the patient. The aim of the present study was to examine the influence of vaginal estrogen cream application in menopausal women on the carbohydrate metabolism as shown in the changes of Glycohemoglobin (A_{1c}) and Glucose tolerance test (GTT).

MATERIAL AND METHODS

Test gorup was composed of 20 menopausal women between the ages af 45-78 years (mean age 62,4), and the aims of the test were explained to them, and their consent was obtained. Every woman was her own control before and during the test period during the estrogen (E) treatment.

The prescribed dose of 20 g of vaginal cream, containing 1.25 mg of conjugated estrogen (Premarin® an Ayerst - Product) administered with a vaginal applicator, was used in the present study. The conjugated E contained in the preparation is a mixture of Estrone sulfate (70%) and equine sulfate (20%) together with smal amounts of equine estrogens and the 3.17 diols of those steroids.

The daily dose was administered every evening for 2-3 months. The women consulted us for allevation of symptoms such as urinary disturbances (frequency and urgency), hot flushes, dryness of the vagina, and "psychiatric" problems such as insomnia, loss of libido, fatigue, the classical symptoms of the menopausal syndrome, which have been recognized and described as long ago as 2000 BC in the Kahans Papyrus from Egypt ([7]).

In four women, in whom the cardinal symptoms were vasamotor disturbances (hot flushes, profuse sweating) we added oral clonidine hydrochloride (Clorinit ® Rafa Jerusalem) 25-75 microgram twice a day, to the vaginal estrogen cream. Clayden *et al.* ([8]) obtained similar results to those in our study in the relief obtained by the use of the medication of the vasomotor symptoms, and it appeared that the glucose metabolism was not affected.

After a three day carbohydrate diet (250 g/day) and a fast of 12 hours, blood was tested for blood sugar levels by venopuncture and subsequently tested after the patient ingested 100 g glucose. Blood samples were taken at 60,

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Table 1. — *Glycohemoglobin levels before and during vaginal estrogen treatmen.*

	No.	Mean	SD	
Before	20	— 6.990%	±1.207	p<0.0001
During	20	—13.785%	±1.957	

Legend: No. = Number of cases
SD = Standard Deviation

120 and 180 minutes, for glucose tolerante test (GTT).

The glycohemoglobin (HbA_1c) was assayed by a commercial kit (a product of ISOLAB, Akron Ohio, USA). The assay is by ion exchange chromatography. This separates the chromatographically faster moving minor Hb fraction from the bulk of the other Hb. The $GHbA_1$ concentration is then recorded as percent of the total Hb [9]. Normal range for our laboratory is 5.5 - 9.0% HbA_1c, intermediate 9.0 - 12.0%, and elevated 12 - 20%. GHb levels for uncontrolled diabetics are over 20%. The higher the percentage, the greater the severity of the disease.

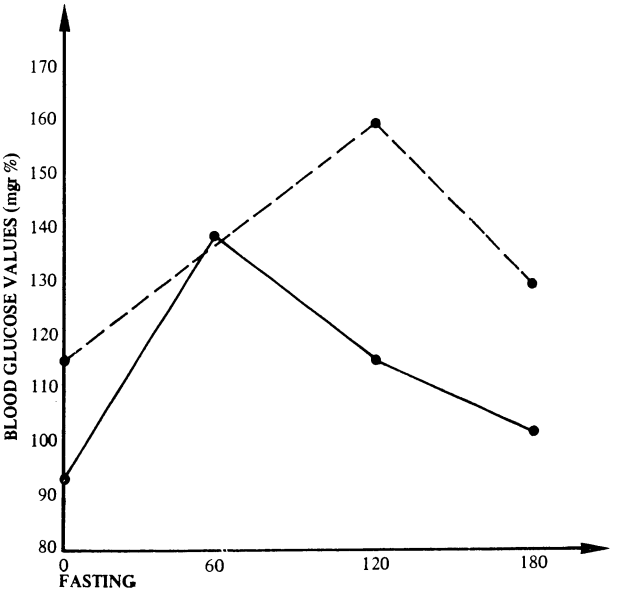
The statistical analysis was performed by Anova with repeated measures covariate. The factors we took as covariate for HbA_1c were age.

As for the "GTT, the factors we took as covariate were age", and the influence of the lasting blood sugar "on the blood sugar values of GTT at 60, 120 and 180 minutes".

We mention that the upper normal values from blood glucose in the GTT before treatment are 139 at 60′, 115 at 120′ and 120 at 180′. The statistical analysis attempted to find a link between the GTT and the levels of $GHbA_1c$.

RESULTS

From table 1 it can be seen that the normal values of GHA_1c rise from a mean of 6.99% before application of vaginal estrogen cream, to a mean of 13.785% during 2-3 months of treatment. The covariate "age" influenced the HbA_1c level ($P < 0.02$). Abstracting the covariate "age" the difference of HbA_1c level before and during the treatment was significant ($P<0.0001$). As for the GTT, the covariate "age" and "fasting blood su-



——— before; — — — — during.

Fig. 1. — G.T.T. before and during topical vaginal estrogen application.

gar" do not play any role on the blood sugar values of the GTT at 60, 120 and 180 minutes, before and during vaginal estrogen cream application. Nevertheless we found a significant difference between GTT before and during treatment $P < 0.0001$ (figure 1).

Despite the fact that both tests were influenced by increased blood sugar levels, the statistical analysis did not find a link between the GTT and the levels of $GHbA_{1c}$.

During the vaginal estrogen cream treatment, no adverse reactions, such as uterine bleeding or breast congestion were recorded.

DISCUSSION

Topical vaginal estrogen cream application is well tolerated and accepted by patients and has the advantage of entering directly into the peripheric circulation, avoiding the hepatic-portal system. As we have shown in the introduction, Authors such as Yen [1], Notelowitz [2], Gow [3] and more recently, Thom [10] agree that estrogen treatment causes glucose intolerance, but does not precipitate the development of a frank clinical diabetes mellitus. The results of Goldsfischer [11] are similar to ours. Our patients were treated with vaginal Premarin ® cream showed midly abnormal GTT values, and higher values of $GHbA_{1c}$, but in no case did frank diabetes develop. From our work it is possible to see that the $GHbA_{1c}$ test shows a true picture of the glucose intolerance.

According to R. O'Shaughnessy [12] the normal complement of Hemoglobin (Hb) in the adult is 90-95% HbAo. The remaining 5-10% is a mixture of HbA_2 (2.5%), HbF (0.5%) and the minor hemoglobins HbA_1. The minor Hb, are postsynthetic transformation of native HbAo in which sugar moietys attached to the N terminal valine of each beta chain of otherwise normal HbAo, hence they are called glycosylated or glycochemoglobins (gHb).

The larger fraction of gHb, HbA_{1c} makes up 80% of the minor Hb, and is formed when glucose in slowly, non-enzymatically and irreversibly linked to the HbAo. The concentration of the gHb is increased in the diabetic patients. It is not affected by rapid changes in the blood sugar. The concentration is proportional to the time averaged blood glucose concentration to which the red blood cell has been exposed during its lifetime, 120 days, until destruction by autolysis.

In every case of treatment with estrogen vaginal cream, a marked improvement was seen in the symptoms such as vaginal dryness, urinary disturbances; also in cases of loss of libido, "mental" problems such as insomnia, there was a noticeable improvement – apparently by a "mental tonic effect" of the estrogen as described by Utian [13].

According to Utian [13] estrogen may have a role in the modification of dopamine and serotonin metabolism in the brain with subsequent mood improvement.

Despite the somewhat small number of patients in our study, it is possible to conclude that topical vaginal estrogen application has a mild effect on the glucose tolerance, but in no case did it cause frank diabetes. Therefore, there is no contraindication of treatment of women with diabetes although in such patients, the monitoring of glucose tolerance at regular intervals is recommended. This may be done by monitoring $GHbA_{1c}$ levels, a rapid, inexpensive and simple test.

A $GHbA_{1c}$ monitoring of all menopausal women on estrogen treatment provides the opportunity of discovering a borderline or unsupected diabetes.

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CEFOXITIN SINGLE DOSE PROPHYLAXIS AND/OR T TUBE SUCTION DRAINAGE FOR VAGINAL AND ABDOMINAL HYSTERECTOMY

(Prospective randomized trial on 155 patients)

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Summary: Pelvic infections represent the most feared complications associated with vaginal and abdominal hysterectomy. In the present paper we show the result of a prospective randomized clinical trial carried out to study different morbidities (F.M. febrile morbidity, U.T.I. urinary tract infections, P.C. pelvic cellulitis, P.A. pelvic abscess, W.I. wound infection) in a sample of 155 patients undergoing vaginal or abdominal hysterectomy for non malignant disease, divided into three groups. 1) group C, treated with 2 g cefoxitin i.v. in the preoperative period; 2) group C+T, the same treatment with the addition of T tube suction drainage; 3) group T, with only the T tube suction drainage. A statistical analysis of the sample showed the homogenity of each group, while the study of the morbidities showed a statistical significant difference for W.I. between the groups treated with antibiotic and the T group ($p < .001$). For all the other morbidities, no statistically significant differences were found between the groups, demonstrating that all three methods are considerably efficient in reducing postoperative morbodity in hysterectomy.

The most common and serious complication after hysterectomy is postoperative pelvic infection. Its incidence varies from 30 to 40% ([1]) and it can reach up to 70% in cases of vaginal hysterectomy ([2]). This type of infection shows up as pelvic abscesses and/or pelvic cellulitis. The most widely followed treatment among those suggested for avoiding these infections is the use of prophylactic antibiotics, particularly because of their easy administration. The treatment usually consists of three or more doses in the perioperative period; one administration before and two or more after surgery at 6 or 12 hours intervals. In recent years, only two clinical studies report data obtained using a single dose of prophylactic anti-