

**UTILITY OF AN ORAL PRESENTATION OF hCG (human Choriogonadotropin) FOR  
THE MANAGEMENT OF OBESITY. A DOUBLE-BLIND STUDY**

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## INTRODUCTION

Quite few substances have been so neglected and misunderstood regarding its potential therapeutic effects as hCG, the acronym for Human Chorionic Gonadotropin.

First discovered by Asheim and Zondek as back as 1927 in the urine from pregnant women (2), thousands of articles were published regarding its action on gonads, but comparatively quite a few investigated its vast therapeutics potentialities, encompassing Kaposi sarcoma (34), asthma (20,66), psychoses (22), artheriopaties (14), thalassemia (57,7,19), osteopenia (57), glaucoma (54).

hCG is the glycoproteic hormone normally secreted by trophoblastic cells of the placenta during pregnancy (67). It consists of two dissimilar, separately, but most presumably coordinately translated chains, called the alpha and beta subunits. (12,26,47,27,18,30)

The three pituitary hormones LH (Luteinising Hormone), FSH (Follicle Stimulating Hormone) and TSH (Thyroid Stimulating Hormone) are closely related to hCG in that all four are glycosilated and have a dimeric structure comprising the alpha and beta chains as well. (31,35,79)

The aminoacid sequence of alpha chain of all four human glycoproteic hormones is nearly identical. The aminoacid sequence of the Beta subunits differs and account for by the unique immunological and biological activities of each glycoproteic hormone (63). Beta hCG contains a carboxylic residue of 30 aminoacids characteristic to hCG (11,52)

Its denomination (Human Chorionic Gonadotropin) dates back from the early days, when it was found hCG rendered mature the infantile sex glands in experimentation animals (Gonadotropin) and it was secreted by the placentary chorion (Chorionic) (2,91).

However, recent data suggests both terms can be quite misleading: normal human tissues from non-pregnant subjects (88,74,48,86,87), trophoblastic and non-trophoblastic tumors (33,6,90), bacteria (49), and plants (46,69) express hCG or an hCG-like substance.

The first report on hCG and obesity was published back as 1954 in The Lancet, by a British physician, Dr. A.T.W. Simeons (70). After his publication, hCG was advocated for several years as a useful approach to obesity. The pendulum of its popularity swunged back and forth until a serial of studies (1,3,8,17,36) but three (3,25,80) concluded hCG was of no use to manage the disease

According to basic pharmacological postulates, the administration route may influence the biological activity of a drug. All previous studies were performed with an hCG preparation administered by injections. One of the authors of this study (DB) theorized that an increase in dose and a shifting in hCG administration to a sublingual-enteral route may modify the pharmacological activity of hCG.

The purpose of this study was to assess the utility of an oral presentation hCG for the management of obesity.

## **MATERIALS AND METHODS**

The study design was of the double-blind type: neither treating physician nor patient knowing who was receiving hCG, or an inert substance (placebo). Female patients for the study were selected, since the clinic where the study was performed specializes in the diagnosis and treatment of gynecologic disorders. Details of the protocol were explained to eighty-three volunteers, who were solicited through a written announcement. Before being entered into the study they signed an informed consent in front of a neutral witness.

### **Inclusion criteria:**

We required selected volunteers to meet the following criteria: being at least 25 % BMI (Body Mass Index) overweight, and in general healthy condition. If taking medication for obesity, such as anorectics or amphetamines, they should discontinue the medication at least one month prior the initiation of the study. Drugs to control their clinical diseases (hypertension, hypothyroidism, etc.) were allowed. No patients under steroid, diuretics or hormones were entered in the study. In the course of the study, volunteers were also asked about starting the use of medical prescribed drugs or pharmaceutical preparations during the trial period.

### **Exclusion criteria:**

No teenagers and patients over 75 y.o were admitted to the study. No patients with severe and/or uncontrolled clinical diseases (cancer, IDDM, heart attacks, infarcts sequelae) were accepted. After applying the inclusion/exclusion criteria, we counted upon seventy subjects to divide in treatment groups. These women were assigned to groups Placebo (P, N=26) or hCG (N=44) by a simple randomized sampling method. This latter group was in turn splitted in two subgroups: G1 (N=36) and G2 (N=8), according to the hCG dose administered (see below).

All these patients were Caucasian, ages ranging from 23 to 73 y.o (group P:  $41 \pm 13$ ; group G1:  $42 \pm 12$ ; group G2:  $41 \pm 14$ ), a range of heights of 1,62 cm. to 1,81 cm., and overweight ranging from 25 to 49,9 on BMI Tables.

Since there were no published reports on the oral use of hCG, except for one study posted by D.B. and L.R. on the Internet (<http://indexmedico.com/obesity/hcg.htm>), group G2 was administered twice the dose of G1, to assess if hCG concentration may affect obtained results.

The pharmacist prepared two types of vials: one containing saline solution (Na Cl 0,9% w/v), and the other containing a diluted solution (saline) of commercial, standardized hCG (from Gonacor, Massone Pharmaceutical Industry). HCG Solution was prepared buffering the drug with Sodium Bicarbonate and glycerin.

(Notice : after uploading this report to the Internet, further research we have performed on oral hCG preparations demonstrating that the addition of certain diluents, degrades hCG molecule, partially inactivating its activity,

[http://hcgobesity.org/Pharmacology\\_and\\_pharmacodynamics\\_of\\_oral\\_hCG.pdf](http://hcgobesity.org/Pharmacology_and_pharmacodynamics_of_oral_hCG.pdf)

Therefore, we have reverted to the use of saline solutions instead. Our results have significantly improved since then.

Vials were randomly labeled, each number corresponding to a patient. The pharmacist kept the codes in a sealed envelope. They were opened after completing the protocol.

**Volunteers from group G1** were administered a diluted solution of hCG (125 IU) b.i.d. (twice daily; total: 250 IU). One of the doses was taken before breakfast (fasting). The remaining was administered 1 hr before dinner.

**Volunteers from group G2** were given twice the amount of group G1: 250 IU b.i.d (a total of 500 IU daily).

Patients were advised to maintain the solution at least two minutes in the oral cavity before swallowing (sublingual, to profit from the rich venous plexus existing in this region, also bypassing the liver). They were also told that medication has to be maintained under refrigeration at all times.

**Diet plan:** the same Very-Low-Calorie-Diet (VLCD), specific and detailed, was prescribed to all groups. Breakfast: tea or coffee in any quantity without sugar. Only one tablespoonful of milk allowed in 24 hr. Saccharin or other sweeteners could be used. Lunch: 100 grms. of veal, beef, chicken breast, fresh white fish, lobster, crab or shrimp. All visible fat was carefully removed before cooking, and the meat weighed raw. Salmon, tuna fish, herring, dried or pickled fish was not allowed. The chicken breast was removed raw from the bird. One type of vegetable could be only chosen from the following: spinach, chard, chicory, beet-greens, green salad, tomatoes, celery, fennel, onions, red radishes, cucumbers, asparagus, and cabbage. One breadstick (grissini) or one Melba toast was allowed, and an apple or an orange, or a handful of strawberries or one-half grapefruit.

For dinner: The same four choices as lunch.

The juice of only one lemon daily was allowed for all purposes. Salt, pepper, vinegar, mustard powder, garlic, sweet basil, parsley, thyme, marjoram, etc., could be used for seasoning, but no oil, butter or dressing. Tea, coffee, plain water, mineral water were the only drinks allowed, but they could be taken in any quantity and at all times.

### **Clinicometric controls:**

Volunteers assisted twice weekly at the clinic to be controlled and weighed. The following evaluations were completed once a week:

- I. **Height and Weight**, performed on a medical scale. Volunteers were weighed using normal underwear
  
- II. **Body circumferences**. Using a flexible, non elastic metric tape, the following anatomic areas were assessed:
  - Wrist (**WRT**), at the level of flexion fold (wrist-forearm);
  - Breast (**BRE**), submammary fold;
  - Waist (**WAT**): at the hypogastric region level;
  - Abdominal (**ABD**), at the navel level;
  - Hips (**HIP**): pubic line;
  - Thighs (**THI**): 8 cm. below pubic line;
  - Suprapatellar (**ROT**), at the patella upper border;
  - Ankle (**ANK**), at the flexion fold (peroneal protuberance).
  
- III. **Skinfold thickness**. Using a Lange Skinfold Caliper (Cambridge Scientific Industries, Cambridge, Maryland), the following folds were examined:
  - Tricipital (**TRI**), arm midline, posterior region and tricipital muscle zone.
  - Anterior Axilar line (**AXA**), at the fold created when pinching the skin region at the level of the pectoralis muscle extending to the arm;
  - Subscapular (**SCA** <i>i</i>): inferior scapular spine;
  - Thoracic (**TOR**): at the fold created when pinching the region located immediately below the ribs, at the level of an imaginary line extending from anterior axilar line;
  - Suprailiac (**ILI**), at the fold created 4 cm above the anterior superior iliac spine;
  - Supraumbilical (**UMB**<sub>(u)</sub>), 3 cm above navel;
  - Infraumbilical (**UMB**<sub>(i)</sub>), 3 cm below navel;
  - Thighs (**THI**), internal aspect of thighs, eight cm below the pubic area;
  - Patellar area (**ROT**), at the fold created when pinching the region located 6 cm medial to the internal patellar border.
  
- IV. **Bioelectrical impedance**. Using Tetrapolar Bioelectrical Impedance (**TBI**) with a body fat analyzer Maltron, model BF-905 (Maltron International Ltd., Rayleigh, Essex).  
 Volunteers were suggested to void, placed on supine position thereafter, and allowed to rest half an hour before determination. Self-adhering electrodes were placed on extremities. Every determination was performed with a separate set of electrodes that were discarded after single use.

The following TBI determinations were assessed:

1. Fat weight (FW),
2. Lean weight (LW),
3. Water weight (WW),
4. Calories (CAL).

**V. (3-hCG determinations):** all subjects enrolled in the trial were studied for plasmatic p-hCG levels by an ELISA test (64) on 0-15-30 study days.

**VI. Mood questionnaire:** from the first study week on, patients were given weekly self-administered questionnaires to be completed at home. It consisted of twenty-four questions related to their mood changes in the course of the study, plus four questions related to adverse drug effects. They returned the data at the time of the subsequent visit to the clinic.

## DATA ANALYSIS

Variables were splitted as follows for a better data processing and statistical results presentation:

- **Category I**, BW plus four bioelectrical impedance records (FW, LW, WW and CAL),
- **Category II**, eight anthropometrical measurements (corporal circumferences WRT, BRE, WAT, ABD, HIP, THI, ROT and ANK).
- **Category III**, nine skinfold assessments (TRI, AXA, SCA<sub>i</sub>), TOR, ILI, UMB<sub>(j)</sub>, UMB<sub>(i)</sub>, THI, ROT) (see long names and definitions for the studied variables at the beginning of this section).

Each set was analyzed with a two-way multivariate analysis of variance (MANOVA), comparing the obtained Wilks-lambda' F with the corresponding critical value.

TREATMENT (VLCD diet plus group-specific pharmacological intervention) was considered the between-subject factor with three levels (P, G1, G2), and WEEK of clinicometric control served as an additional within-subject factor with six levels: weeks 0 to 5.

To estimate how the differences between treatment' groups depended on the trial time elapsed since week zero (comparison of pattern trend changes in function of treatment time) we obtained the MANOVA result for the effect of the INTERACTION (also presented in the text as *TREATMENTx WEEK*).

Moreover, to prevent any possible influence of acute effects specifically associated to any VLCD program in the adaptation phase (first 5-7 days), we additionally evaluated with separate MANOVA analyses the differences between groups and within subjects in the course of the last four treatment's weeks.

After obtaining a statistically significant multivariate test for a particular main effect or interaction, we further examined the univariate F tests for each dependent variable. When parameters from these tests displayed significant modifications, data were further analyzed to ascertain which group (P, G1 or G2) was the

responsible for the previous p values obtained. We also compared data basal values from each group against those obtained in subsequent weeks (e.g., records of week 0 against week 1, thereafter against week 2, and so on). These pair-wise comparisons were statistically assessed applying a *post hoc* Scheffe F tests.

Questionnaire responses were converted into percentages and submitted to a chi-square ( $\chi^2$ ) test to compare between-groups and within-groups (pairing off *final vs. initial data*) statistic results.

To attenuate the natural source of within-subject variation, inherent to all assessments of subjective symptoms, we averaged data results from identical questionnaires completed weekly during the initial first two study weeks. Thus, we obtained a more precise "initial questionnaire" (avoiding the potential "adaptation effect" common to any VLCD regime in the first treatment week).

To obtain the final mood behavior results over the last two treatment weeks, they were averaged using the same schema as detailed before. Criteria for significance was  $p < 0.05$ . Statistica 4.2 (from StatSoft, Inc.) for Windows software was used in all statistical processing.

## RESULTS

All volunteers were submitted to the same VLCD schedule lasting five weeks. The objective of this work was to gather data on the potential synergism between hCG administration and a VLCD plan. At the end of the study we counted a total of 4.3 % missing data due to the absence of subjects in control days (no one absent in more than two opportunities) as a consequence of personal situations not associated with the experimental conditions. No statistic differences were obtained between Placebo and hCG groups regarding missing data.

### **1. Regarding weight loss, similar results (with/without hCG administration) were obtained. Bioelectrical impedance exhibited discrete modifications**

As expected, for all types of clinicometric assessments, significant results were obtained through MANOVA analysis on factor WEEK. Figures 1-2 (bioelectrical impedance and anthropometrical data, respectively) show that the time-dependent changes were uniformly present in all tested groups. We therefore estimated that the decreasing observed patterns were the consequence of VLCD acting upon overweight patients. However, regarding skinfold thickness findings (Figures 3-4), we detected in P group a noticeable tendency to attenuation of the within-subject variation during the last (third to fifth) study weeks. This data suggested us that this latter period might be the focus of our interest (see detailed analysis below).

Figure 1 shows the data patterns resulting in all groups from three representative variables (BW, FW and LW) of the variable category I. The MANOVA analysis revealed nearly significant differences for the INTERACTION (TREATMENT x WEEK) [ $F(50,58) = 1.35$ ,  $p = 0.13$ ] in the absence of statistical significance on analysis of TREATMENT as main effect [ $F(10,98) = 1.22$ ,  $p = 0.29$ ].

When all groups were submitted to multivariate and univariate analyses taking exclusively data from weeks 2-5, we observed no significant difference result for the INTERACTION between group P and hCG-treated groups. This finding could be related to differences in mean basal body weights and treatment-dependent responses to the acute effects of VLCD during former weeks.

When *post hoc* Scheffe test was applied to compare the result from each weekly record (weeks 1-5) to its corresponding basal value (week zero), we found similar patterns for all groups concerning analysis of BW and TBI records (compare P vs. hCG-treated groups in every panel of Figure 1).

However, regarding the analysis of FW and BW data, we detected significant differences for the effect of the INTERACTION ( $p < 0.005$  and  $p < 0.05$ , respectively). Comparing FW patterns from groups P and G1:  $F(5,230)=4.55$ ,  $p < 0.001$ . For the comparison P vs. G2, (BW and FW data), we obtained:  $F(5,140)=4.20$  and  $2.97$ , respectively ( $p < 0.01$  for both cases).

## **2. Ability of hCG to enhance diet-induced decreasing of waist and abdominal circumferences**

Figure 2 shows the results for three (category II) body circumference assessments (WAT, ABD and HIP). MANOVA analysis showed significant differences for factor TREATMENT as main effect [ $F(16,92)=1.92$ ,  $p < 0.04$ ], which we do not consider relevant due to the presence of higher basal records in group G2 when compared to the rest of the studied groups.

As a whole, the effect of the INTERACTION did not reveal statistical significance.

Nevertheless, significant differences were obtained after further analysis for the effect of the INTERACTION upon variable WAT [ $F(10,265)=2.44$ ,  $p < 0.01$ , see panel A].

Data assessments from other circumferences did not show statistical differences for this effect between groups [as representative examples, see ABD ( $p=0.35$ ) and HIP records in panels B and C, respectively]. When the records of weeks 0-1 were subtracted from MANOVA analysis, almost all  $p$  values were slightly affected. WAT and ABD measurements demonstrated to be still more affected by the INTERACTION: for WAT,  $p < 0.003$ ; for ABD,  $p < 0.08$ . The INTERACTION significance increased when P controls were compared to subjects from group G2: comparing P vs. G2, and considering data from weeks 0-5, we obtained:  $F(5,140)=2.87$  ( $p < 0.02$ ) for WAT, and  $F(5,140)=1.80$ , ( $p=0.12$ ) for ABD. But when we analyzed data from weeks 2-5, we found the following: for WAT,  $F(3,84)=3.43$  ( $p < 0.02$ ), for ABD,  $F(3,84)=2.73$  ( $p < 0.05$ ).

## **3. Weak effects of hCG on a series of skinfold thickness reductions patterns**

Figures 3-4 show results from subcutaneous fat evaluations, as assessed by skinfold thickness, on nine selected skinfolds. Figure 3 presents three representative folds [TRI, SCA<sub>(i)</sub>, ILI<sub>(u)</sub>] 3 out of five (those previous mentioned plus AXA and TOR) that demonstrated to be slightly affected by the pharmacological treatment.

Analyzing skinfold data from weeks 0 to 5, the main effect TREATMENT showed statistical significance ( $F(10,98)=2.39$ ,  $p < 0.02$ ). However, prevailing higher basal records in group G2 might account for this statistical significance. After studying the effect of the INTERACTION on skinfold results, statistics were as follows: TRI (see panel A),  $p < 0.08$ ; AXA,  $p=0.98$ ; SCA<sub>(i)</sub> (see panel B),  $p < 0.005$ ; ILI (see panel C),  $p=0.23$ ; TOR,  $p=0.35$ .



Performing pairwise comparisons between control P and hCG-treated groups, we observed that the higher significances obtained for SCA<sub>(i)</sub> and TRI skinfolds derived mainly from the comparison between P and G2: for TRI,  $F(5,140)=2.55$ ,  $p<0.04$ , for skinfold SCA<sub>(i)</sub>,  $F(5,140)=6.02$ ,  $p<0.0001$ . MANOVA analysis run on weeks 2-5 data resulted in a significance increase for TREATMENT as main effect [ $F(10,98)=2.55$ ,  $p<0.009$ ]. In addition, the INTERACTION was enhanced on data from SCA<sub>(i)</sub> assessment ( $p<0.00005$ ): by comparing data from groups P and G2 during weeks 2 to 5: for TRI,  $F(3,84)=2.08$  ( $p<0.04$ ), for SCA<sub>(i)</sub>,  $F(3,84)=9.31$ .

#### 4. Higher response rates in a different skinfold series by treatment with hCG plus a VLCD

In Figure 4 we display skinfold thickness results obtained from another series of four examined skinfolds [UMB<sub>(U)</sub>, UMB<sup>^</sup>THI, ROT<sub>(U)</sub>]. MANOVA analysis resulted in a nearly significant INTERACTION [ $F(40,68)=1.55$ ,  $p<0.06$ ] in the absence of statistical significance for TREATMENT as main effect [ $F(8,100)=1.43$ ,  $p=0.20$ ].

When the specific effect of the INTERACTION was evaluated for each skinfold, highly significant differences were found. By computing  $F(10,265)$  values, we obtained the following results: UMB<sub>(U)</sub> (see panel A),  $p<10^{-3}$ ; UMB<sub>(i)</sub> (see panel B),  $p<10^{-5}$ ; ROT (see panel C),  $p<0.05$ ; THI (see panel D),  $p<10^{-6}$ . When we restricted the data analysis from weeks 2 to 5, we found nearly significant results for factor TREATMENT as main effect [ $F(8,100)=1.75$ ,  $p<0.1$ ] and for the effect of the INTERACTION [ $F(24,84)=1.55$ ,  $p<0.06$ ]. The INTERACTION was further studied pairing P group against each hCG-treated group in separate multivariate analyses. By comparing P vs. G1, we found: for UMB<sub>(i)</sub>,  $p<0.04$ , and for RQT,  $p<0.03$  (UMB<sub>(U)</sub> and THI achieved nearly significant  $p$  values). Again, the strength of the INTERACTION [TREATMENT x WEEK] was higher when group G2 was selected for the comparison.

From the obtained data, it becomes clear that skinfolds determinations in Q2 subjects showed a differential response to VLCD schedule with respect to that of P controls (for INTERACTION, in these points of skinfold assessment,  $p<0.0005$ ).

#### 5. The selective response of some skinfolds to hCG was suggestive to be dependent on dose

The experimental design of this investigation was not intended to determine the dose-response curve for hCG acting on diet-induced effects.

However, the effects of hCG on some of these skinfolds seemed to be dependent on dose, since it was found significant differences for the effect of the INTERACTION after the comparison between G1 vs. G2 groups for UMB<sub>(U)</sub> ( $p<0.001$ ) and UMB<sub>(i)</sub> ( $p<0.005$ ), and a nearly significant  $p$  value for THI ( $p=0.11$ ). Figure 4 also displays the percentages of skinfold thickness reduction from the beginning to the end of the clinical trial. We found skinfolds decreases for group G1 ranging from over 22% (for UMB<sub>(U)</sub>, see panel A) up to over 115% (for THI, see panel D) over respective decreases in P group. These differences were still higher when G2-subjects were compared to P controls: by computing the ratio between decrease percentages, G2 had over twice (for UMB<sub>(U)</sub>, see panel A) to over four-fold (for THI, see panel D) the skinfold records drops observed in group P (see each actual percentage, group by group, in Fig. 4).

Most of the differences between hCG-treated subjects and P controls regarding skinfold reduction rates were enhanced when data corresponding to week five was compared to records of week two instead week zero (data not shown).

### **6. Improvement of mood-related parameters by the effect of hCG treatment**

In Figure 5 we display the responses to four representative questions asking about the occurrence frequency for specific mood-related events, according to a multiple choice designed questionnaire completed every treatment week by all the subjects enrolled in the trial.

Panels A to D display the initial and final questionnaire results, expressed as percentages for each optional response (covering a four-option frequency scale from never to frequent).

Using this procedure, we expected to find in tested volunteers skewness towards either sense concerning their behaviors and feelings in response to a diet and a pharmacological intervention. For all these questions, and compared to control subjects, hCG-treated volunteers (G1+G2) showed a trend to improvement of inter-personal contacts and mood control when confronting upsetting or conflicting situations. Pairing off final (f) vs. initial (i) distribution of percentages for optional responses, we particularly found statistical significance in two of these questions in group G (after  $\chi^2$  test:  $\chi^2=16.3$ ,  $p<0.002$ , and  $\chi^2=7.82$ ,  $p<0.05$ ; see right sectors of panel A and B, respectively).

P group-subjects did not present temporal differences (see panel A), or were adversely affected in their mood during the trial ( $\chi^2=14.4$ ,  $p<0.002$  (compare in panel B corresponding initial and final values for group P and G).

Furthermore, group P exhibited in other two questions certain skewness to the impairment of its mood (see left half of panels C and D,  $p<10^{-5}$ ); for group G we obtained the  $\chi^2$  values 1.51 and 3.98, respectively ( $p>0.3$ ), indicating the absence of temporal mood changes.

For all other mood-related questions, no statistical significant difference between groups was found (data not shown).

We also included some questions intended to evaluate the potential occurrence of treatment-dependent clinical anomalies regarding hormonal, physiological or metabolic disorders. We found no significant difference after final vs. initial records' comparison (data not shown).

7. No detectable (3-hCG plasmatic levels in all tested groups. On treatment days 0, 15 and 30 we have tested all volunteers, screening for the presence of plasmatic p-hCG. Concentrations were undetectable in all cases (data not shown).

## DISCUSSION

Concerning hCG and its utility for the management of obesity, this study introduces two new aspects, and adds new data for a third:

- I) This is the first report assessing variables not included in previous reports (, 38,51,68,89);
- II) We report a new administration route for hCG management of obesity, the oral approach, which has never been reported before;
- III) We have detected mood changes in hCG treated patients, regarding a better confrontation of daily emotionally conflicting situations.

These assertions will be separately discussed:

### I) Skinfold thickness (SKF) and Tetrapolar Bioelectric Impedance (TBI) records.

Both approaches have been extensively discussed in the literature. It was shown that the correlation between the values obtained with the two methods to be linear and highly significant for both sexes (42,81,27).

There is general agreement that skinfolds calipers are particularly useful in the clinical setting (56,82,16,76,10,65, 9,15,75), particularly in view of the fact that measurement of subcutaneous body fat at different body sites is becoming increasingly important for the characterization of risk of certain disease states (55).

When comparing skinfolds assessments to body circumference estimates, despite some data suggests that the latter approach appears to be more sensitive in the determination of subcutaneous body fat (53), this procedure is in our opinion subjected to clinical variables (bloating syndrome after a meal, premenstrual water retention, etc.) that may affect negatively on the final estimates results. Also, when comparing SKF to body contour assessments, some data suggests that the pattern of fat thickness body distribution measured over a number of specific sites by one method of measurement is unlikely to be duplicated by of the other method on the same individual (40,41).

Adipose tissue patterns show great variability, indicating the importance of using skinfold caliper readings from a variety of different anatomic sites including upper limbs, lower limbs and trunk (30,65).

According to the above conclusions from several authors (72,13,60, 25,73,62), we would like to suggest that former studies on hCG and obesity lacked of sufficient data to accurately estimate modifications of adipose tissue distribution in tested volunteers. Consequently we designed the study to assess as many as possible variables.

As far as our study concerns, we subjected each volunteer enrolled in the trial to four bioelectrical impedance, eight anthropometrical plus nine SKF evaluations. Performing this multiple site determinations, our results indicate that specific SKF are highly responsive to hCG pharmacological intervention (upper and lower umbilical). The greater response was obtained in those regions where the corresponding circumference assessments resulted in nearly significant or significant decreases through the trial period (see waist and abdomen records in Fig. 2 and the above detailed description of statistical results for the effect of the interaction).

### **II) Oral hCG might be an alternative therapeutic administration route.**

No data appears on the scientific literature regarding an oral administration of hCG in humans. But results from this study suggest hCG may be used by the sublingual-enteral route. Despite plasmatic B-hCG remained undetectable both in Placebo and hCG groups throughout the study, an oral administration of hCG proved to possess therapeutic activity.

Since commercial preparations of hCG contains B-endorphin (see below), it may be tempting to hypothesize that this pentapeptide might account for the pharmacological activity observed on mood stability in the course of the Protocol.

### **III) Volunteers treated with hCG coped better with daily irritating situations.**

As can be seen on Figure 5, hCG-treated groups handled better their irritability, their mood at home, and were less prone to episodes of extreme nervousness capable of provoking violent discussions . Several reports proposed hCG might be used for the treatment of psychoses or neurosis (29,61,24). Our study appears to corroborate these proposals.

To conclude, this study poses several still unanswered questions:

**1. hCG absorption.** We have tested all volunteers, screening for the p-hCG in plasma. Concentrations were undetectable in all cases.

Therefore, which hCG fraction is responsible for the pharmacological activity observed in our study?. hCG molecular size (alpha chain -14,500 KD; beta chain -22,200 KD) makes highly improbable that the entire molecule has been absorbed. Our hypothesis is that only a fraction of the entire hCG molecule is absorbed through this administration route .

**2. hCG and lipid metabolism.** We do not know precisely how hCG acts on adipose tissue metabolism. However, some reports (32,84,85,83 ) suggest hCG possesses a metabolic activity on adipose tissue (i.e. decrease lipogenesis). These actions are not directly exerted upon adipocytes, since fat cell membranes have no receptors for hCG (32).

**3. hCG and mood.** A stable mood and lack of attrition characterized the hCG-treated group. It is well known that VLCD's are associated with mood changes, particularly attrition (78) during the dieting period. In one study, disinhibition and hunger were significantly related to anxiety and depression while restraint was not (44). Another study concluded that elevated levels of anxiety persist in female patients throughout a VLCD course of treatment (45).

Also many patients complain about fatigue in the course of a VLCD (4)

Conversely, our data suggests that hCG-treated volunteers rather improved their attitude towards their environment, in the sense of an enhanced well-being, less irritability and lack of fatigue. Since commercial preparations of hCG contains (3-endorphin (39) and this neuropeptide has been demonstrated to affect the function of limbic-emotional circuits (21,58,5,28), we hypothesized that the p-endorphin fraction present in commercial preparations of hCG might account for the activity observed regarding mood control.

Additional studies remain to be performed to test the validity of this hypothesis.

## CONCLUSIONS

1. Female obese volunteers participating in a double blind study, and submitted to the administration of an oral presentation of hCG plus a VLCD, decreased specific body circumferences and skinfold thickness from conspicuous body areas more efficiently than Placebo+VLCD -treated subjects. Since a significant fat proportion from total body fat is subcutaneously located (50 to 65 percent, depending on sex and fat distribution), this hCG metabolic activity would result in a reduction of the total body fat mass, the main cause for obesity. We suggested that the combination of a VLCD and oral hCG could not only trigger clinically significant changes in subcutaneous fat stores but simultaneously decrease body weight and modelate body contour.
2. hCG oral administration proved to be a safe and effective procedure on obese treated volunteers. No side effects were observed in the course of the study. There are no reports in the literature regarding this administration route to compare our findings.
3. Compared to placebo treated subjects, volunteers managed with an oral administration of hCG coped more efficiently with daily irritating situations, were in a better mood, and handled home conflicts without stepping up family discussions.

This study appears to contradict former conclusions on the issue of hCG and obesity. We attribute those differences to a different approach, including variables not assessed in former publications.

### Acknowledgements:

One of the authors of the report (Dr. Belluscio, Daniel) was granted with a staying period at the Bellevue Klinik, Zurich, Switzerland, to be trained on the clinical management of the hCG method. He would like to thank Dr. Trudy Vogt (Clinic Director) for her generous contribution through this grant to part of the ongoing Research Program performed at her Institution.

## FIGURES

### Figure 1. Body weight and bioelectrical impedance records.

During five weeks of hypocaloric diet the subjects enrolled in the clinical trial were simultaneously administered a daily dose of 250 UI hCG (group G1, N=36), or 500 UI (group G2, N=8). A third group (Placebo) received an equivalent volume of saline solution (group P, N=26). Data was obtained at the beginning and weekly during the trial period (records 0 to 5) for *Body Weight* (panel A) and four bioelectrical impedance assessments (here it is only displayed details from *Fat* and *Lean* weights on panels B and C, respectively).

Data are expressed in *kg*, mean  $\pm$  SD (bars at top). Results were submitted *a priori* to MANOVA analysis. When multivariate and univariate analyses were performed taking exclusively data from weeks 2 to 5, differences between groups were strongly attenuated (see details in the text). The asterisks mark statistically significant differences between weekly records (weeks 1 to 5), and the corresponding *basal* values determined in week 0 (analyzed *a posteriori* by Scheffe F test).

p<0.05, \*\* p<0.0002, \*\*\* p<0.0005

### Figure 2. Body circumferences.

Here we display the *basal* ("0") and subsequent five weekly results (weeks 1 to 5) from three out of eight anthropometrical parameters examined in this work. Panel A=Waist. Panel B=Abdomen. Panel C=Hip.

All results are expressed in *cm*, mean  $\pm$  SD (bars at top). Regarding all corporal circumferences assessed, only *Waist* and *Abdomen* were significantly affected by the interaction of TREATMENT [diet plus pharmacological treatment] and WEEK (trial stage). These differences appeared enhanced when only data from weeks 2 to 5 was gathered to perform a separate MANOVA analysis (other details in legend of Figure 1)

p<0.05    \*\*p<0.0005    \*\*\*p<10<sup>-6</sup>    #p<0.005

**Figure 3: Skinfold thickness reduction on five "low-responsive" skinfolds.**

Simultaneously with bioelectrical impedance and anthropometrical assessments, we examined subcutaneous fat stores by plicometries. Results are expressed in *mm*, means  $\pm$  SD (at top). Only *Tricipital* (see panel A) and *Sub-scapular* (see panel B) skinfold assessments demonstrated significant or nearly significant differences by comparing group G2 and the control P for the effect of TREATMENT or the INTERACTION (see statistical analysis details in the text).

It is also shown the data obtained for *Suprailiac* (see panel C) skinfold. Concerning these series of *low responsive* skinfolds, no relevant difference between groups was raised after pairwise comparisons of each treatment weeks' record with its corresponding basal value: by Scheffe test, \*  $p < 0.03$ , \*\*  $p < 0.0005$

**Figure 4: Plicometries on four "high-responsive" skinfolds.**

Here it is shown a different series of skinfolds displaying a clear treatment-dependent behavior, most noticeable from the second week of treatment on. When last four treatment' weeks were submitted to study, MANOVA analysis resulted in nearly significant differences for factor TREATMENT and the INTERACTION. For each of these skinfolds, highly significant statistical results were found between G2 and P groups for the effect of the INTERACTION.

In this Figure we can observe the percentages of skinfold thickness reductions, comparing data obtained at the end of the trial with the corresponding basal values (week zero). P values resulting from Scheffe test are marked by asterisks as follows: \*  $p < 0.05$ , \*\*  $p < 0.0005$ , \*\*\*  $p < 10^{-4}$ , #  $p < 0.01$ , ##  $p < 10^{-6}$ . See other details in the legend of Fig. 3 and the text.

**Figure 5: Mood assessment.**

The figure presents the responses to four representative questions from a total of twenty-eight asked to volunteers at the end of every treatment' week by means of an auto administered questionnaire.

Questions included were related to aspects of inter-personal relations, well-being, mood self control when confronting conflictive situations, etc. (see titles of panels A to D).

All data from subjects pertaining to groups G1 and G2 were pooled ("group G") for data analysis. Initial and final results are shown with letters *i* and *f*, respectively. In the abscissa axis: *Pi* (*Placebo: initial*), *Pf* (*Placebo: final*); *Gi* (*hCG: initial*) and *Gf* (*hCG: final*) respectively. Statistical significant differences within groups between *final* and *initial* questionnaires responses were obtained by applying  $\chi^2$  test as follows: for group G, \*  $p < 0.05$  (panel A) and \*\*  $p < 0.002$  (panel B); for group P, \*\*  $p < 0.002$  (panel B) and \*\*\*  $p < 10^{-5}$  (panels C and D)













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**PHOTOGRAPHIC DOCUMENTATION**  
*(BEFORE AND AFTER TREATMENT)*

















