Benefits of Neuromediators in the treatment of overweight and obese patients:

STUDY COMPARING STANDARD PROTEIN DIETS WITH PROTEIN DIETS ENRICHED WITH NEUROMEDIATOR PRECURSORS
INTRODUCTION

PROTEIN DIET (SPD) AND NEUROMEDIATORS IN THE TREATMENT OF PRE-OBESITY

At present, 62% of the British population is overweight, and 23% is obese.

There is agreement that these patients require a complete treatment which should be conceived as a long term strategy. Initial treatment will vary in accordance with the medical facilities available: some recommend starting with moderately hypocaloric diets, while others begin treatment with very low calorie diets (VLCD).

On the other hand, some patients request VLCD treatments in order to lose the first kilos quickly (Gougeon, Saris) and so keep their motivation up.

Notable among these diets is the Standard Protein Diet (SPD), which has been used for so long that its effectiveness need not be tested any further (Saris). There is, however, one important issue in relation with these VLCD: on returning to a hypocaloric diet that is closer to the quality and energy intake of normal food, a phenomenon known as disinhibition sometimes occurs. At the end of the initial phase there is a risk of losing control, when the patient may revert to overeating again in compensation for the frustrations undergone, thereby putting the weight lost back on.

The Standard Protein Diets involve the administration of products containing between 65 and 70% protein for one or several weeks, often providing between 75 and 100 grams in total per day Potassium, vitamins, NaCl and other micronutrients are added to compensate for deficits in intake and their elimination through urination.

An SPD can only be prescribed by a doctor who has received specific training, and who can also ensure regular monitoring of the patients.

Although Protein Diets are generally well-accepted, there are three potential inconveniences:

1- It is very different from normal eating, and cannot be followed strictly for a long period.

2- The patient’s stress and eating behaviour cannot be treated.

3- In some cases, they can provoke or worsen an eating disorder, because intake of energy nutrients, which are below the real needs, can cause deficiencies and minor cerebral dysfunctions that can develop into behavioural disorders. Only a few studies have been carried out to demonstrate these disorders and, above all, eating disorders among patients following a standard protein diet.

Hypocaloric diets can lead to a number of disorders, and more so the more restricted they are: sleep disorders, compulsive eating, anxiety, depression, irritability, mood swings, restlessness... This may be partly due to a decline in the production of neuromediators in the brain that regulate mood and food intake (Westerterp-Plantega etc).

Among these neuromediators are Serotonin and Dopamine. they are produced in situ, from essential or semi-essential amino acids such as tyrosine and tryptophan. In the case of a severely hypocaloric diet, one part of the protein ingested is used to provide energy for basic metabolism and metabolism related with everyday activity, however minimal. We can conclude, then, that the prescription of a tryptophan and tyrosine supplement with these Protein Diets may help to maintain the level of these amino acids in the brain.

There is only limited data on this subject in international studies, and no complete therapeutic trials that have evaluated the effectiveness of this treatment.

This new study has therefore aroused interest.

STUDY

Objectives

• Supplement a SPD with precursors of neuromediators, in comparison with a standard PD.

• Using a double blind trial including over a hundred patients.

• Verifying its effectiveness in patients’ weight loss, mood disorders and eating behaviour.
OBESITY: AN ALARMING EPIDEMIC

In all countries, obesity and overweight have been increasing steadily for many years. The United Kingdom is the 3rd OECD country with higher obesity prevalence. (figure 2) In 2008, 61% of its population was overweight. Nowadays, 25% of the British population is obese, whereas 17% was 10 years ago and only 8% 20 years ago. (figure 3)

BODY MASS INDEX - BMI: weight (Kg.) / height squared (m) = W/H

- Normal weight: 20 to 25 Kg./m
- Overweight: 25 to 30 Kg./m
- Obesity: 30 to 40 Kg./m
- Morbid obesity: > 40 Kg./m

Figure 1: Precursors of Neuromediators

AMINO ACIDS PRECURSORS OF NEUROMEDIATORS

TYROSINE

Tyrosine hydroxylase

DIHYDROXY PHENYLALANINE (L-DOPA)

DOPAMINE

Dopa decarboxylase

TRYPTOPHAN

Tryptophan hydroxylase

5 HYDROXY TRYPTOPHAN (5-HTP)

SEROTONIN

L amino acid Decarboxylase

Figure 2: comparison of the percentage of obese among total population in OECD member countries, 2000-2001.

Figure 3: evolution in obesity rate in some OECD member countries

Table:

<table>
<thead>
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**TYPES OF STUDY**

- 110 patients included in the study, 102 suitable cases in Spain and France.
- Randomised double blind study with random assignation of patients to create four groups, with prior written informed consent of the patients.
- 1st active 4-month phase for inclusion and treatment, 2nd phase after 6 months, to collect patient data
- Statistical analysis in order to handle:
  - Cases where treatment is interrupted, and the patient results will be analysed as part of the therapeutic group, without completing the missing data.
  - The inclusion of an analysis of variance (ANOVA) and some analyses of covariance of several factors: treatment effect, time effect (D30, D60, D90), BMI effect, gender effect.

**APPLICATION**

- The doctor, in practice, is responsible for the conditions of the SPD
- In accordance with an identical fixed protocol in each case:
  - Overweight: 4 Protéine products from the first day (D0) and reduction of one product every 15 days until D90. In the STT group, an STT supplement is added every two days.
  - Obese: 5 Protéine products from D0 and reduction of 1 product every 15 days until D90. In the STT group, an STT supplement is added every two days.
  - We therefore have some short ketogenic phases (1-2-3) lasting 30 to 45 days, and gradual reintroduction of food.
  - The patient cannot choose the flavours of the products. The patient receives a standard product set.
  - Similarly, micronutritional supplements are the same for both groups (potassium, vitamins, calcium, magnesium, omega 3-6 and occasional sodium).
  - To ensure compatibility, the diet products have been manufactured with the same flavours and packaging, so that they cannot be identified by either the patients or the doctors.

**SELECTION OF THE GROUPS (102 PATIENTS)**

<table>
<thead>
<tr>
<th>Control Group = SPD</th>
<th>Treatment Group = STT</th>
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<tbody>
<tr>
<td>Classic Standard Protein Diet</td>
<td>Classic SPD with tyrosine and tryptophan supplement</td>
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</tbody>
</table>

| 18 obese patients | 33 overweight patients | 18 obese patients | 33 overweight patients |

**MEASURED PARAMETERS**

At D0 D30 D60 D90

- Weight, BMI, waist measurement, fatty mass, eating behaviour
- Biological analysis at D0 and D90: glycaemia, HbA1c, cholesterol, triglycerides
- Quality of life questionnaire to reveal perceptions of mental and physical health (SF36 questions), dynamism, anxiety (Hamilton score questions) and tendency towards depression (Backscore questions).
- A questionnaire with 17 questions on eating behaviour which will give us results on 4 subjects: obsessions towards food and eating, somatic effects of cognitive restriction, snacking, compulsive eating
RESULTS

1) OVERALL

The STT group obtained the best results among overweight patients:

- The STT group lost 9 kg over the 90 days of the programme, which is about 20% more than the SPD group, who lost 7.5 kg. (Figure 4)

- Waist measurements results were similar: the STT group lost 10 cm, as opposed to the 7.7 cm which the SPD group lost, about 23% more. (Figure 5)

Therefore, the STT patients lost 1.5 kg more than the other group.
2) WEIGHT LOSS IN OBESE PATIENTS

The results of the STT group were even more spectacular in the obese group:
- Over the 90 days of the programme, the STT group lost 13.5 kg, 30% more than the SPD group, which lost 9.7 kg.
- Waist measurements results were similar: the STT group lost 14.4 cm, as opposed to the 7.5 cm which the SPD group lost, about 52% more.

![Figure 6: Weight loss in obese patients](image)

Figure 6: Weight loss in obese patients

![Figure 7: Waist measurements – obese patients](image)

Figure 7: Waist measurements – obese patients

**Dynovance** provides Proteins and Tyrosine (3.4 g) for brain tone and appetite regulation

**Sérovance** provides Proteins and Tryptophan (1.4 g) for mood, eating behaviour and regulation of satiation.
3) QUALITY OF LIFE
CHANGES IN THE QUALITY OF LIFE IN THE TWO THERAPEUTIC GROUPS (OBESE AND OVERWEIGHT)

In general, the STT group enjoy greater improvement in their quality of life than the SPD group (compared with D0).

At D0, the obese group had a lower quality of life than overweight patients (obesity: -5.5 + 15 vs. overweight +13 +25), the quality of life of the obese declined until D60, but at D90 there was no difference between the obese and overweight patients (27 + 18 vs. 30 + 23, not significant). (Figure 8)

![Figure 8: Changes in the quality of life in the two therapeutic groups (obese and overweight)](image)

This means that whatever diet is proposed, the intake of proteins and weight loss correct the differences between the two groups, so that obese patients feel that they have a quality of life comparable with overweight patients when they lose weight.

The quality of life improves significantly in comparison, whether the patients are overweight or obese (vs. D0; P<0.01). This improvement is greater with STT than SPD, in all phases from D15 to D90.

4) EATING BEHAVIOUR
REDUCTION OF EATING DISORDERS IN BOTH THERAPEUTIC GROUPS (OBESE AND OVERWEIGHT)

The reduction of eating disorders is greater among the STT patients than SPD (compared with D0)

The overall result with regard to eating disorders among obese patients is no different to overweight patients. The results regarding compulsive eating, snacking, food obsessions and disorders related with cognitive restriction were no different between obese and overweight patients.

Nearly 15% of obese and 3% of overweight patients maintained a high level of eating disinhibition from D30 (contrasting with previous levels of 21% and 8% respectively).

At D90, no obese patients suffered these disorders, compared with 5% of overweight patients (insignificant).

![Figure 9: Reduction of eating disorders in both therapeutic groups (obese and overweight)](image)

This means that improvement in eating behaviour is faster among overweight patients, regardless of the protein diet proposed. However, after 90 days of treatment, the intake of proteins and the loss of weight even out so that obese patients obtain, with regard to eating behaviour, results comparable with ordinary overweight patients when they lose proportionally more weight.

No patient in the STT group conserved a high level of disinhibition (compulsive eating) at D90, as opposed to 4% with the protein diet group (insignificant). The average sensation of hunger is slightly less important with STT (1.16 + 0.56) than the protein diet (1.29 + 0.30 on a scale of 0 to 9, insignificant).
In both the STT and protein diet group, there was predictable improvement in clinical and biological parameters linked above all to weight loss and changes in eating habits.

- Systolic blood pressure diminished in 52 of the 102 patients during treatment
- Total cholesterol and calculated LDL, glyceria and HbA1c all diminish significantly during the diet (P<0.05). The reduction of triglycerides and HbA1c is greater among obese than overweight patients (P<0.05).

**CONCLUSION**

This study has demonstrated that eating behaviour and quality of life can be optimised during a high hypocaloric diet if supplemented with tyrosine and tryptophane. It also indicates the probability, or at least the possibility, that mood and eating behaviour (restriction, disinhibition) are responsible for the cases of patients abandoning these diets, and hypocaloric diets in general.

Voluntary restriction leads to well-known psychological, somatic, behavioural and eating disorders (sleep and mood disturbance, tiredness and fatigue, compulsive eating, dichotomous thinking ”eating makes you fat”), and finally, in some cases, eating behaviour disorders (gorging, vomiting, anorexic behaviour).

With the protein diet, all measured factors display a visible improvement, although there are obvious differences between the two groups STT vs PD:

- Weight loss is clearly higher in the STT group vs. the traditional Protein Diet group (table 10).
- The results of the questionnaires also reveal a greater improvement in quality of life and eating behaviour in the STT group.
The addition of precursors of neuromediators (tyrosine and tryptophan) in Protéifine products has clear benefits for any patient.

The greatest difference, however, is to be found in the obese group, who benefited most from the STT programme.

It is therefore recommended to propose systematic tyrosine and tryptophan supplements, precursors of neuromediators, for obese patients from the moment they are placed on a programmed diet.

The following question remains: How long should the supplement be used? For the duration of the diet, plus a lengthy stabilization period: for one year or several years?

WHAT IS BEHIND THIS INTERESTING RELATION BETWEEN NEUROMEDIATORS AND OBESITY?

How has this study been able to show that a tyrosine and tryptophan supplement is more effective in obese than overweight patients?

SEVERAL HYPOTHESES ARE POSSIBLE:

1. Neuro-physiological dysfunctions are more serious among obese patients, being lesser or entirely absent among overweight patients. A supplement which modifies mood and behaviour is therefore more likely to succeed.

2. Obese persons have a real deficit of tyrosine and/or tryptophan in the brain (or at least in vital areas: hypothalamus, arcuate nucleus), while this deficit is lower or absent in overweight patients.

3. There may be causes for the physical deviation of neuromediators in obese persons, reducing the level of these in their brains:
   - Digestive disorders, chronic constipation, alterations of the intestinal flora which reduce the absorption of the neuromediators;
   - Disturbance of the relation between tryptophan and neutral amino acids caused by the eating behaviour of the obese person (and therefore a reduction in free tryptophane in the brain);
   - Low level chronic inflammation, reducing the synthesis of Serotonin in the brain from tryptophan, favouring instead the synthesis of toxic cerebral acids which cause stress and depression;

   Consumption of neuromediator amino acids in the processing of classic HDP for its use as energy, which leads to certain shortages in the cerebral synthesis of neuromediators that are more noticeable in obese persons due to their energy requirements.

The Rythmonutrition®, concept developed by Ysonut laboratories, associates nutritional treatments with chronobiology data (biological rhythms) adapted to nutrition.

Rythmonutrition® for this application, proposes a protein diet, which has been shown to be an efficient way to lose weight, with the intake of protein products enriched with precursors of neuromediators at certain times of day to optimise results.

OBESITY = ADVANTAGES OF AN «OBLIGATORY» STT

The obese patient benefits more from a supplement of neuromediator precursors during the diet, which lead to unmistakably better results than a classic protein diet: for example, 30% more weight lost after a 90-day diet.
**PATIENT FILE IN FIRST CONSULTATION (D0)**

1st Surname (first 3 letters): .................................................................
Name (first 3 letters): .................................................................
Sex: □ Female □ Male
Age (years) : Weight (Kg): Height (m): BMI :
Clinical context at D0:
□ HBP □ Dyslipemia □ Diabetes □ Surgery □ Stop Tobacco □ Hypothyroidism
□ Others (specify):

Medicines at D0 (list):

Additional commentaries:

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**QUESTONNAIRE ON MOOD AND QUALITY OF LIFE**

**(TO BE COMPLETED BY PATIENT)**

In order to help you, we would like to know more about your experiences and feelings before and during the diet. By answering this questionnaire drawn up for you, you can help us to get to know you better. It will only take a few minutes. Let’s go!
Answering is simple. You will see a scale ranging from minus 5 to plus 5 (from \(-5\) to \(+5\)).

- 5: very bad, highly negative (\(+5\), or more)
- 0: neither/average (\(+0\), or more)
+ 5: very good, highly positive

If the result is much worse than very bad, put a cross to the left of \(-5\), on the other hand, if it is really good, put a cross to the right of \(+5\).

1 - How would you describe your health at present? (very bad = \(-5\); very good = \(+5\))

2 - Have you reduced your professional or leisure activities due to your physical condition? (I don’t do anything anymore = \(-5\), or less; I do a lot more things = \(+5\), or more)

3 - Have you reduced your professional or leisure activities for psychological reasons? (I don’t do anything anymore = \(-5\), or less; I do a lot more things = \(+5\), or more)

4 - In the last 4 weeks, have you felt uncomfortable in your relations with other people (at work, at home, with your family) due to your physical condition or excess weight? (I don’t go out or see anyone anymore = \(-5\), or less; I do a lot more things = \(+5\), or more)

5 - In the last 4 weeks, have you noticed a lack of energy due to your physical condition? (I feel more exhausted/tired = \(-5\), or less; I feel a lot more active = \(+5\), or more)

6 - In the last 4 weeks, have you felt sad (so sad it’s hard to bear = \(-5\), or less), or in contrast, a lot happier \(+5\), or more)?

7 - In the last 4 weeks, have you lost interest in other people and become more introverted \(-5\), or less), or in contrast, become more open and communicative \(+5\), or more)?

8 - In the last 4 weeks, have you felt a lack of motivation so that you can’t start anything = \(-5\), or less), or in contrast, a lot more motivated \(+5\), or more)?

9 - In the last 4 weeks, have you stopped doing things = \(-5\), or less), or in contrast, you enjoy things more \(+5\), or more)?

10 - In the last 4 weeks, have you had mood swings, sometimes feeling overjoyed, other times despairing = \(-5\), or less), or in contrast do you feel more stable and content \(+5\), or more)?

11 - In the last 4 weeks, have you felt unbearable stress or anguish = \(-5\), or less), or in contrast were you serene and relaxed \(+5\), or more)?

12 - In the last 4 weeks, have you been far less active = \(-5\), or less), or in contrast were you clearly more active than before \(+5\), or more)?

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**QUESTIONNAIRE ON EATING BEHAVIOUR (TO BE COMPLETED BY THE PATIENT)**

Mark the best answer with a cross Lately,

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REFERENCES

- Markus CR, Olivier B, de Haan EH. Whey protein rich in alpha-lactalbumin increases the ratio of plasma tryptophan to the sum of the other large neutral amino acids and improves cognitive performance in stress-vulnerable subjects. Am J Clin Nutr 2002; 75: 1051-56.