Anorexigen (TNF-α, cholecystokinin) and orexigen (neuropeptide Y) plasma levels in peritoneal dialysis (PD) patients: their relationship with nutritional parameters

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Abstract

**Background.** Malnutrition has definitely been related to mortality among dialysis patients. Persistent loss of appetite is one of the major symptoms found in these patients. It is also well recognized that several substances produce anorexia or disorders of the hunger–satiety cycle in several diseases. The aim of this study was to identify the role of anorexigen substances (TNF-α and cholecystokinin or CCK) and an orexigen substance (neuropeptide Y or NPY) in anorexia and malnutrition among 55 clinically stable peritoneal dialysis (PD) patients.

**Results.** High TNF-α plasma levels were found in 38 of 45 patients (84%), mean 45.9 ± 32.3 pg/ml. Patients with anorexia showed no difference in CCK values compared with those without. A direct association was found between CCK values and some nutritional markers (albumin, fibronectin, triglycerides, folic acid and nPCR in non diabetic patients). Although CCK has a recognized anorectic effect, this direct association might be because of an abnormal stimulation of CCK–glucose feedback (trypsin) due to continuous peritoneal glucose absorption. This suggests that CCK could be an immediate food intake marker in PD patients.

The NPY plasma levels were normal in 33 patients, high in 6 and low in 11. Patients with anorexia showed lower NPY levels than those without. NPY values greater than 50 pg/ml were directly associated with higher transferrin, prealbumin, RBP, nPCR and urea KT/V values. Importantly, a negative linear correlation between NPY and TNF-α was found (r = −0.42, n = 41, P < 0.01).

There was no significant relationship between residual renal clearance and the serum levels of the three peptides.

**Conclusion.** In conclusion, our data suggest that high TNF-α and low NPY serum levels are associated with anorexia. High TNF-α, low CCK and low NPY serum levels are also related to a poor nutritional status. Further research on these circulating substances is required.

**Key words:** nutrition; peritoneal dialysis; uremic anorexia; TNF-α; cholecystokinin; neuropeptide Y; acidosis

Introduction

Protein–energy malnutrition has been demonstrated in 20–40% of patients on maintenance dialysis [1,2]. Malnutrition has definitely been related to high morbidity and mortality both in hemodialysis (HD) [3] and peritoneal dialysis (PD) patients [4,5].

Several factors have been associated with a poor nutritional status: decreased nutrient intake (anorexia, prescribed diets, sociocultural and economic factors, depression and sleep disturbances), decreased nutrient utilization, nutrient loss, altered hormonal and enzym-
Five milliliters of plasma were drawn. Plasma TNF-α and cholecystokinin (CCK) have been recognized as having an anorexigen effect under different conditions. TNF-α is associated with anorexia in wasting syndromes [9], anorexia nervosa [10], rheumatoid cachexia [11] and cancer [12]. In dialysis patients, studies on the effects of TNF-α almost never include this recognized consequence [13,14].

CCK is an intestinal peptide released by duodenal cells in the presence of carbohydrates in intestinal lumen. It has a satiety effect through central and peripheral action [15,16]. CCK has been implicated in anorexia nervosa [15,16], cancer [17], senile [18] and alcoholic anorexia [19]. CCK has renal clearance, therefore ESRD patients have high plasma levels [20–23].

Neuropeptide Y (NPY) is the most potent orexigen known in relation to the pathogenesis of obesity [24], even diabetic obesity [25]. To our knowledge, NPY plasma levels have not been related to uremic hunger–satiety processes.

The ultimate aim of this cross-sectional study was to identify the role played by orexigen–anorexigen substances in uremic anorexia, hunger–satiety regulation and poor nutritional status.

Methods

For reasons outside our control, not all determinations were performed in all patients. Throughout the paper, we expressly indicate the exact figures for each analysis.

The following parameters were determined:

1. Dialysis adequacy: urea KT/V and nPCR (normalized protein catabolic rate) [5].
2. Long-term nutritional markers: plasma creatinine, albumin, cholesterol (colorimetric method, Hitachi 704) and transferrin by the immunonephelometric method (Boehringer Nephelometer-Terminal S.A., Spain). Plasma levels of vitamin B₁₂ and folic acid (radioimmunoassay), ferritin and iron (Hitachi 911) and triglycerides (Hitachi 704). Short- to medium-term nutritional markers (short half-life proteins) include plasma prealbumin, retinol-binding protein (RBP), fibronectin, antithrombin III (AT III), ceruloplasmin and α-1-antitrypsin analyzed by immunonephelometric methods. NPCR, urea nitrogen, phosphorus and potassium were also considered representative of short-term food intake markers. Body mass index (weight in kg/height² in m) was the nutritional anthropometric method used to evaluate severe obesity (BMI ≥ 30).

TNF-α plasma levels

Five milliliters of plasma were drawn. Plasma TNF-α was measured using the enzyme-amplified sensitive immunoassay (ELISA) performed on micro-titer plates. It is based on the oligoclonal system, in which several monoclonal antibodies are used. The minimum detectable concentration is estimated to be 3 pg/ml and is defined as the TNF-α concentration corresponding to the mean of 20 replicates of the zero standard ± 2 standard deviations. It is specific as TNF-α ELISA does not cross-react with TNF-β, IL-1, IL-2 and IFN-α, β or γ. Normal values ranged from 3 to 20 pg/ml (Easia Medgenix Diagnostics S.A. Belgium).

Fifteen of the 16 anorectic patients, 13 of the 20 asymptomatic patients and 14 of the 19 with mild GI symptoms had TNF-α levels determined (42 patients). TNF-α determination was performed on 30 of the 43 patients without previous GI disease and on the 12 patients with this antecedent, 8 were diagnosed with acid pylori disease.

Patients

We studied 55 clinically stable peritoneal dialysis (PD) patients, 47 on continuous ambulatory peritoneal dialysis (CAPD) and 8 on automatic peritoneal dialysis (APD) (2 continuous cycler-assisted peritoneal dialysis (CCPD) and 6 nocturnal peritoneal dialysis (NPD)), 21 male and 34 female, ranging in age from 22 to 86 years (mean 51 ± 14.2). No acute disorders were present during the 2 months prior to the study. Patients who suffered intestinal, pancreatic and chronic liver diseases, active infections, neoplasms and chronic obstructive lung disease were not included. The causes of chronic renal failure were glomerulonephritis in 12 cases (21.8%), diabetes in 11 (20%), chronic pyelonephritis in 7 (12.7%), polycystic kidney disease in 7 (12.7%), nephrosclerosis in 7 (12.7%), unknown etiology in 4 (7.2%), systemic diseases in 4 (7.3%) and congenital diseases in 3 (5.4%). The mean period on PD was 30.3 ± 34.8, (1–179) months.

Anorexia, assessed by an interview with the patient guided through a 3-day food intake survey, was present in 16 patients, isolated in 11 and associated with nausea/vomiting in 5. Twenty patients were asymptomatic and 19 referred to mild occasional gastrointestinal (GI) symptoms (dyspepsia, sporadic abdominal pain, nausea or vomiting and pyrosis). Forty-three patients (78.2%) had never been diagnosed with GI disease. Of the remainder, eight had been previously diagnosed with acid pylori disease, two with hiatus hernia and two with spastic colon and diverticulosis.

Peritoneal ultrafiltration capacity was considered normal in 43 patients (800 ± 200 ml/day, using a combination of 1.36 and 2.27% dextrose), high in 7 (using most of their bags with dextrose 1.36%) and low in 5 patients (requiring at least 25% of the daily bags with dextrose 3.6%).

Nutritional parameters in PD patients

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Cholecystokinin (CCK)

The 26–33 unsulfated fragment was determined (Peninsula Laboratories, Inc.) with an IC_{50} of 35 pg/100 ml. Specificity to CCK 26–33, CCK 33 with a percentage cross-reactivity 100%. Values considered normal were 12–20 pg/ml. CCK determination was performed in 15 of the 16 anorectic patients, 15 of the 20 asymptomatic patients and 15 of the 19 patients with other GI symptoms (45 patients). CCK was also studied in 38 of the 43 patients without prior GI diagnoses and in 12 with antecedents.

Neuropeptide Y (NPY)

The method used was radioimmunoassay (Peninsula Laboratories, Inc.). The IC_{50} was 23 pg/100 ml (normal values were 20–80 pg/ml). NPY was determined in 50 of the 55 patients studied: 14 of the 16 anorectic patients, 19 of the 20 asymptomatic and 17 of the 19 patients with other GI symptoms. NPY was also studied in 38 of 43 patients without prior GI diagnoses and in 12 with antecedents.

The statistical study was performed by Student’s t and Mann–Whitney tests and linear regression analysis. When linear regression analysis gave no statistically significant results, a stratified analysis for different values of the three target variables was performed. The appropriate comparative test was then applied. The values are expressed as mean ± 1 SD.

Results

Table 1 shows the general analytical data, short-, medium- and long-term nutritional markers. Mean levels of cholesterol, vitamin B_{12}, ferritin, RBP and fibronectin are all over the normal range. There was no association between anorexia and peritoneal ultrafiltration capacity or peritoneal glucose load.

TNF-α plasma levels

High TNF-α levels were detected in 41 of 42 patients (97.6%), with a mean of 70.5 ± 32.3 (18.1–156.3 pg/ml) (Figure 1). PD duration was longer in patients with TNF-α levels greater than 65 pg/ml (45.8 ± 42.4 months in 22 patients vs 23.3 ± 27.2 months in the 20 patients with levels less than 65 pg/ml, P < 0.05).

Patients with anorexia or anorexia with nausea or vomiting showed higher plasma TNF-α levels than patients without GI symptoms (75.9 ± 34, n = 15 vs 52.1 ± 24.5 pg/ml, n = 13; P < 0.05). Non-anorectic patients suffering other GI symptoms also had higher levels of TNF-α than asymptomatic patients (81.7 ± 31.5, n = 14 vs 52.1 ± 24.5 pg/ml; n = 13, P < 0.05).

Higher plasma TNF-α levels were found in eight patients previously diagnosed with acid pylori disease, (87.2 ± 24.3, n = 8) compared with patients without GI disease (63.6 ± 30.5 pg/ml, n = 30, P < 0.05).

Table 2 shows the statistically significant differences for several nutritional parameters according to TNF-α levels greater and less than 65 pg/ml.

A significant negative linear correlation appeared between TNF-α and plasma RBP levels (r = −0.37, n = 34, P < 0.05). A similar situation was observed between TNF-α and venous pH (r = −0.4, n = 42, P < 0.01). We found no statistically significant relationship between plasma TNF-α levels and the age of the patients, renal creatinine clearance, plasma albumin, triglycerides, AT III, fibronectin, vitamin B_{12}, folic acid, P, K, creatinine or ferritin.

Cholecystokinin (CCK) plasma levels

High plasma CCK levels were found in 38 of 45 patients, mean 45.94 ± 32.28 (3.8–131.5 pg/ml)
Table 2. TNF-α plasma levels and nutritional markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>TNF-α (pg/ml)</th>
<th>Mean ± SD</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBP &lt;65 mg/dl</td>
<td>13.4 ± 6.7</td>
<td>13</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Transferrin &gt;65 mg/dl</td>
<td>9.6 ± 2.6</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol &lt;65 mg/dl</td>
<td>54.9 ± 19.9</td>
<td>22</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Blood urea &lt;65 mg/dl</td>
<td>213.6 ± 41.8</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCK &lt;65 pg/ml</td>
<td>55.5 ± 34.1</td>
<td>20</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;30 (mg/kg/m²)</td>
<td>76.5 ± 35</td>
<td>29</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>46.1 ± 10</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nPCR (g/kg/day) &lt;1.1</td>
<td>79.3 ± 32.6</td>
<td>26</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>nPCR &gt;1.1</td>
<td>56.1 ± 27</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea KT/V &lt;2.2</td>
<td>78.3 ± 32.9</td>
<td>27</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Urea KT/V &gt;2.2</td>
<td>56.3 ± 26.6</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Non-diabetic patients.

Table 3. Cholecystokinin plasma levels and nutritional markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>CCK (pg/ml)</th>
<th>Mean ± SD</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &lt;34 (g/dl)</td>
<td>3.66 ± 0.5</td>
<td>21</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Fibronectin ≥34 mg/dl</td>
<td>3.97 ± 0.4</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &lt;30 mg/dl</td>
<td>50.1 ± 13.9</td>
<td>22</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Folic acid ≥30 mg/dl</td>
<td>5.6 ± 1.9</td>
<td>17</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>nPCR (g/kg/day)* &lt;1.1</td>
<td>36.7 ± 28.6</td>
<td>22</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>nPCR &gt;1.1</td>
<td>56.4 ± 34.3</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z-1-antitrypsin &lt;350 (mg/dl)</td>
<td>42.6 ± 25.1</td>
<td>32</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>≥350</td>
<td>102 ± 46.3</td>
<td>4</td>
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</table>

*For non-diabetic patients.

Table 4. Neuropeptide Y plasma levels and nutritional markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>NPY (pg/ml)</th>
<th>Mean ± SD</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin &lt;50 mg/dl</td>
<td>238.4 ± 46.9</td>
<td>23</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Prealbumin ≥50 mg/dl</td>
<td>31.1 ± 10</td>
<td>23</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>RBP &lt;50 mg/dl</td>
<td>9.8 ± 3.3</td>
<td>20</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>nPCR &lt;50 (g/kg/day)</td>
<td>0.96 ± 0.17</td>
<td>23</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>KT/V &lt;45</td>
<td>1.1 ± 0.2</td>
<td>27</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;30 kg/m²</td>
<td>46.6 ± 27.1</td>
<td>32</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>70.6 ± 23.4</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Non-diabetic patients.

levels of 39.9 ± 29.4 (n = 25), whereas patients with plasma albumin levels greater than 3.9 g/dl showed levels of 57.5 ± 34.6 pg/ml (n = 17, P < 0.05). Table 2 shows that TNF-α levels greater than 65 pg/ml are associated with significantly lower CCK levels.

We found no statistically significant relationship between CCK and peritoneal glucose load, renal creatinine clearance, cholesterol, AT III, transferrin, serum iron and urea KT/V. However, we found higher CCK levels in patients with KT/V greater than 2.1 (38.6 ± 22.9, n = 23) compared with those with values less than 2.1 (53.6 ± 39, n = 22, P < 0.1, within the limit of statistical significance).

Neuropeptide Y plasma levels

Lower than normal NPY plasma values were found in 11 patients (22%), normal values in 33 patients (66%) and high values in 6 patients (12%). Patients with anorexia showed lower NPY values (43.2 ± 27.5 pg/ml, n = 14) than patients without anorexia (64.9 ± 25.5, n = 19, P < 0.05). Patients with GI symptoms also showed lower values (42.8 ± 25.3, n = 17) than those without GI symptoms (64.9 ± 25.5, n = 19, P < 0.05). Patients with prior GI disease showed no significant differences with respect to non-diagnosed patients.

Table 4 shows the relationship between NPY values and nutritional markers. A direct linear relationship appeared between NPY and RBP levels (r = 0.27, n = 37, P < 0.05). The six patients (one diabetic) with NPY values greater than 80 pg/ml had a shorter PD term (9 ± 10.52 months) than the patients with NPY less than 80 pg/ml (34.1 ± 36.7 months, n = 44, P < 0.01; nine were diabetics). These differences were maintained for non-diabetic patients.

The NPY plasma levels had a significant inverse correlation with plasma TNF-α levels (r = −0.42, n = 41, P < 0.01, Figure 2). The mean plasma TNF-α level was also significantly lower in patients with NPY levels greater than 80 pg/ml (33.5 ± 8.9, n = 4) compared with patients with levels lower than 80 pg/ml (74.4 ± 31.9, n = 37, P < 0.001). We found no association between...
NPY values and renal creatinine clearance, plasma albumin, CCK, AT III, fibronectin, ceruloplasmin, α1-antitrypsin, cholesterol, triglycerides, P, K, BUN, glucose concentration in dialisate and peritoneal ultrafiltration capacity.

Finally, Table 5 shows a summary of nutritional and dialysis parameters in anorectic and asymptomatic patients. Notable statistically significant differences are found in age, PD duration (months), serum albumin, AT-III, TNF-α, NPY, nPCR and urea KT/V, this last only the case of non-diabetic patients.

**Discussion**

Anorexia is one of the most frequent symptoms in dialysis patients. Several factors have been related to anorexia: middle molecular weight molecule retention [7,26,27], uremic toxicity [28], metabolic and biochemical disorders and abnormalities in cell composition and metabolism [20]. The results of the present study concuro with the idea that several plasma substances (TNF-α, cholecystokinin and neuropeptide Y), related to the hunger–anorexia cycle, might also be of importance in PD patients. This is suggested by direct and indirect relationships between nutritional parameters and the circulating levels of these substances.

TNF-α, is responsible for cachectic and anorectic effects in wasting syndrome [9–12,29]. Under experimental conditions, TNF-α administered by the peripheral or intracerebral route decreases food intake through effects on the hunger center [29,30]. Nine fragments have been isolated, each with different actions. The 69–100 fragment has suppressive effects on food intake [30].

We found high TNF-α plasma levels in 97.6% of our patients. Patients with anorexia showed higher levels than those without. Several reports [13,31] have found increased TNF-α plasma levels in non-dialyzed and PD patients. However, McKenna et al. [32] did not find high TNF-α production in cultured CAPD patient mononuclear cells. Methodological differences (plasmadialysis patients. Several factors have been related to levels instead of biological activity) may in part explain these discrepancies. TNF-α increased synthesis by cells damaged by hypertension, atherosclerosis, cardiomyopathy [33], liver diseases [34] and uremia [13,14,31] have been shown. Chronic elevated TNF-α levels are more important than acute increments for anorexia (TNF-α, cholecystokinin and neuropeptide Y), related to the induction, this is likely to be due to the short TNF-α half-life (27 min). Plasma concentration peaks are less

**Table 5. Differences between anorectic and asymptomatic patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anorectic</th>
<th></th>
<th>Asymptomatic</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>n</td>
<td></td>
<td>Mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.1 ± 15.9</td>
<td>16</td>
<td></td>
<td>45 ± 13.7</td>
<td>20</td>
</tr>
<tr>
<td>PD duration (months)</td>
<td>42.2 ± 30.8</td>
<td>16</td>
<td></td>
<td>15.4 ± 27.8</td>
<td>20</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.8 ± 1.3</td>
<td>16</td>
<td></td>
<td>5.7 ± 1.5</td>
<td>20</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5 ± 0.6</td>
<td>16</td>
<td></td>
<td>3.9 ± 0.3</td>
<td>20</td>
</tr>
<tr>
<td>Prealbumin (mg/dl)</td>
<td>28.2 ± 13.3</td>
<td>13</td>
<td></td>
<td>35.2 ± 5.8</td>
<td>15</td>
</tr>
<tr>
<td>Antithrombin-III (%)</td>
<td>89.5 ± 14.7</td>
<td>11</td>
<td></td>
<td>104.7 ± 12.5</td>
<td>17</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>75.9 ± 34</td>
<td>15</td>
<td></td>
<td>52.1 ± 24.5</td>
<td>13</td>
</tr>
<tr>
<td>NPY (pg/ml)</td>
<td>43.2 ± 27.4</td>
<td>14</td>
<td></td>
<td>64.9 ± 25.5</td>
<td>19</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>0.91 ± 0.15</td>
<td>16</td>
<td></td>
<td>1.06 ± 0.2</td>
<td>20</td>
</tr>
<tr>
<td>Urea KT/V</td>
<td>2 ± 0.32</td>
<td>16</td>
<td></td>
<td>2.37 ± 0.54</td>
<td>20</td>
</tr>
<tr>
<td>Urea KT/V^a</td>
<td>1.91 ± 0.24</td>
<td>12</td>
<td></td>
<td>3.29 ± 2.2</td>
<td>20</td>
</tr>
<tr>
<td>Cr. Clearance (ml/min)</td>
<td>0.78 ± 1.2</td>
<td>16</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

^aNon-diabetic patients.
important than stable brain concentrations. Chronic administration of low doses of recombinant-murine-TNF-α causes persistent anorexia [35]. TNF-α might operate in this way in PD patients.

Long-term PD patients showed higher TNF-α plasma levels. This relationship has been found in HD patients by Herbelin et al. [14]. Although PD patients do not suffer stimulation by HD membranes, a decrease in renal clearance and an increase of synthesis by other conditions [13,14,31–34,36] may explain these data. Our results suggest that lower TNF-α values are associated with urea KT/V values greater than 2.2, whereas no relationship with residual renal function is demonstrated, suggesting that dialysis efficacy plays a role in TNF-α elimination.

Another TNF-α source is GI tract [37,38]. Our patients with prior acid pylori disease had higher TNF-α plasma levels. TNF-α may be produced by intestinal cells in inflammatory bowel disease [37] and anti-TNF-α monoclonal antibodies have been used for relapse treatment in Chron’s disease [38]. Patients with pyloric ulcer associated with Helicobacter pylori infection have high TNF-α, IL-1-β and IL-8 production by antral mucosa cells [39].

If we recognize an anorexigenic effect of TNF-α in PD patients, we should demonstrate that the high levels found influence nutritional markers. The negative correlation between TNF-α and short-half life plasma proteins rules out the existence of an increase in acute phase reactants. Plasma albumin, transferrin, cholesterol and creatinine are representative of long-term nutritional parameters. TNF-α showed a negative relationship with transferrin and cholesterol; transferrin is a marker of energy status and low levels of cholesterol have been related to mortality [1,2]. However, we found a non-significant tendency in the relationship between TNF-α and plasma albumin. TNF-α inhibits hepatic albumin synthesis in rats, possibly by direct inhibition of gene expression [40]. Peritoneal or renal protein losses and the slower albumin synthesis rate than that of prealbumin or RBP, may modify this relationship.

Prealbumin, RBP, AT III, fibronectin, ceruloplasmin and lymphocyte count are medium-term nutritional markers. There was a statistically significant negative linear correlation between TNF-α plasma levels and RBP. TNF-α values also showed an inverse association with prealbumin levels greater and lower than 30 mg/dl. Prealbumin and RBP have proved useful in the recognition of moderate and severe malnutrition in PD patients [6].

We also found a negative association between TNF-α levels and early food intake markers (nPCR and urea nitrogen). An important factor in the genesis of dialysis anorexia is underdialysis. Several authors have observed transitory improvements of appetite after increasing dialysis dosage [41,42]. According to our data, lower urea KT/V values are associated with anorexia in non-diabetics and high TNF-α plasma levels (Tables 2 and 5).

Obese patients showed lower TNF-α levels than non-obese patients (BMI<30 kg/m²). A similar observation was found by Chollet-Martin et al. [43]. A direct lipolytic effect of TNF-α has been demonstrated [29]. TNF-α induced an increase in serum triglycerides over a 10-day period [29], but no significant relation between these parameters was found (r=0.22, n.s.).

Another factor involved in dialysis malnutrition is acidosis [44]. Metabolic acidosis is an effect of R-m-TNF-α long-term administration [29,35]. The inverse correlation between TNF-α and blood pH (r=-0.4, n=42, P<0.01) agrees with this finding. Acidosis increases muscle proteolysis in rats via the ubiquitin–proteasome pathway [45]. Other conditions associated with inflammation, and presumably high TNF-α values, exhibit catabolism by activating the same system of protein degradation as acidosis [46]. We cannot rule out that high TNF-α plasma levels could represent a chronic inflammatory state as it has been found in haemodialysis, although not in PD patients, to be related with malnutrition [32,47]. TNF-α seems therefore to contribute to acidosis and malnutrition in PD patients.

CCK is a GI peptide released by duodenal cells in the intestinal lumen in response to protein, fat, acid and calcium intakes. It stimulates gall bladder contraction and pancreatic enzyme secretion and inhibits gastric emptying. Through peripheral and brain receptors, CCK causes anorexia by a satiety effect [15–19]. High CCK plasma levels were found in 84% of our patients. The decrease in CCK-33 the fragment renal clearance [21,23] and its longer half-life, 10× that of CCK-8, may explain this feature [22]. In our patients, anorexia showed no relationship with CCK plasma levels. The influence of other factors on CCK release, such as peritoneal glucose absorption could explain this apparent contradiction. Plasma glucose is a negative factor in the feedback of CCK release by exocrine pancreatic stimulation (trypsin) [48]. In addition, α-1-glycoprotein composed of hexoses such as glucose, mannose or galactose, and amino acids have a satiety effect per se [20]. Some studies of anorexia nervosa indicate that peak CCK plasma levels, stimulated by food intake, occurred earlier than in normal subjects (30 min vs 60 min). This finding suggests that high initial CCK plasma rise may contribute to the abnormal perception of satiety [49]. Although we did not investigate the CCK cycle, the high levels of plasma CCK and the continuous peritoneal glucose absorption could induce a loss of the normal CCK–glucose feedback function in PD patients.

With respect to CCK and nutritional markers, lower CCK plasma levels were associated with malnutrition data. The difference was observed with CCK values lower and higher than 30 pg/ml. Plasma albumin showed a direct association with CCK levels; levels greater than 3.9 g/dl were associated with CCK levels greater than 30 pg/ml. However, as albumin binds CCK, this association could be explained [50]. The remaining nutritional parameters (Table 3) were also positively correlated with CCK. These features may
indicate that CCK plasma levels are a food intake marker in PD patients.

Neuropeptide Y (NPY) belongs to the pancreatic polypeptide family and is involved in drinking and eating [51,52] and in intestinal motility and secretion [48]. It is the most potent orexigen known to be related to the pathogenesis of obesity [24].

Thirty-four percent of our patients showed abnormal NPY plasma values (22% lower and 12% higher than normal). In uremic patients, the state of NPY plasma levels is poorly known. Factors related to NPY release were excluded in our population (inadequate hydration state, no fasting or insulin use, which was postponed to after sampling in diabetics) [25]. NPY values were not related to peritoneal ultrafiltration capacity or glucose concentration in PD fluid. An increase in NPY plasma levels has also been reported during hemodialysis sessions associated with fluid removal [52] but this factor did not contribute in our patients. Since several animal models have suggested that the splanchenic area and kidney are important sources of NPY [53,54], we cannot rule out that different nephropathies or renal functions explain these differences.

A negative linear correlation was found between NPY and TNF-α (Figure 2). To our knowledge, this has not been described previously and could be another way by which TNF-α causes anorexia. There are several studies demonstrating that cytokines produce stimulation of GI peptide release. For instance, IL-1 induces insulin secretion [55] and contributes to the anorexigenic effect of CCK [56]. TNF-α increases serum growth hormone levels and catabolic stress hormone release [57]. We suggest that TNF-α could contribute to lower NPY levels in anorectic PD patients. The powerful orexigen effect of NPY injected into the hypothalamic region is well known [58]. We have found a positive relationship between nutritional markers and NPY. Non-diabetic obese patients showed high NPY plasma levels. NPY has been implicated in body weight regulation [59] and lipolysis inhibition in human fat cells [60]; NPY inhibition has been demonstrated by the obese gene product, leptin [24]. NPY may improve nutritional status by increasing food intake and through its metabolic effects, such as reduction of glycogenolysis and stimulation of gluconeogenesis [59].

In conclusion, our data suggest that high TNF-α and low NPY serum levels are associated with anorexia. High serum TNF-α levels might be responsible for uremic anorexia in PD patients. High TNF-α, low CCK and low NPY serum levels are also related to poor nutritional status. Further research on these endogenous substances is required.

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