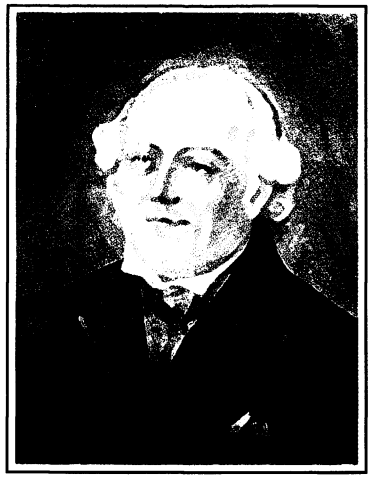
PARADIGMA HOMEOPATHICA



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Круглый стол

THE EFFECT OF THYROIDINUM 30CH ON THE BODY WEIGHT REDUCTION OF FASTING PATIENTS. A RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND CLINICAL TRIAL

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Summary

Background: During fasting the daily reduction of body weight is partly counteracted by low triiodothyronine (T3) plasma level and corresponding reduction of protein and fat catabolism, an adaptation that can be overcome by T3 treatment. This study investigates whether an ultramolecular dilution of a preparation of thyroid gland (thyroidinum 30cH) affects the course of body weight of fasting patients in so called „fasting crisis".

Methods: In this randomized double-blind placebo-controlled trial 208 fasting patients encountering a stagnation or increase of weight received a single oral dose (5 pellets) of thyroidinum 30cH or placebo. Body weight and subjective complaints were measured on days 1-3, blood samples were taken on days 0-2 after medication. There were no drop-outs. 14 patients showed minor deviations from the protocol but were included in

the intention-to-treat analysis. Main outcome measure was the reduction of body weight two days after medication.

Findings: The reduction of body weight two days after medication was significantly lower in the thyroidinum group (347g, SD 304g, n=102) than in the placebo group (439g, SD 313g, n=106). The mean difference was 92 g, 95% CI 7 to 176 g, p=0.034. Covariate adjustment for baseline imbalances, however, weakened the result to non-significant level (p=0.083). No striking differences were found in the laboratory data and complaints.

Interpretation: The moderate evidence for efficacy of an ultramolecular dilution of thyroidinum in „fasting crisis" was not strong enough to clearly reject the null hypothesis. On the other hand, post-hoc analysis suggests that by predefining distinct outcome measures this clinical model may be able to yield significant results, resistent to baseline imbalances.

Background

One of the most prominent and criticized stumbling-blocks of homeopathic doctrine is its principle of „potentization", i.e. the idea that gradual dilution and succussion of a drug enhances rather than diminishes its medicinal forces. The claim, however, that even ultramolecular dilutions of homeopathic remedies might be therapeutically effective clearly exceeds the basic paradigm of pharmacology that holds that without active substance no pharmacological efficacy is to be expected. Although a number of clinical trials seems to show some evidence for ultramolecular effects, apart from few exceptions, methodological quality largely lags behind the exacting demands to studies of that kind.

To help breach this gap we designed and conducted a monocentred GCP-conforming controlled clinical trial with objective und subjective outcome measures to test an alleged effect of a homeopathic remedy in ultramolecular dilution. As a clinical model we chose the putative influence of a 10^{-60} dilution of thyroidinum (preparation of thyroid gland) on the course of weight reduction of fasting patients encountering an unexpected stagnation or increase of body weight.

From literature fasting is well known to reduce triiodothyronine (T3) plasma levels, mainly due to an inhibition of extrathyroidal conversion of thyroxine (T4) to triiodothyronine (T3). This low-T3-state is regarded to be an adaptive mechanism to save energy expenditure by reducing protein and fat catabolism and thermogenesis. T3-treatment, on the other hand, overcomes this mechanism and thus augments the otherwise hampered reduction of body weight in fasting patients.

During fasting patients usually are loosing weight every day in declining amounts ranging from about 1.0 kg/d in the first days to about 0.3 kg/d after one or two weeks. Despite food restriction, on some day of the fasting period a stagnation or even increase of weight, accompanied with typical psychic and somatic complaints (so called „fasting crisis"), may occur at individual patients. According to clinical experience, treatment of

these states with high dilutions („potencies") of thyroidinum as a homeopathically matching remedy usually was followed by a normalisation, i.e. a compensatory increase of the daily weight reduction on the next day. Considering the pathophysiological relations between fasting, thyroid hormone, and weight reduction we decided to test whether treatment of a „fasting crisis" with thyroidinum 30cH yields different objective and subjective outcomes than treatment with placebo.

Methods

Protocol

The present double-blind study was based on the well established infrastructure of a simultaneously conducted 5-year quality-assurance documentation of fasting therapy. During that period body weight of all fasting patients of the hospital was checked daily under standardized conditions and supervision of attending nurses. All patients had to fill out questionaires on contentment and quality of life before and after fasting and had to report their caloric and liquid intake, their activities and their complaints daily. Doctors had to document history, examination, diagnoses, medication, therapies, and laboratory findings at the beginning and the end of fasting. At the Krankenhaus fuer Naturheilweisen fasting therapy is applied to a broad spectrum of diagnoses comprising hypertension, diabetes, osteoarthritis, bronchial asthma, migraine, etc. and consists in a 160 kcal diet with unlimited drinking of mineral water and neutral herbal tea.

Out of these fasting patients those who encountered a spontaneous stagnation or increase of body weight were checked for eligibility (inclusion and exclusion criteria). They had to be fasting 3 days so far and 3 more days prospectively, had to have a weight decrease during the last 3 days of at least 100 g on each single day, comply with the documentation requirements and have collected (complete) data in their checklists, be major, and sign an informed consent. They might not have a severe endocrinologic, metabolic, hematologic, infectious, cardiovascular, respiratoric, hepatic, renal, tumorous or psychiatric disease, might not take thyroid hormones, thyreostatics, strong psychochemicals, opiates or iodine containing medication, not have had radioiodotherapy or strumectomy, not participate in another clinical study or have already participated in this study, not be abusing alcohol or drugs, not be pregnant or breast-feeding, and not have been incorrect in their diet.

Patients entered into the study were subjected to blood examinations on three successive days (day 0, 1, and 2), always at the same daytime. Immediately after the first blood sample was taken, study medication was administered, one single dose of 5 pellets – thyroidinum 30cH or placebo. As already instructed before, patients continued to measure their body weight under quality-assured conditions and report their complaints, physical activities, caloric and liquid intake etc. in structured diary-forms on each of the following three days (day 1, 2 and 3).

Initially, the main outcome measure was prespecified to be the reduction of body weight on the day after medication. Secondary outcome

measures were determined to be the reduction of body weight on the two following days, the course of 34 laboratory data from day 0 to day 1 and day 2 respectively, and the course of 15 complaints during the days 1 to 3. Additionally, physicians and patients were asked for a global assessment of well-being, toleration, and effectiveness of the medication on day 3 after administration.

The target sample size was calculated to be 300 patients. Expecting a recruitment of two patients per week the study was scheduled for 3 years. According to the sequential plan after 50 patients an interim analysis (for $p<0.005$, sic!) and after 300 patients the final analysis (for $p<0.048$) was determined. A significant result of the interim analysis would have terminated the study. Statistical analyses were intended to be confirmatory for the primary and explorative for the secondary outcome measures.

Assignment and blinding

The study medication was manufactured by a German pharmaceutical company specialized in homeopathy (DHU, Karlsruhe). Powder of dried thyroid gland of German pigs was triturated, diluted, and succussed in the ratio 1:100, 30 times, according to the German homeopathic pharmacopoeia (HAB). With the last dilution pellets of sucrose were impregnated and thus constituted the active medication, while another part of the same charge of sucrose pellets was used as control medication. This procedure guaranteed that both sets of study medication consisted basically of identical components (including possible traces of contamination, etc.) with the only difference of the dilution of thyroidinum 30cH having been poured on one of them.

Study medication was randomized in blocks of six, stratified for males and females to ensure equal representation of the outnumbered men in both treatment groups, by the Biometric Center for Therapy Studies in Munich where the list with the code was deposited in a sealed envelope. Since nobody in the hospital knew the code or perceived any difference in appearance or taste between the single units of the study medication, blinded assignment was completely guaranteed. Prior to inclusion every patient had to sign an informed consent. The protocol was approved by the ethic committee of the Bavarian board of physicians.

Findings

Participant flow and follow up

At the Krankenhaus fuer Naturheilweisen out of 499 fasting patients reported to be encountering a stagnation or increase of body weight 211 patients were eligible and allocated to a randomization number. Three patients (2 thyroidinum, 1 placebo), however, withdrew their consent before opening the container. Thus, 208 patients actually received study medication. In 14 cases shortly after administration it was noticed that by mistake on the part of the physician on duty one of the eligibility criteria had been overlooked. Nevertheless, all 208 patients were followed up and analysed.

Analysis

After one year file-closing, „semi-deblinding", and interim analysis were carried out. Contrary to full deblinding which tells the analyst what medication the groups had received (thyroidinum or placebo), „semi-deblinding" reveals just the information which individuals belong to one group (A) and which to the other (B), but not which group was the treatment and which the placebo group. Per-protocol analysis (n=53) showed a mean reduction of body weight on the day after medication of 476 g (SD 351 g, n=29) in group A and of 575 g (SD 251 g, n=24) in group B. Since the *p*-value (0.25) was not < 0.005 the study was continued.

A comparison of reduction of weight on days 1, 2, and 3, however, showed that the most striking difference between both groups (A and B) appeared on the second rather than on the first day after medication (181 g on day 2, versus 99 g on day 1). Considering a possible delay of metabolic changes as well as the bipolarity of many homeopathic effects, it seemed in fact more plausible to expect the main – if any – effect of a remedy supposed to modulate thyroid metabolism and reduction of body weight of fasting patients at the later date. Hence, in default of any hints from literature to our pioneering research model, in an amendment to the protocol the main outcome measure was changed from weight reduction on the first to weight reduction on the second day. This amendment was written down, signed and sent to the Biometric Center (were it was kept in a safe) at this early stage of (just semi-deblinded) interim analysis when neither the analyst nor the investigators knew what medication the groups had received.

After three years and three months final file-closing, full deblinding, and analysis took place. Study medication had been administered to 208 patients (intention-to-treat collective). 14 patients showed one minor deviation from the protocol each, such as not having had a reduction of weight for three consecutive days preceeding the stagnation of weight (5 thyr. and 1 plac. patients), not having had a stagnation or increase of weight on day 0 (1 thyr. patient), having taken thyroid hormone (1 thyr. and 1 plac. patient) or an iodine containing drug (1 thyr. and 1 plac. patient) during the study period, having had radioiodine therapy before (1 thyr. patient), not being major (1 thyr. patient) or having already been subject to the study (1 thyr. patient, eight months before). There were no drop-outs. The per-protocol collective thus contained 194 patients. One single unintended severe adverse effect (transient ischemic attack with hemiplegia) receded under therapy, while the code remained unbroken. After analysis it turned out that this patient had received placebo medication.

Statistical analysis of the intention-to-treat collective showed that the average reduction of body weight two days after medication was significantly lower in the thyroidinum group (347g, SD 304g, n=102) than in the placebo group (439g, SD 313g, n=106). The difference between the sample means was -92 g, with a 95% confidence interval from -176 to -7 g. The *t*-test statistic was 2.14, with 206 degrees of freedom and an asso-

ciated p-value of p=0.034. Removing outliers increased rather than decreased significance.

No striking differences between the groups, however, were found in the secondary outcome measures, i.e. reduction of weight on day 1 (difference of means: 17 g) and day 3 (difference of means: 18 g). Nor did exploratory analysis of the course of the laboratory findings from day 0 to day 1 or 2 respectively and the course of daily complaints during the days 0 to 3 reveal major differences regarding direction or quantity of the changes. The same was true for the assessment by physicians and patients regarding well-being, toleration, and effectiveness.

Both groups were comparable in some 200 baseline parameters, indicating that randomization had been quite successful. A few random differences, however, had to be considered as confounding factors of the result. E.g. the mean body weight was higher in the placebo group (not significant) as well as the mean daily weight reduction in the run-in period (significant on days -2 and 0). To determine their impact, a covariate adjustment was carried out using a general linear model (GLM, univariate), analysing each confounding variable in sequence. In the intention-to-treat collective (n=208) significance of the main outcome, i.e. the difference in weight reduction on day 2, remained after adjustment for the covariates body mass index (p= 0.046) and weight reduction on day 0 (p=0.021), but not after adjustment for total body weight (p=0.061) and for each weight reduction preceding the day of medication: day -3 (p=0.055), day -2 (p=0.083), and day -1 (p=0.053). The portion of group difference which was independent of sex difference yielded a p-value of 0.039 in both collectives. Thus, adjustment of the main outcome for baseline imbalances of weight and previous weight reduction between the groups weakened the otherwise significant result to p-values greater than the critical level of 0.048. After removal of the two extremes and nine outliers, however, the difference in the main outcome became highly significant (p=0.009) and maintained significance even after covariate adjustment (p=0.043).

Interpretation

Although initially significant, the result of this study was weakened by baseline adjustment and thus ultimately missed significance to refute the null hypothesis which denies that one dose of thyroidinum 30cH affects the weight reduction of fasting patients differently than one dose of placebo.

To meet the exacting demands of a clinical trial that deals with a highly controversial subject like homeopathy, this study was rigorously designed, conducted, monitored, and audited according to the regulations for quality-assurance of clinical trials, the EG-GCP-guidelines „Good Clinical Practice for Trials on Medicinal Products in the European Community", etc. Through personal dedication and high compliance data quality eventually proved to be excellent (virtually no missing or unplausible data). Comparability of both groups was assessed by means of some 200 parameters collected from each patient on voluminous case report

forms: demographic data, physical examination, diagnoses, history, diagnostics, therapeutics, medication, 34 laboratory data, 15 complaints, liquid and caloric intake, stool, bowel movement, laxatives, etc. Apart from three patients who withdrew their previously given consent before receiving study medication, there were no drop-outs. Estimation of sample size together with a stochastic curtailment ensured sufficient power when the trial was ended after 208 enrolled patients.

The clinical model was chosen according to observations made by doctors at the Krankenhaus fuer Naturheilweisen for several decades and based on pathophysiological as well as homeopathic reflections. Since the (energy sparing and weight reduction restricting) low-T3-state of fasting patients can be overcome by T3 intake, administration of a homeopathic preparation of thyroid gland was as well expected to affect this system. According to homeopathic materia medica, thyroidinum is reported to provoke many symptoms similar to „fasting crises" experienced by patients encountering a stagnation or increase of weight, e.g. headache, nausea, irritability, weakness of memory, palpitation, flushes of heat, etc. and thus qualifies to be – according to the principles of similars – homeopathically indicated in this specific condition. If the alleged effect of thyroidinum on thyroid metabolism and the course of weight reduction in fasting patients should be demonstrable even in ultramolecular dilution by means of objective measures, this would be a major challenge to the common rejection of the concept of „potentization" on the part of mainstream medicine. According to clinical experience and homeopathic/physiological reflections, we expected an augmented weight reduction on day 1 in the treatment group which could possibly be followed by a secondary impairment of weight reduction on day 2.

For lack of previous research and literature on this topic the main outcome measure was predefined in terms of absolute weight reduction. The null hypothesis read: there is no difference in the reduction of weight between the thyroidinum and placebo group after administration of the study medication. Contrary to initial expectation, the semi-deblinded interim analysis after 53 patients (without knowing what medication the groups had received) showed less difference in weight reduction on day 1 than on day 2 and therefore prompted a revision of the protocol with a change of the main outcome measure (weight reduction on day 2 rather than on day 1). In fact, in the final analysis the difference in weight reduction two days after medication was significant (p=0.034) but covariate adjustment for baseline imbalances weakened the p-value to levels between 0.053 and 0.083. No significance would have been achieved had the original main outcome measure (weight reduction on day 1) been kept unchanged (p=0.71), or had the analysis of the amended outcome parameter (weight reduction on day 2) been confined only to those patients recruited after the interim analysis was performed (p=0.33). In view of these facts, the null hypothesis can hardly be rejected.

Post-hoc inspection of the chart of the daily weight reduction in each group, however, suggests an alternative interpretation of the data. Since

in the thyroidinum group the average body weight and the weight reduction on five of the seven days was consistently lower than in the placebo group, the really odd results seem to appear on day 1 and 3 when this difference was not only extinguished but inverted. Had the main outcome measure – instead of emphasizing the absolute amount of weight reduction – been predefined as change on day 1 from the mean baseline difference in weight reduction (from day -3 to day 0), the result would have been an augmented reduction of weight in the thyroidinum group on that day (difference 92 g, 95% CI -7 to 191 g, p=0.070). Using body mass index instead of body weight and percentual instead of absolute reduction this finding would even have yielded significance (difference 0.12% of BMI, 95% CI 0.01 to 0.23 %, p=0.034) and proved to be robust to covariate adjustment. This result would be consistent with our initial expectation of an increase of weight loss, i.e. hyperthyroid effect, on day 1 after treatment. Although data driven post-hoc testing has no confirmative value these speculations may serve as suggestions for further studies of this kind.

Neither the claim of an increase on day 1 nor of a decrease on day 2 of the daily weight reduction, however, would be corroborated by the objective and subjective secondary outcomes which failed to show corresponding differences between the groups, in the course of laboratory findings as well as in the course of daily complaints. This discrepancy casts additional doubt on the validity of the isolated result. Certainly, a difference of 92 g in weight reduction two days after medication is not clinically relevant all the more when its direction (impaired weight reduction, i.e. weight gain) is the opposite of what fasting patients usually desire. However, a difference of 0.12% in body mass reduction one day after medication (increased weight reduction) would not seem to be completely irrelevant because it would 1. help patients to overcome their „fasting crisis" more quickly and 2. demonstrate significantly the remedy's efficacy confirming clinical experience hitherto collected.

Despite the puzzling results of this study, in an under-researched field like homeopathy it may still be a valid contribution to detect and present a promising clinical model for proving its most intriguing claim of the efficacy of ultramolecular dilutions. The outcome measures of this study were certainly neither appropriate nor sophisticated enough, but replications – e.g. on the basis of changes in percentual reduction of body mass index – may be of interest.

Conclusion

Despite meeting high quality standards and assuring randomization and blind assignment, a random imbalance of a few prognostically important baseline parameters attenuated the otherwise significant result of the study (impaired weight reduction two days after treatment). Due to the lack of previous research and literature, the main outcome measure was predefined in such a way that no convincing evidence was detected for an alleged effect of an ultramolecular dilution of thyroidinum on the weight

reduction of fasting patients after a stagnation/increase of weight. Post-hoc analysis, however, suggests that by using the same clinical model with more appropriate and sophisticated outcome measures efficacy may indeed possibly be demonstrated in replication studies (increased weight reduction one day after treatment). In conclusion, this study failed to disprove the null hypothesis relating to this outcome measure and a specified preparation of this homeopathic remedy for a special clinical indication, but must not be misunderstood as a refutation of the principles of homeopathy at large.