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Short Communication

Leptin and adiponectin as new markers of undernutrition in cancer

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ABSTRACT

Objectives: To evaluate leptin and adiponectin as markers of undernutrition in cancer patients, and compare their performances with those of other biomarkers.

Design and methods: This was a prospective and observational study of 132 patients with various types of cancer. Following the recommended professional criteria, we diagnosed undernutrition at the time of blood sampling for the biological analysis of leptin, adiponectin, paraoxonase (hydrolysis rate of three substrates: paraoxon (PON), phenylacetate (ARE) and thiolactone (LAC)), and the calculation of the Prognostic Inflammatory and Nutritional Index (PINI). Patients were monitored for one year to establish the mortality rate of the group. Relationships between biological variables and undernutrition were evaluated using univariate and multivariate logistic regression models. The Kaplan Meier method was used to analyse survival curves. Hazard ratios for death were calculated according to the quartiles of each biological variable.

Results: In the case of undernutrition, a decrease was observed in levels of leptin and in the lactonase activity (LAC) of paraoxonase, while adiponectin levels increased. Besides PINI, leptin was the only parameter that was independently related to undernutrition. While no relation was found between survival and leptin or adiponectin levels, evidence was found that PINI, LAC and ARE were associated with survival, even in multivariate analysis.

Conclusions: Leptin and PINI are good markers of installed undernutrition, and PINI and ARE or LAC are reliable markers of the risk of death in patients suffering from cancer.

1. Introduction

Cancer patients are particularly susceptible to nutritional depletion, and an estimated 40–80% of patients suffer from malnutrition, depending on the tumor type and localization, the stage of the disease and the treatment received, including nutritional care [1]. In cancer patients, a link has been identified between undernutrition and worse outcome, with nearly 20% of cancer patients dying of malnutrition rather than the disease itself [2]. These observations highlight the necessity for adequate tools to diagnose undernutrition in all cancer patients. Several methods have been developed to assess undernutrition, including anthropometric measurements, biochemical assays and subjective global assessment [3]. The French Health Authority recommends the combined measurement of age, body mass index (BMI), weight loss and albumin levels (http://www.has-sante.fr/portail/upload/docs/application/pdf/synthese_denutrition_personnes_agees.pdf). An inflammatory state is known to affect protein synthesis, and may therefore interfere with albumin concentration in cancer patients. The Prognostic Inflammatory and Nutritional Index (PINI) is an index combining albumin, prealbumin (transthyretin) and two inflammatory markers, namely C-Reactive Protein (CRP) and orosomucoid [4]. PINI is considered a reliable indicator of both nutritional status and prognosis in several diseases [5]. We have previously shown that paraoxonase, an enzyme that plays a role in xenobiotic metabolism, is also affected by inflammation [6] and identified it as a potential marker of short-term death in patients suffering from recurrent breast cancer [7]. However, weight loss due to the cancer-anorexia syndrome is associated with reduced muscle mass and adipose tissue [8]. Leptin and adiponectin are adipokines secreted by the adipocyte. Low serum leptin concentrations have been found in several critical pathological illnesses such as renal insufficiency and malnutrition [9]. A low adiponectin level has been linked to a better outcome in hemodialysis patients and in the elderly [10,11]. However, to our knowledge, little is known about the interest of these adipokines in cancer-associated undernutrition. The goal of this study was to evaluate the interest of leptin and adiponectin as markers of undernutrition in cancer patients, and to compare their performances with those of other markers, including PINI and paraoxonase.

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2. Material and methods

2.1. Patients

This observational and prospective study was run at the René Gauducheau Integrated Center for Oncology (ICO). Patients gave informed consent for the use of their biological specimens and clinicopathological data for research purposes, as required by French legislation and the French Committee for the Protection of Human Subjects. According to the French regulation, this committee has authorized ICO to run research on its human biological sample collection. Patients were randomly sampled during their stay in our hospital. A total of 132 patients (104 females and 28 males) with various cancer diseases took part in the study. The majority of patients had breast cancer (81). Other patients suffered from gynaecologic, digestive, testis and glioma tumors. 52% of the patients had multiple metastases of their initial cancer. Undernutrition was diagnosed if at least one of the following criteria was noted: weight loss of 10% or more during the previous six months, weight loss of 5% or more during the previous month, BMI below 18.5 (or 21 for patients over 70 years old), albumin below or equal to 35 g/L. Patients were monitored for one year to establish the mortality rate of the group over this period.

2.2. Biochemical analyses

Heparin blood samples were centrifuged immediately at 1500*g* for 5 min, then plasma was frozen immediately at −80 °C until analysis. After thawing, samples were centrifuged again at 1500*g* for 5 min before analysis. Leptin and adiponectin were determined using ELISA (R&D systems, Abingdon, UK). Albumin, transthyretin, CRP and orosomucoid were determined by routine analyzer (Olympus AU 480, Beckman Coulter, Villepinte, France). The intra- and inter-assay coefficients of variation were 0.62% and 1.1%, 1.39% and 3.32%, 0.91% and 2.27%, 0.90% and 1.76% for albumin, transthyretin, CRP and orosomucoid respectively. Minimum detectable concentrations were respectively 15 g/L, 0.03 g/L, 0.2 mg/L and 0.2 g/L. PINI was calculated using the following formula: PINI = [CRP (mg/L) × orosomucoid (g/L)] / [albumin (g/L) × transthyretin (g/L)]. Leptin was introduced in PINI calculation to obtain LPINI (LPINI = [CRP (mg/L) × orosomucoid (g/L)] / [albumin (g/L) × transthyretin (g/L) × leptin (μg/L)]). Paraoxonase values were determined using the hydrolysis rates of its three known substrates, namely paraoxon (PON), phenylacetate (LAC) and thiolactone (LAC), as previously described [6,7]. The intra- and inter-assay coefficients of variation were 2.6% and 3.5%, 4.1% and 3.5%, 2.5% and 7.9% for PON, ARE and LAC respectively. Minimum detectable activities were respectively 6 μmol/L/min, 2 mmol/L/min and 0.03 μmol/L/min.

2.3. Statistics

Statistical analysis was run on SAS software version 9.3 (Chapel Hill, NC, USA). Median and distribution (25th–75th) of the variables were estimated. The relationships between biological variables and undernutrition were pinpointed using logistic regression analyses. Multiple models were used to evaluate the independence of these relationships. Odds ratios were calculated for each quartile of the biological variables. Survival curves were analyzed using the Kaplan Meier method.

3. Results

3.1. Biological variables and undernutrition

On the day of blood sampling, a total of 38 patients suffered from undernutrition, *i.e.*, 28.8% of the total population. The sex ratio was identical in patients with and without undernutrition. As shown in Table 1, age was slightly higher in the group of patients with undernutrition. As expected, weight, BMI, albumin and transthyretin levels were lower in these patients, while CRP, orosomucoid and PINI levels were higher. In patients with undernutrition, leptin and LAC values were lower, while adiponectin levels increased. Univariate regression models confirmed the positive association between undernutrition and age, CRP, orosomucoid, PINI, as well as LPINI and adiponectin, with odds ratios above 1 for each quartile of the variables. However, adiponectin did not reach significance. By contrast, a negative association was found with weight, BMI, albumin, transthyretin, leptin and paraoxonase lactonase (LAC) activity, with odds ratios below 1 for each quartile of the variable.

A first multiple model was run to demonstrate the independent association between undernutrition and leptin, adiponectin, LAC, albumin, transthyretin, CRP, orosomucoid and age. This model confirms the potential use of leptin as a marker, as it is the only parameter that is independently related to undernutrition. In the second model, leptin, adiponectin and LAC were tested in association with PINI or LPINI and age. This model confirmed the independent association of leptin and PINI with undernutrition. When LPINI replaced PINI and leptin, its association with undernutrition was also highly significant.

3.2. Biochemical variables and survival

Fig. 1 illustrates the results of survival curve analysis, according to the Kaplan Meier method. Undernutrition and PINI were significantly related to shorter survival time, while ARE and LAC were significantly related to longer survival time. In this analysis, there is no relation between survival and leptin or adiponectin (not shown, log rank test: $p = 0.28$ and $p = 0.71$ respectively). ARE and LAC remained associated with survival time when introduced together with PINI and undernutrition in the model, while undernutrition lost its significance.

4. Discussion

Low concentrations of circulating leptin have been observed during critical pathological situations such as renal insufficiency or malnutrition [9]. Studies in hemodialysis patients have also shown adiponectin to be positively correlated with not only the Subjective Global Assessment (SGA) but also the Malnutrition-Inflammation Score (MIS), suggesting that lower adiponectin levels are associated with better nutritional status [10,11]. In elderly patients, high levels of adiponectin were related to incident disability and death [11]. The present study confirms that low levels of leptin and high levels of adiponectin are associated with undernutrition in cancer patients, as defined by the French health authority recommendations for diagnosis. Unlike leptin, the relationship between adiponectin and undernutrition is barely significant. Inflammation markers and the calculated PINI composite index also appear to be closely related to undernutrition. The inflammation process could explain the change in paraoxonase activities in this situation. However, while inflammatory cytokines have been shown to reduce *PON1* gene expression *in vitro* [12], an association between inflammatory markers and paraoxonase activity is not systematically observed *in vivo*. In our own experience [6,13], ARE was related to CRP but not to SAA, another acute phase protein. It is not therefore clear why only LAC was inversely related to undernutrition in our study. These results do not argue in favor of an interference with inflammation, and could be specific to malnutrition. Nevertheless, in a multivariate analysis, LAC lost its relationship with undernutrition, as did adiponectin, while leptin and PINI remained significantly associated. This result strongly suggests that both leptin and PINI would be reliable clinical markers of undernutrition in cancer patients. It should also be pointed out that PINI is a better marker of undernutrition than the individual parameters used to calculate this marker. The main weakness of our study is that the cancer types of our patients are considerably varied. Most probably, some subtypes are more prone to undernutrition than others.