

Impact of type 2 diabetes on the clinical outcome of malnourished hospitalized patients managed by the Nutrition Support Team at Rennes University Hospital

Mathilde Barrallier

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1

Thèse en vue du DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par

Mathilde Barrallier

Impact of type 2 diabetes on the clinical outcome of malnourished hospitalized patients managed by the Nutrition Support Team at Rennes University Hospital

Thèse soutenue à Rennes le 25 octobre 2021

devant le jury composé de :

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Introduction

Malnutrition is a pathological condition caused by a decrease of food intake, an increase of metabolic expenditure, an increase of energy losses or the combination of two or three of these events. It is characterized by a decrease in fat-free mass, due to muscle mass, as well as other changes in body composition (decrease in fat mass, increased total body water) and physiological functions [1]. The prevalence of malnutrition in hospitalized patients is estimated to be 30 to 40% in France [2]. The prevalence of malnutrition in particularly high in the older people; it is estimated between 23 and 60% in acute care [3].

The diagnosis of malnutrition for adults under 70 years has been recently updated by the Global Leadership Initiative on Malnutrition (GLIM) international consensus in 2018, and in France by Haute Autorité de Santé (HAS) in 2019 [4,5]. Malnutrition in this population is now diagnosed by the presence of at least one phenotypic criterion and at least one etiologic criterion. Phenotypic criteria are a significant weight loss, low body mass index (BMI), and a quantified reduction in muscle mass and / or function. Reduction in muscle function can be defined by a low handgrip strength measured by a dynamometer [5]. Reduction in muscle mass can be defined by a low muscle mass index or a low Fat-Free Mass Index (FFMI), measured by bioimpedance analysis (BIA) [5]. Etiologic criteria are a reduction in food intake, any chronic gastro-intestinal condition that adversely affects food assimilation or absorption, or an acute or chronic disease [5]. In the older population, the updated recommendations for the diagnostic criteria for malnutrition are expected for 2022. Awaiting the update, malnutrition should be diagnosed with the criteria published by HAS in 2007 [6]. The diagnostic of malnutrition adults over 70 years requires on the presence of one or more of the following criteria: significant weight loss, BMI under 21 kg/m², albuminemia under 35 g/L or Mini Nutritional Assessment (MNA) under 17 [6].

The diagnosis of malnutrition is a necessity regarding its complications. Malnutrition negatively impacts the wound healing process [7] by prolonging the inflammation phase, decreasing fibroblast proliferation and altering collagen synthesis [8]. A perfect example is the occurrence of pressure ulcers, In a cross-sectional study of hospitalized and nursing home patients, Shahin *et al.* [9] have shown that pressure ulcers were related to weight loss, low nutritional intake and low BMI. In the same way, malnutrition is also associated with increase in nosocomial infections. Schneider *et al.* [10] have shown that the severity of weight loss and hypoalbuminemia at admission are associated with an increased risk of nosocomial infections during the hospital stay. Main infection sites were urinary tract and surgical site. More infections induce an increase use of antibiotics as it has been shown by Pressoir *et al.* in a prospective multicenter study of 1545 patients [11]. Surgery in malnourished patients leads to more post-operative complications: bleeding, infections, wound dehiscence, circulatory insufficiency, renal failure, hepatic dysfunction, etc. [12] Malnutrition is significantly associated with high fall risk in

hospitalized older people, as demonstrated by Aldy *et al.* [13] in a cross-sectional study. Moreover, Charlton *et al.* [14] have shown that older patients, that are admitted to a subacute setting, in a malnourished state, experience poorer clinical outcomes (admission to higher level care and/or dead during hospitalization), and an increased risk of mortality within the subsequent 18 months, compared with their well-nourished peers.

Increased mortality and length of stay related to malnutrition are also found in the community setting [15,16]. In an observational study performed in 1996 patients from The Health Improvement Network (THIN) database, Guest *et al.* [16] have shown that malnourished patients utilized significantly more healthcare resources: they had more general practitioner consultations than non-malnourished patients, three times more hospital admissions, and the length of hospital stay was significantly longer. In 2021, in the PREDyCES study leads by Álvarez-Hernández *et al.* [15], malnutrition was associated with an increase in length of hospital stay, with an associated additional cost of 1,409 \in per malnourished patients not presenting with malnutrition at any time and those who were non-malnourished at admission but were malnourished at discharge: the additional cost was 5,829 \in per patients.

The early identification of malnutrition is of utmost importance since a dedicated management could improve the clinical outcomes. Indeed, Schuetz *et al.* [17] have conducted a large multi-center study, including 2088 patients at risk of malnutrition. They showed that early screening then management of malnutrition improved important clinical outcomes as mortality, admission to the intensive unit care, readmission after discharge and decline of in functional status.

Altogether, these data indicate the importance of an early screening and diagnosis of malnutrition in the hospital setting to undergo the early as possible the appropriate nutritional care. However, since the publication of the GLIM and HAS criteria, little is known about the GLIM or HAS phenotypic profile of malnourished hospitalized patients, and how they are managed in the daily practice of a Nutrition Support Team (NST) in a University Hospital. There are also only a few data about the clinical outcomes (mortality, infections and 1-month hospital readmission) of the malnourished patients managed by the NST.

In 2019, one out of 11 adults had diabetes in the world [18]. In France in 2015, 3.7 million people were taking an anti-diabetic treatment in France, i.e., 5.4% of the population had diabetes, of any type [19]. Prevalence of malnutrition in older diabetic hospitalized patients has been estimate at 21,2% by Sanz-Paris *et al.* [20] a. and 18,5% by Liu *et al.* [21]. Type 2 diabetes mellitus is closely linked to malnutrition as it has been shown that leads to a loss of skeletal muscle. Park *et al.* [22] have examined the body composition of 2675 older adults aged 70-79 years, with dual energy X-ray absorptiometry (DXA), annually for 6 years and measured their mid-thigh muscle cross-sectional area with computed tomography at year 1 and year 6. Fifteen per cent of the patients had a known diabetes and with a systematic 75-g oral glucose tolerance test, they newly diagnosed diabetes in 8.4% of the patients. The

patients who report the highest prevalence of body weight loss were older people with undiagnosed diabetes, followed by those with previously known diabetes, and then those without diabetes, especially in women. The annual declines in appendicular lean mass were higher in older adults with previously unknown diabetes and known diabetes than in those without diabetes. Sugimoto *et al.* [23] have shown in the MUSCLES-DM study that loss of muscle mass was directly related to hyperglycemia. This study includes 768 Japanese patients with stable type 2 diabetes aged over 40 years. They found that glycated hemoglobin (HbA1c) level was specifically associated with low skeletal muscle mass index measured by BIA.

These data suggest that diabetic patients could be at high risk of severe malnutrition. Yet, the phenotype of malnourished diabetic patients based on the GLIM or HAS criteria has never been studied.

The primary objective of this study was to determine whether diabetes mellitus is a risk factor for a severe form of hospital malnutrition based of the newly published HAS criteria.

The secondary objectives were to:

- Compare the levels of fat-free mass, muscle strength, and food intake between diabetic and non-diabetic patients;
- Characterize the profile of malnourished patients or patients at risk of malnutrition managed by the NST;
- Study the prevalence of loss of fat-free mass, in patients with anthropometric phenotypic criteria of malnutrition, i.e. weight loss or low BMI;
- Identify the factors associated with mortality in our population of malnourished patients or patients at risk of malnutrition, and especially to assess whether the HAS thresholds of fat-free mass or muscle strength were associated with patient mortality.

Material and Methods

1. Study design and population

We conducted an observational, retrospective, cross-sectional, monocentric study at CHU Rennes from November 2019 to May 2021 in a population of patients hospitalized and followed by the Nutrition Support Team (NST) (Unité Transversale de Nutrition). The CHU Rennes NST is composed of a resident (working 70% of time, 30% of the remaining time being devoted to the Diabetes Support Team), supervised on a daily basis by a senior physician, and a dietician (working 40% of time). The NST is responsible for the care of malnourished or at risk for malnutrition hospitalized patients. NST health caregivers offer assistance in screening for malnutrition, particularly in targeted departments: digestive surgery, ENT and urology. Twice a week, a systematic screening of malnutrition is performed. A computer program analyzes the data from the medical record (DxCare) of the patients hospitalized in these three departments. Patients at risk of malnutrition are identified according to one of the following criteria:

- BMI lower than 21 kg/m²;
- BMI higher than 30 kg/m² (obese people are at risk for sarcopenic obesity);
- Decreased food intake assessed by the food monitoring sheet filled in by the paramedical staff or a low Simple Evaluation of Food Intake (SEFI)® score (<7) [24];
- Albuminemia under 30 g/L.

Thus, about six patients per week are identified as at risk of malnutrition. Then, the dietician and the resident interviewed and examined these patients to confirm the diagnostic of malnutrition and to advice about their nutritional management. NST health caregivers are also giving their advice for the prescription of nutrition support on the request of physicians from all the hospital departments.

For this study, we included all the patients seen by the NST from November 2019 to May 2021 and for whom a bioimpedance analysis (BIA) had been performed. If BIA was not performed, the patient was excluded. Note that during the Covid-19 epidemic, the NST consultation activity in hospital wards was replaced by phone consultations during several weeks, explaining a lower number of included patients than expected (n=540).

2. Definitions

We defined malnutrition according to the 2019 [5] and 2007 (for older people) [6] HAS criteria: presence of at least one phenotypic criterion and one etiologic criterion.

Phenotypic criteria are:

- A weight loss of at least 5% in 1 month or at least 10% in 6 months or at least 10% compared to the usual weight before the beginning of the disease;
- A BMI under 18.5 kg/m² for patients under 70 years, a BMI under 21 kg/m² for older patients;
- A quantified reduction in muscle mass and/or function:
 - Grip strength under 26 kg for men and under 16 kg for women

• FFMI under 17 kg/m² for men and under 15 kg/m² for women

To diagnose malnutrition in the older subjects, we voluntarily did not use the criteria of serum albumin and MNA as we supposed that they will not be used as they are in the HAS recommendation 2022 update.

Etiologic criteria are:

- A reduction in food intake, assessed by the SEFI® < 7, to match with the HAS criteria of at least 50% for more than 1 week, or any reduction in intake for more than 2 weeks relative to quantified usual food intake, or estimated protein-energy requirements;
- Reduced absorption (malabsorption/maldigestion)
- A situation of aggression (protein hypercatabolism with or without inflammatory syndrome): acute pathology or evolving chronic pathology or evolving malignant pathology.

Then, according to HAS criteria, patients were classified according to malnutrition severity. Moderate malnutrition was defined by one of the following criteria:

- A BMI between 17 and 18,5 kg/m² for patients under 70 years and a BMI between 18 and 21 kg/m² for older patients.
- A loss of weight > 5% in 1 month or > 10% in 6 months or > 10% compared to the usual weight before the onset of the disease

Severe malnutrition was defined by one of the following criteria:

- A BMI under 17 kg/m² for patients under 70 years and a BMI under 18.5 for older patients.
- A loss of weight > 10% in 1 month or > 10 % in 6 months or > 10% compared to the usual weight before the onset of the disease
- Serum albumin level less than 30 g/L.

3. Assessment of body composition by bioimpedance analysis (BIA)

Body composition was assessed by BIA. BIA was performed by the NST resident at patient's bed during the first consultation. The device used was a double frequency bioimpedancemeter (5 kHz and 50 kHz) (Bodystat 1500 MDD, Bodystat Ltd, Man Island, UK) (**Figure 1**). The patient had to be lying down for at least five minutes, wearing underwear. Four single-use electrodes were placed on the patient's right or left hemisphere. Two electrodes were placed on the upper limb: one on the back of the hand and the other on the back of the wrist. Two electrodes were placed on the lower limb: one on the dorsal surface of the foot and the other on the anterior surface of the ankle (**Figure 1**). Dedicated cables connected the device to the appropriate electrodes. The patient was asked to touch anything, and particularly to not touch the cables, the impedancemeter, or any metal object. The operator entered in the device software the patient's gender, age, weight and height in order to start the measurement that took about five seconds. The whole procedure took about 5 minutes.

Figure 1 - Bioimpedance analysis.



Through a safe battery generated signal, the resistance R (in Ohm) which depends on the intraand extra-cellular water and the reactance X which depends on the cell members, were measured. These parameters were used to automatically calculate the phase angle α (in degrees) and the impedance Z (in Ohm) according to the formula $Z^2 = R^2 + X^2$. Then, from multi-variable regression equations preregistered (and kept secret by the manufacturer) in the bioimpedancemeter using sex, age, weight and height, several parameters are obtained:

- Fat mass (in kg and % of total body mass),
- Fat-free mass (in kg and % of total body mass),
- Dry fat-free mass (in kg),
- Total body water (in L and % of total body mass),
- Extracellular water (in L and % of total body mass),
- Intracellular water (in L and % of total body mass).

The Body Fat Mass Index (BFMI = body fat mass (kg) / height (m)²) and the Fat-free Mass Index (FFMI = fat-free mass (kg) / height (m)²) were then calculated. FFMI, was considered low, i.e. in favor of malnutrition, if < 15 in females or < 17 in males.

4. Assessment of food intake

Food intake was assessed using the SEFI®[24] (**Figure 2**), which is a simple tool that can be used in two ways:

- A visual analogue scale: the patient indicates the amount of food she/he presently eats using the slider on the scale between "nothing at all" to "as usual". The result, between 1 and 10, is seeing on the verso of the scale.
- A visual assessment of consumed portions: the patient assesses the portions she/he eats during her/his last meal, generally lunch.



Figure 2- The Simple Evaluation of Food Intake (SEFI®)

The interpretation of the results of the SEFI® is based on the results clinical studies. In adult patients malnourished or at risk of malnutrition, a strong correlation has been shown between the score of the visual analogue scale and the daily energy intakes assessed by the 3-day dietary record [25]. In this study, 81% of those with scores < 7 were at risk of malnutrition according to the Nutritional Risk Index (NRI). These results were confirmed by an independent study conducted in 1762 medical oncology patients [26].

5. Assessment of handgrip strength

Handgrip strength was assessed using an electronic handheld dynamometer (Camry EH101 digital hand dynamometer - 90 kg / 200 lbs., Camry Scale Store, California, USA) (**Figure 3**).

Figure 3- Handgrip dynamometer



The patient had to be sitting. The patient had to grip the dynamometer as hard as possible, during 5 seconds, using her/his dominant hand. The arm had to be bend at 90°, without pressing the instrument against the body or helping with the other hand. Three tests were performed and the best performed was used for the analysis. Handgrip strength was considered low, i.e. in favor of malnutrition, if < 16 kg in females and < 26 kg in males.

6. Data collection

A first set of data were collected prospectively, during the first consultation by the NST, and were those used for the routine use for malnutrition diagnosis and patient management:

- Cause of hospitalization and history of illness;
- Demographic data: age, gender, and place of residence;
- Comorbidities and surgical, medical and psychiatric history;
- Anthropometric data: weight, height and BMI (ratio of weight (in kg) to height squared (in m²)) on the day of the consultation;
- Weight kinetics: weight 1 month before, weight 6 months before, and usual weight. These weights were obtained from the patient interview and the computerized medical record.
 Weight loss was considered if the patient has lost more than 1% of the initial weight;
- Clinical data: presence of edema, ascites, amyotrophy or diarrhea;
- Assessment of food intake by the SEFI® and considered low if under 7;
- Possible intake of Oral Nutritional Supplements (ONS) or artificial nutrition (enteral and/or parenteral nutrition);
- BIA to study body composition including the calculation of the FFMI, considered low if < 15 kg for females and < 17 kg for males;

 Handgrip strength via a dynamometer, considered low if < 16 kg for females and < 26 kg for males.

Comorbidities or history considered were cardiovascular, respiratory, autoimmune, gastrointestinal (GI), psychiatric, oncological and urorenal comorbidities, active or passive misuse of tobacco, alcohol or other toxic substances. Patients were also classified according to whether their comorbidities were associated with malabsorption/maldigestion or not and whether they were receiving or had recently received chemotherapy (less than 6 months). Serum albumin (g/L) and HbA1c (%) data were obtained from the routine blood tests performed at CHU Rennes during the hospital stay and were collected from the computerized medical record.

The second set of data were collected retrospectively, one month after patient's discharge:

- Length of hospital stay (day);
- Possible complications of malnutrition: pressure sores, infection, surgical complication, refeeding syndrome;
- Hospital readmission at CHU Rennes one month after the release.

For diabetic patients, were collected the type of diabetes, its duration, treatment and microvascular and/or macrovascular complications, as well as HbA1c level to estimate the glycemic control.

7. Statistics

For data description, quantitative results are reported as mean \pm standard deviation (min; Q1; median; Q3; max) and qualitative results are expressed as numbers (%). For group comparison, Student test, or Mann-Whitney test if necessary, were used to compare quantitative variables. The Chi2 test, or Fisher test if necessary, were used to compare quantitative variables. Factors associated with death and hospital readmission were identified using stepwise logistic regressions and presented by Odds Ratio (OR) and its 95% Confidence Interval (CI). Variables significant at 0.20 were included in a multivariate model and a stepwise top-down selection was performed. All statistical tests had a significance level of 0.05. Statistical analyses were performed using SAS software, v.9.4® (SAS Institute, Cary, NC, USA).

Results

1. Description of the study population

In our study, 231 patients were included. The mean age was 62.2 ± 15.9 years. Half of them were hospitalized in the digestive surgery department (50.2%). The others were in other surgery departments (16.5%), in medicine departments (30.3%) or in intensive care units (3.0%). Around 50% (48.1%) of our patients had a history of cancer (**Table 1**). The mean BMI at admission was 23.5 ± 6.4 kg/m². Seventy-five % of patients reported a low SEFI® (< 7), 54.4% had a low FFMI, and 49.7%, a low handgrip strength.

Variables	Global population $(n = 231)$	Non diabetics (n = 184)	Diabetics (n = 47)	р
Demographics		· · · · · ·		
Age (years)	62.2 ± 15.9	61.6 ± 16.9	64.5 ± 11.0	0.65
Female	131 (56.7)	96 (52.2)	35 (74.5)	0.006
Lifestyle				
Alone	78 (35.0)	59 (33.3)	19 (41.3)	0.31
In institution	4 (1.8)	4 (2.2)	0 (0.0)	0.58
Comorbidities				
Diabetes	47 (20.3)	-	-	-
Cardiovascular diseases	97 (42.0)	71 (38.6)	26 (55.3)	0.04
Respiratory diseases	54 (23.4)	39 (21.2)	15 (31.9)	0.12
Autoimmune diseases	27 (11.7)	19 (10.3)	8 (17.0)	0.20
Gastro-intestinal diseases	108 (46.8)	80 (43.5)	28 (59.6)	0.048
Psychiatric diseases	27 (11.7)	24 (13.0)	3 (6.4)	0.20
Oncological diseases	82 (35.5)	62 (33.7)	20 (42.6)	0.26
Urogenital diseases	43 (18.6)	33 (17.9)	10 (21.3)	0.60
Liver transplant	26 (11.3)	13 (7.1)	13 (27.7)	0.0001
Malabsorption or digestion	38 (16.5)	29 (15.8)	9 (19.1)	0.58
Cancer	111 (48.1)	92 (50.0)	19 (40.4)	0.24
Chemotherapy				
current	28 (12.1)	25 (13.6)	3 (6.4)	0.34
recent history	13 (5.6)	11 (6.0)	2 (4.3)	
Substance use				
Smocking				0.15
current	55 (25.7)	44 (26.0)	11 (24.4)	
former	18 (8.4)	11 (6.5)	7 (15.6)	
Use of alcohol				0.18
current	36 (15.9)	25 (13.9)	11 (23.4)	
former	14 (6.2)	10 (5.6)	4 (8.5)	
Use of other substances				0.23
current	6 (2.6)	6 (3.3)	0 (0.0)	
former	2 (0.9)	1 (0.6)	1 (2.1)	
Admission				
Reason				0.41
digestive cancer	24 (10.4)	21 (11.4)	3 (6.4)	
nondigestive cancer	12 (5.2)	11 (6.0)	1 (2.1)	
non-oncologic digestive surgery	64 (27.7)	47 (25.5)	17 (36.2)	
oncologic digestive surgery	41 (17.7)	34 (18.5)	7 (14.9)	
non-oncologic non-digestive surgery	17 (7.4)	15 (8.2)	2 (4.3)	

Table 1- Description of the study population.

Variables	Global population $(n = 231)$	Non diabetics (n = 184)	Diabetics $(n = 47)$	р
oncologic non digestive surgery	12 (5.2)	11 (6.0)	1 (2.1)	
digestive disease	24 (10.4)	16 (8.7)	8 (17.0)	
others	37 (16.0)	29 (15.8)	8 (17.0)	
Admission department				0.91
Intensive care unit	7 (3.0)	6 (3.3)	1 (2.1)	
Digestive surgery	116 (50.2)	91 (49.5)	25 (53.2)	
Others surgery departments	38 (16.5)	32 (17.4)	6 (12.8)	
Medicine department	70 (30.3)	55 (29.9)	15 (31.9)	
Anthropometry				
Weight measurement at admission (yes vs no)	199 (86.1)	164 (89.1)	35 (74.5)	0.009
Reason for non-measurement				
Covid-19	1 (8.3)	0 (0.0)	1 (33.3)	0.046
Surgical emergency	10 (83.3)	9 (100.0)	1 (33.3)	
Intensive Care Unit	1 (8.3)	0 (0.0)	1 (33.3)	
BMI at admission (kg/m ²)	23.5 ± 6.4	22.8 ± 6.3	26.3 ± 6.4	0.001
Weight kinetics				
Weight loss in 1 month	90 (51.7)	69 (50.7)	21 (55.3)	0.62
% of weight loss	2.3 ± 7.9	1.8 ± 8.9	1.7 ± 5.3	0.91
Weight loss in 6 months	147 (67.4)	24 (51.1)	30 (66.7)	0.90
% of weight loss	7.5 ± 11.0	4.9 ± 12.5	6.3 ± 11.7	0.41
Weight loss compared to usual weight	158 (74.2)	31 (67.4)	28 (63.6)	0.07
% of weight loss	9.4 ± 11.9	9.2 ± 11.8	6.4 ± 13.8	0.06
Weight loss during hospitalization	105 (50.2)	21 (46.7)	21 (46.7)	0.59
% of weight loss	1.3 ± 8.9	1.1 ± 9.2	2.1 ± 7.6	0.78
Clinical and biological signs for malnutrition	ı			
Edemas	62 (26.8)	47 (25.5)	15 (31.9)	0.38
Ascites	19 (8.2)	11 (6.0)	8 (17.0)	0.03
Amyotrophy	29 (20.7)	21 (18.9)	8 (27.6)	0.31
Diarrhea	41 (18.8)	36 (20.7)	5 (11.4)	0.16
Albuminemia (g/l)	30.1 ± 6.8	30.2 ± 6.8	29.8 ± 6.8	0.71
Hypoalbuminemia	162 (77.9)	105 (77.2)	34 (82.9)	0.43
Bioimpedance analysis (BIA)				
BMI at measurement (kg/m^2)	23.5 ± 6.3	23.0 ± 6.2	25.6 ± 6.5	0.01
Weight at measurement (kg)	65.4 ± 18.3	63.6 ± 17.8	72.6 ± 18.8	0.005
Cautionary results				0.80
Cautionary	42 (24.3)	32 (23.5)	10 (27.0)	
Out of range results	2 (1.2)	2 (1.5)	0 (0.0)	
Fat Mass (%)	30.2 ± 10.5	29.5 ± 8.4	30.7 ± 10.7	0.16
Female	35.5 ± 10.8	35.5 ± 10.5	35.2 ± 13.5	0.69
Male	26.7 ± 8.8	27.0 ± 9.0	25.7 ± 8.4	0.50
Fat-free Mass (%)	69.6 ± 10.5	69.1 ± 10.6	71.3 ± 10.3	0.27
Female	63.6 ± 10.6	63.5 ± 10.2	64.2 ± 14.0	0.85
Male	73.5 ± 8.4	73.5 ± 8.6	73.5 ± 7.9	1
Dry Fat-free Mass (%)	11.2 ± 7.5	10.7 ± 8.0	13.2 ± 4.8	0.07
Female	9.3 ± 6.8	9.1 ± 7.1	10.4 ± 3.9	0.59
Male	12.5 ± 7.7	11.9 ± 8.5	14.1 ± 4.8	0.24
Total body water (%)	58.2 ± 11.6	58.3 ± 11.6	58.0 ± 11.9	0.92
Extracellular water (%)	31.8 ± 27.5	31.7 ± 27.9	32.0 ± 26.6	0.10
Intracellular water (%)	27.0 ± 26.9	27.2 ± 27.4	26.2 ± 25.5	0.84
BFMI (kg/m ²)	7.3 ± 4.1	7.2 ± 4.1	7.5 ± 4.2	0.61
FFMI (kg/m ²)	16.0 ± 4.0	15.5 ± 4.1	17.9 ± 3.4	< 0.0001
Resistance 50 kHz (Ohm)	561 ± 153	574 ± 151	512 ± 153	0.006
Reactance 50 kHz (Ohm)	50.7 ± 23.4	52.7 ± 24.4	43.0 ± 17.6	0.04

Variables	Global population $(n = 231)$	Non diabetics (n = 184)	Diabetics (n = 47)	р
Phase angle 50 kHz	5.3 ± 2.3	5.4 ± 2.4	4.9 ± 1.9	0.26
Malnutrition criteria				
Low FFMI	123 (54.4)	109 (60.9)	14 (29.8)	0.0001
SEFI®	4.3 ± 3.5	4.2 ± 3.4	4.7 ± 3.8	0.54
Low SEFI® (<7/10)	144 (75.0)	116 (77.3)	28 (66.7)	0.16
Handgrip strength (kg)	21.2 ± 8.4	21.2 ± 8.2	21.3 ± 9.2	0.93
Female	16.8 ± 5.8	16.9 ± 5.4	16.3 ± 8.3	0.76
Male	24.6 ± 8.5	25.0 ± 8.3	23.4 ± 8.9	0.37
Low handgrip strength	95 (49.7)	68 (45.6)	27 (64.3)	0.03
Hypoalbuminemia	162 (77.9)	105 (77.2)	34 (82.9)	0.43
Diagnostic of malnutrition	193 (83.5)	154 (83.7)	39 (83.0)	0.91
Severe malnutrition	141 (73.1)	117 (76.0)	24 (61.5)	0.07
Nutrition support			(0.51
ONS	111 (48.5)	84 (46.2)	27 (57.4)	
Dietary advice	24 (10.5)	18 (9.9)	6 (12.8)	
EN	63(275)	54 (29 7)	9(191)	
EN combined with PN	10(4.4)	8 (4.4)	2(4.3)	
PN	21(92)	18 (9 9)	$\frac{2}{3}(64)$	
duration	168 + 210	136 + 120	346 + 456	0.42
Clinical outcomes	10.0 ± 21.0	15.0 ± 12.0	51.0 ± 15.0	0.12
Discharge				0.20
Other hospital	19 (8 2)	13(71)	6(12.8)	0.20
Home	139 (60.2)	110 (59.8)	29 (61 7)	
Death at hospital	13 (5.6)	8 (4 3)	5(10.6)	
Nursing home	2(0.9)	2(11)	0(0.0)	
Hospital at home	5(2,2)	5(27)	0(0.0)	
Rehabilitation center	53 (22.9)	46(250)	7(14.9)	
Death	25(22.9)	17(92)	9(14.)	0.06
Length of stay	26(11.5)	24.8 ± 24.0	32.2 ± 33.7	0.00
Complications	20.3 ± 20.3	24.0 ± 24.0	52.2 ± 55.1	0.15
1 month hospital readmission	48 (23 1)	38 (22 6)	10(250)	0.75
Department of readmission	46 (23.1)	38 (22.0)	10 (23.0)	0.75
digestive surgery	19 (39 6)	16(42.1)	3 (30 0)	0.70
other surgery department	5(10.4)	A(10.5)	1(10.0)	
medicine department	20(41.7)	$\frac{1}{14}(36.8)$	1(10.0)	
intensive care	20 (41.7) A (8 3)	4(10.5)	0(00.0)	
Pressure ulcers	19 (8 2)	16(87)	3(6.4)	0.77
Refeeding syndrome	43(18.6)	34(185)	0(101)	0.07
Surgical revision	34(14.7)	25(13.6)	9(19.1) 9(10.1)	0.72
Infactions	130(563)	25(13.0) 26(54.2)	9(19.1)	0.34
Bacteremia	52 (22 5)	20(34.2) 34(18.5)	90(02.3) 18(383)	0.51
Central line infection	15(65)	10(54)	5(10.6)	0.004
Proumonia	13(0.3)	10(3.4)	5(10.0)	0.20
Abdominal infection	$\frac{27}{11.7}$	21(11.4) 50(27.2)	20(12.0)	0.00
Urogenital infection	35(152)	30(27.2) 30(16.2)	20(42.0)	0.04
Others infections	15(65)	10(5.3)	5(10.0) 5(10.6)	0.33
Antibiotics	135 (58 4)	10(3.4) 102(554)	33 (70.2)	0.20

BFMI, Body Fat Mass Index; BMI, Body Mass Index; EN, Enteral Nutrition; FFMI, Fat-Free Mass Index; ONS, Oral Nutritional Supplements; PN, Parenteral Nutrition; SEFI®, Simple Evaluation of Food Intake®. Qualitative data are presented as n (%), and quantitative data as mean ± standard deviation.

2. Description of the diabetic population

Forty-seven patients (20.3%) had diabetes, including 68.1% of type 2 diabetes (**Table 1**). There were more males in the diabetic subgroup. This population had more cardiovascular and GI diseases, including more liver transplantation. This may explain why they were more presented with ascites than the non-diabetic patients were. Diabetes was unbalanced for 48.9% of them and 30.4% had at least one complication (**Table 2**).

The weight of diabetic patients was more missing at admission than for the non-diabetic patients (89.1% vs 74.5%, p=0.0094). The BMI of diabetic patients was higher than in non-diabetic patients (26.3 \pm 6.4 kg/m² vs 22.8 \pm 6.3 kg/m², p=0.0013). Unexpectedly, diabetic patients had higher FFMI (15.5 \pm 4.1 vs 17.9 \pm 3.4 kg/m², p < 0.0001) with lower bioimpedance parameters (50-kHz resistance and 50-kHz reactance). The phase angle was not significantly different. In contrast, more of them had low handgrip strength (64.3% vs 45.6%, p=0.03). Diabetes was not significantly associated with malnutrition or its severity. During follow-up, they developed bacteremia or abdominal infection more frequently, while the rate of infection of all types was not significantly higher.

Variables	Population
Diabetes characteristics	
Type 1	3 (6.4)
Type 2	32 (68.1)
Secondary corticoid	1 (2.1)
Secondary liver disease	1 (2.1)
Immunosuppressive secondary	3 (6.4)
Secondary pancreatic disease	7 (14.9)
Discovery	5 (10.6)
Uncontrolled	23 (48.9)
Last HbA1c (%)	6.4 ± 1.9
Treatment	
Oral antidiabetics	14 (29.8)
Oral antidiabetics + insulin	5 (10.6)
No treatment	8 (17.0)
Insulin multi-injection	17 (36.2)
Only basal insulin	2 (4.3)
Insulin pump	1 (2.1)
Complications	14 (30.4)
Type of complications	
Macrovascular	7 (50)
Retinopathy	5 (35,8)
Severe	2 (14,3)
Neuropathy	7 (50)
Severe	1 (7,1)
Nephropathy	2 (14,3)
Number of complications	
1	8 (57, 1)
2	4 (28,6)
3	1 (7, 1)
4	1 (7, 1)
Severe hypoglycemia < 1 year	0 (0.0)

 Table 2 - Description of diabetic population.

Hyperosmolarity < 6 months	0 (0.0)
Ketoacidosis <6 months	0 (0.0)
Ketosis <6 moist	1 (2.1)
Foot injury >3 months	3 (6.4)
Ub 1 a glycostad homoglobin Qualitative data	is presented as n (%) and quantitative data

HbA1c, glycated hemoglobin. Qualitative data is presented as n (%) and quantitative data as mean \pm standard deviation.

3. Description of the malnourished patients

83.5% of our patients (n=193) were malnourished according to the HAS definitions. Among them, 73.1% had a severe malnutrition. As expected, malnourished patients had a lower BMI than the nonmalnourished patients (22.6 \pm 6.4 vs. 27.7 \pm 4.3 kg/m², p<0.0001), lower handgrip strength (19.9 \pm 7.5 vs. 28.9 \pm 8.9 kg, p<0.0001) and lower FFMI (15.5 \pm 4.1 vs. 18.7 \pm 2.3 kg/m², p<0.0001). They had lost more weight in the last month, in the last 6 months, or compared to their usual weight (**Table 3**). Oral nutritional supplements and enteral nutrition were more often provided. During the follow-up, the occurrence of a complication, death, or hospital readmission one month after hospital release were not significantly different from the non-malnourished population.

Variables	Non-malnourished	Malnourished	n	
v al lables	(n = 38)	(n = 193)	þ	
Demographics				
Age (years)	57.4 ± 16.9	63.1 ± 15.6	0.06	
Male	16 (42.1)	84 (43.5)	0.87	
Lifestyle: alone				
Alone	8 (22.9)	70 (37.2)	0.10	
In institution	0 (0.0)	4 (2.1)	1.00	
Comorbidities				
Diabetes	8 (21.1)	39 (20.2)	0.91	
Cardiovascular diseases	18 (47.4)	79 (40.9)	0.46	
Respiratory diseases	7 (18.4)	47 (24.4)	0.43	
Autoimmune diseases	8 (21.1)	19 (9.8)	0.06	
Gastro-intestinal diseases	19 (50.0)	89 (46.1)	0.66	
Psychiatric diseases	4 (10.5)	23 (11.9)	1.00	
Oncological diseases	12 (31.6)	70 (36.3)	0.58	
Urogenital diseases	2 (5.3)	41 (21.2)	0.02	
Liver transplant	4 (10.5)	22 (11.4)	1.00	
Malabsorption or digestion	6 (15.8)	32 (16.6)	0.90	
Cancer	14 (36.8)	97 (50.3)	0.13	
Chemotherapy			0.77	
current	3 (7.9)	25 (13.0)		
recent history	2 (5.3)	11 (5.7)		
Substance use				
Smocking			0.73	
current	9 (25.7)	46 (25.7)		
former	4 (11.4)	14 (7.8)		
Use of alcohol			0.56	
current	4 (10.8)	32 (16.8)		
former	3 (8.1)	11 (5.8)		
Use of other substances			0.48	

 Table 3 - Description of the malnourished population.

Variables	Non-malnourished	Malnourished	n
variables	(n = 38)	(n = 193)	р
current	2 (5.4)	4 (2.1)	
former	0 (0.0)	2 (1.1)	
Admission			
Reason			0.01
digestive cancer	0 (0.0)	24 (12.4)	
nondigestive cancer	1 (2.6)	11 (5.7)	
non-oncologic digestive surgery	13 (34.2)	51 (26.4)	
oncologic digestive surgery	10 (26.3)	31 (16.1)	
non-oncologic non-digestive surgery	6 (15.8)	11 (5.7)	
oncologic non digestive surgery	2 (5.3)	10 (5.2)	
digestive disease	4 (10.5)	20 (10.4)	
others	2 (5.3)	35 (18.1)	
Admission department			0.01
Intensive care unit	2 (5.3)	5 (2.6)	0101
Digestive surgery	$\frac{2}{24}$ (63.2)	92 (47 7)	
Others surgery departments	8 (21.1)	30 (15 5)	
Medicine department	4(105)	66 (34 2)	
Anthronometry	r (10. <i>3)</i>	00 (34.2)	
Weight measurement at admission (ves ve	29 (76 3)	170 (88-1)	0.05
no)	2) (10.3)	170 (00.1)	0.05
Reason for non-measurement			0.68
Covid_10	0 (0 0)	1(1/2)	0.00
Surgical amergency		1(14.3) 6(857)	
Intensive Core Unit	4(00.0) 1(20.0)	0(0,0)	
Intensive Care Unit	1(20.0)	0(0.0)	- 0.0001
DIVIT at aumission	21.1 ± 4.5	22.0 ± 0.4	< 0.0001
Weight kinetics	9 (25 0)	92(57.7)	0 0000
weight loss in 1 month	8 (25.0)	82 (57.7)	0.0008
% of weight loss	-1.8 ± 5.5	3.2 ± 8.1	0.0002
Weight loss in 6 months	11 (30.6)	136 (74.7)	0.0001
% of weight loss	-1.6 ± 6.2	9.3 ± 10.9	0.0001
Weight loss compared to usual weight	13 (36.1)	145 (81.9)	0.0001
% of weight loss	-1.6 ± 7.2	11.6 ± 11.4	0.0001
Weight loss during hospitalization	24 (66.7)	81 (46.8)	0.03
% of weight loss	2.6 ± 7.5	1.2 ± 5.7	0.11
Clinical and biological signs for malnutriti	on		- - -
Edemas	11 (28.9)	51 (26.4)	0.75
Ascites	1 (2.6)	18 (9.3)	0.33
Amyotrophy	0 (0.0)	29 (24.6)	0.008
Diarrhea	4 (11.8)	37 (20.1)	0.25
Albuminemia (g/l)	29.1 ± 7.5	30.4 ± 6.7	0.3
Hypoalbuminemia	34 (94.4)	128 (74.4)	0.009
Bioimpedance analysis (BIA)			
BMI at measurement	26.7 ± 4.4	22.9 ± 6.4	0.0001
Weight at measurement	78.6 ± 15.8	63.1 ± 17.8	0.0001
Cautionary results			0.003
Cautionary	2 (8.0)	40 (27.0)	
Out of range	2 (8.0)	0 (0.0)	
Fat Mass (%)	30.0 ± 8.5	30.2 ± 10.8	0.92
Female	32.2 ± 11.1	36.0 ± 10.7	0.3
Male	28.3 ± 5.8	26.4 ± 9.1	0.49
Fat-Free Mass (%)	69.5 ± 8.9	69.6 ± 10.8	0.98
Female	66.3 ± 11.7	63.1 ± 10.5	0.39
Male	72.0 ± 5.1	73.7 ± 8.8	0.49

Variables	Non-malnourished	Malnourished	
variables	(n = 38)	(n = 193)	р
Female	15.2 ± 4.7	8.3 ± 6.6	0.001
Male	17.3 ± 2.5	11.8 ± 8.0	0.0009
Total body water (%)	53.6 ± 8.3	58.9 ± 11.9	0.04
Extracellular water (%)	28.1 ± 15.9	32.3 ± 28.9	0.02
Intracellular water (%)	25.5 ± 15.3	27.2 ± 28.3	0.03
BFMI	8.4 ± 3.4	7.1 ± 4.2	0.03
FFMI	18.7 ± 2.3	15.5 ± 4.1	< 0.0001
Resistance 50 kHz	489 ± 102	573 ± 157	0.01
Reactance 50 kHz	45.0 ± 11.9	51.5 ± 24.6	0.30
Phase angle 50 kHz	5.6 ± 3.0	5.2 ± 2.2	0.43
Malnutrition criteria			
Low FFMI	0 (0.0)	123 (64.4)	0.0001
SEFI®	4.1 ± 3.1	4.3 ± 3.5	0.97
Low SEFI® (< 7/10)	24 (77.4)	120 (74.5)	0.73
Handgrip strength (kg)	28.9 ± 8.9	19.9 ± 7.5	< 0.0001
Female	21.5 ± 5.7	15.9 ± 5.5	0.0009
Male	35.0 ± 6.0	22.8 ± 7.5	< 0.0001
Low handgrip strength	0 (0.0)	95 (58.6)	< 0.0001
Nutritional support		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	< 0.0001
ONS	10 (27 0)	101 (52.6)	
Dietary advice	13(35.1)	11 (5.7)	
EN	8 (21.6)	55 (28.6)	
EN combined with PN	0(0,0)	10(52)	
PN	6 (16 2)	15(7.8)	
duration	10.3 + 7.9	18.5 + 23.1	0.37
Clinical outcomes			
Discharge			0.23
Other hospital	2 (5.3)	17 (8.8)	
Home	28(73.7)	111 (57.5)	
Death at hospital	1 (2.6)	12 (6.2)	
Nursing home	0(0.0)	2(1.0)	
Hospital at home	2(5.3)	$\frac{1}{3}(1.6)$	
Rehabilitation center	5 (13.2)	48 (24.9)	
Death	3(79)	23(11.9)	0 59
Length of stay	28.8 ± 21.3	25.8 + 27.2	0.07
Complications		2010 - 2112	0.07
1 month hospital readmission	7 (20.0)	41 (23.7)	0.64
Department of readmission	, (2010)	()	0.63
digestive surgery	4 (57.1)	15 (36.6)	0100
other surgery department	1 (14.3)	4 (9.8)	
medicine department	2 (28.6)	18 (43.9)	
intensive care unit	0(00)	4 (9.8)	
Pressure ulcers	4(105)	15 (7.8)	0.53
Refeeding syndrome	8 (21.1)	35 (18.1)	0.67
Surgical revision	11 (28.9)	23(11.9)	0.007
Infections	25 (65.8)	105(544)	0.2
Bacteremia	10(263)	42 (21.8)	0.54
Central line infection	3(79)	12 (6 2)	0.72
Pneumonia	2 (5 3)	25 (13 0)	0.27
Abdominal infection	14 (36 8)	56 (29 0)	0.27
Urogenital infection	4 (10 5)	31 (16 1)	0.38
Others infections	5 (13.2)	10(52)	0.08
Antibiotics	25 (65.8)	110(57.0)	0.31

BFMI, Body Fat Mass Index; BMI, Body Mass Index; EN, Enteral Nutrition; FFMI, Fat-Free Mass Index; ONS, Oral Nutritional Supplements; PN, Parenteral Nutrition; SEFI, Simple Evaluation of Food Intake. Qualitative data are presented as n (%), and quantitative data as mean \pm standard deviation.

4. <u>Description of the phenotypic criteria of the malnourished patients according to the HAS</u> malnutrition diagnostic criteria

All the included hospitalized patients had, by definition, an etiological criterion of malnutrition: situation of metabolic stress with protein hypercatabolism, due to an acute disease. To be considered as malnourished, the patients should report one or more phenotypic criteria: low BMI for 29% of them, weight loss compared to the usual weight in 62%, low FFMI in 64.4%, and low handgrip strength in 58.6% (**Table 4**). The malnutrition diagnosis was based on one phenotypic criterion for 36.8% patients, two criteria for 33.7%, three criteria for 19.2%, and four criteria for 10.4% (**Table 4**).

Variables	Malnourished patients
Low BMI	56 (29.0)
Loss of weight	118 (62.4)
Low FFMI	123 (64.4)
Low strip strength	95 (58.6)
Number of positive phenotypic criteria	
1	71 (36.8)
2	65 (33.7)
3	37 (19.2)
4	20 (10.4)

Table 4 - Phenotypic criteria for the diagnosis of malnutrition.

BMI, Body Mass Index; FFMI, Fat-Free Mass Index; Data are presented as n (%).

5. Factors associated with mortality

In our study, the mortality rate was 11.3%. Univariate analysis showed that patients hospitalized in medical or non-digestive surgical departments had a greater risk of dying during hospitalization or in the months following hospitalization. Patients hospitalized for cancer management (especially non-digestive cancers) were at greater risk of mortality. Clinical amyotrophy was significantly associated with mortality. Malnutrition, severity of malnutrition, BMI, low FFMI and low handgrip strength were not significantly associated with mortality. Cardiovascular or respiratory associated diseases, admission department, weight loss in 6 months, amyotrophy, SEFI® score or SEFI® in classes, 50 kHz phase angle, low handgrip strength, and diabetes, were included in the stepwise top-down multivariate logistic model as they were associated with mortality (P<0.20) in the univariate analysis. The multivariate analysis did not show any factor significantly associated with mortality. The last remaining variable was diabetes (p=0.0604), but it was below the level of statistical significance (**Table 5**).

Variables OR [IC95%] p OR [IC95%] p Demographics Age 1.00 [0.97 ; 1.02] 0.91 0.91 Age 1.00 [0.97 ; 1.02] 0.91 0.92 $1.19 [0.51 ; 2.18]$ 0.92 Lifestyle $0.00 [0.00 ; I]$ 0.98 $0.00 [0.00 ; I]$ 0.98 Comorbidities $2.33 [0.96 ; 5.62]$ $0.06 = 2.33 = 0.06$ $0.06 = 5.621$
Demographics Age $1.00 [0.97; 1.02]$ 0.91 Female $0.96 [0.42; 2.18]$ 0.92 Lifestyle $1.19 [0.51; 2.75]$ 0.69 Alone $1.19 [0.51; 2.75]$ 0.69 Institution $0.00 [0.00; I]$ 0.98 Comorbidities $2.33 [0.96; 5.62]$ $0.06 = 2.33 = 0.06$ Diabetes $2.33 [0.96; 5.62]$ $0.06 = 2.33 = 0.06$
Age $1.00 [0.97; 1.02]$ 0.91 Female $0.96 [0.42; 2.18]$ 0.92 Lifestyle $1.19 [0.51; 2.75]$ 0.69 Institution $0.00 [0.00; I]$ 0.98 Comorbidities $2.33 [0.96; 5.62]$ $0.06 2.33 0.06$ Diabetes $2.33 [0.96; 5.62]$ $0.06 2.33 0.06$
Female $0.96 [0.42; 2.18]$ 0.92 Lifestyle1.19 [0.51; 2.75] 0.69 Alone1.19 [0.51; 2.75] 0.69 Institution $0.00 [0.00; I]$ 0.98 ComorbiditiesDiabetes2.33 [0.96; 5.62] 0.06 2.33 0.06
Lifestyle $1.19 [0.51; 2.75]$ 0.69 Institution $0.00 [0.00; I]$ 0.98 Comorbidities $2.33 [0.96; 5.62]$ 0.06 $2.33 0.06$ Diabetes $10 96 \pm 5 621$
Alone 1.19 [0.51 ; 2.75] 0.69 Institution 0.00 [0.00 ; I] 0.98 Comorbidities 2.33 [0.96 ; 5.62] 0.06 2.33 0.06 Diabetes 2.33 [0.96 ; 5.62] 0.06 2.33 0.06
Institution 0.00 [0.00 ; I] 0.98 Comorbidities 2.33 [0.96 ; 5.62] 0.06 2.33 [0.96 : 5.62] Diabetes 2.33 [0.96 ; 5.62] 0.06 2.33 [0.96 : 5.62]
Comorbidities Diabetes 2.33 [0.96 ; 5.62] 0.06 2.33 0.06
Diabetes 2.33 [0.96 ; 5.62] 0.06 2.33 0.06 [0.96 · 5.62]
[0.90, 3.02]
Cardiovascular diseases 2.05 [0.89 ; 4.68] 0.09
Respiratory diseases 1.88 [0.79 ; 4.51] 0.16
Autoimmune diseases 0.98 [0.27 ; 3.52] 0.98
Gastro-intestinal diseases 0.82 [0.36 ; 1.86] 0.63
Psychiatric diseases 1.44 [0.46 ; 4.54] 0.54
Oncological diseases 1.15 [0.50 ; 2.68] 0.74
Urogenital diseases 1.05 [0.37 ; 2.95] 0.93
Liver transplant 1.51 [0.48; 4.79] 0.48
Cancer 1.30 [0.57 ; 2.94] 0.53
Chemotherapy 0.81
Current 1.34 [0.42 ; 4.24]
Recent history 0.67 [0.08 : 5.42]
Malabsorption or digestion 0.63 [0.18 : 2.23] 0.48
Substance use
Smocking 0.82
Current 1.33 [0.53 : 3.31]
Former 0.98 [0.21 : 4.64]
Use of alcohol 0.94
Current 1.20 [0.42 : 3.42]
Former 0.00 [0.00 : 8.13E275]
Use of others toxic substance 0.93
Current 1.55 [0.17 : 13.83]
Former 0.00 [0.00 : I]
Admission
Reason for admission 0.006
digestive cancer $1.16[0.19 \cdot 7.29]$
nondigestive cancer $4.07 [0.84 \cdot 19.74]$
non-oncologic digestive surgery $20.33 [4.02 \cdot 102.73]$
oncologic digestive surgery 1 04 [0 17 : 6 52]
non-oncologic non-digestive surgery $2.71 [0.42 \cdot 17.70]$
$\frac{1}{2}$ on cologic non digestive surgery $\frac{4}{2}$ 07 [0.60 : 27.46]
digestive disease $5.35 [1.17 \cdot 24.49]$
others 1
Admission department 0.02
Digestive surgery 1
Intensive Care Unit $0.00 [0.00 \cdot 1]$
Others surgery departments $3.44 [1.04 \cdot 11.39]$
$\begin{array}{c} \text{Medicine department} \\ Medicine dep$
Anthronometry
Weight measurement at admission $1.26[0.36:4.48]$ 0.72
(ves vs no) $(120[0.00, -1.00])$
Weight kinetics
Weight at admission $1.26 [0.36 \cdot 4.48] = 0.72$
BMI at admission 0.97 [0.90 : 1.04] 0.41

 Table 5- Univariate and multivariate analyses of factors associated with mortality.

Variables Univariate		lysis	Multivariate a	nalysis
variables	OR [IC95%]	р	OR [IC95%]	р
Weight loss in 1 month	2.38 [0.93; 6.11]	0.07		
% of weight loss	1.03 [0.97 ; 1.09]	0.33		
Weight loss in 6 months	2.79 [0.92; 8.47]	0.07		
Weight loss compared to usual	0.98 [0.37 ; 2.64]	0.98		
weight				
Weight loss during hospitalization	0.81 [0.33 ; 1.96]	0.64		
% of weight loss	0.96 [0.92 ; 1.01]	0.13		
Clinical and biological signs for ma	Inutrition			
Edemas	0.80 [0.30 ; 2.09]	0.65		
Ascites	1.54 [0.42; 5.69]	0.52		
Amyotrophy	3.14 [1.14 ; 8.64]	0.03		
Diarrhea	1.71 [0.67 ; 4.39]	0.26		
Albuminemia (g/l)	1.00 [0.94 ; 1.06]	0.99		
Hypoalbuminemia	1.15 [0.41; 3.27]	0.79		
Bioimpedance analysis (BIA				
BMI at measurement	1.01 [0.94 ; 1.08]	0.79		
Weight at measurement	1.00 [0.98 ; 1.03]	0.78		
Fat Mass (%)	1.01 [0.97 ; 1.06]	0.56		
Fat Mass (kg)	1.01 [0.96 ; 1.05]	0.81		
Fat-Free Mass (kg)	0.99 [0.96 ; 1.03]	0.76		
Fat-Free Mass (%)	0.99 [0.95 ; 1.04]	0.66		
Dry Fat-Free Mass (kg)	0.97 [0.89 ; 1.05]	0.48		
Dry Fat-Free Mass (%)	0.97 [0.91 ; 1.02]	0.26		
Total body water (%)	0.99 [0.95 ; 1.03]	0.56		
Total body water (L)	0.99 [0.94 ; 1.05]	0.83		
Extracellular water (%)	1.00 [0.99 ; 1.02]	0.83		
Extracellular water (L)	1.00 [0.97 ; 1.03]	0.98		
Intracellular water (%)	1.00 [0.98 ; 1.02]	0.97		
Intracellular water (L)	1.00 [0.97 ; 1.03]	0.97		
BFMI	1.00 [0.89 ; 1.12]	0.97		
FFMI	0.98 [0.89 ; 1.09]	0.73		
Resistance 50 kHz	1.00 [1.00 ; 1.00]	0.67		
Reactance 50 kHz	0.98 [0.96 ; 1.01]	0.21		
Phase angle 50 kHz	0.72 [0.50 ; 1.03]	0.07		
Malnutrition criteria				
Low FFMI	0.97 [0.43 ; 2.21]	0.95		
SEFI®	0.90 [0.79 ; 1.03]	0.14		
Low SEFI® (< 7/10)	2.42 [0.69 ; 8.53]	0.17		
Handgrip strength (kg)	0.97 [0.92 ; 1.03]	0.36		
Low handgrip strength	2.02 [0.77 ; 5.30]	0.16		
Diagnostic of malnutrition	1.58 [0.45 ; 5.55]	0.48		
Severe malnutrition	1.87 [0.60 ; 5.78]	0.28		
Nutritional support		0.44		
ONS	1			
Dietary advice	1.03 [0.21 ; 5.10]			
EN	1.89 [0.71 ; 5.04]			
EN combined with PN	2.83 [0.52 ; 15.40]			
PN	2.67 [0.74; 9.64]			
Clinical outcomes				
Length of stay	1.01 [1.00; 1.02]	0.08		
Complications				
1 month hospital readmission	6.91 [0.61 ; 77.97]	0.12		
Pressure ulcers	$154[042 \cdot 560]$	0.52		
	1.34[0.42, 5.09]	0.52		

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Variables	Univariate ana	Multivariate analysis		
variables	OR [IC95%]	р	OR [IC95%]	р
Surgical revision	1.44 [0.50 ; 4.14]	0.49		
Infection	0.90 [0.39 ; 2.03]	0.79		
Central line infection	1.23 [0.26 ; 5.79]	0.79		
Pneumonia	1.98 [0.68 ; 5.78]	0.21		
Abdominal infection	0.51 [0.19; 1.42]	0.2		
Urogenital infection	1.02 [0.33 ; 3.17]	0.97		
Others infections	1.23 [0.26 ; 5.79]	0.79		
Antibiotics	0.90 [0.39 ; 2.03]	0.79		

BFMI, Body Fat Mass Index; BMI, Body Mass Index; EN, Enteral Nutrition; FFMI, Fat-Free Mass Index; PN, Parenteral Nutrition; ONS, Oral Nutritional Supplements; SEFI®, Simple Evaluation of Food Intake®.

Discussion

1. <u>Summary of the results</u>

To our knowledge, our study is the first to characterize the phenotype of malnourished diabetic patients based on the newly published HAS criteria. We showed that diabetes mellitus was associated with lower handgrip strength but higher fat-free mass. Diabetic patients had poorer outcomes, especially mortality, unless it fell to reach the statistical level of significance in the multivariate analysis. None of the diagnostic criteria for malnutrition was associated with mortality. Diabetes mellitus was not associated with a higher risk of severe malnutrition. Finally, our data constitute an evaluation of the CHU Rennes NST practices that would help us to improve our practice in the future. We report that 64.4 % of malnourished patients had a low FFMI justifying the need of a global assessment of malnutrition as proposed by the GLIM and the HAS.

2. Diabetes and sarcopenia

In the literature, more articles are found regarding the relation between diabetes and sarcopenia [27–31] than with malnutrition. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. It results in a decrease in physical performance. It is associated with a risk of falls, fracture, physical disability, decrease of quality of life, and death [32]. According to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), sarcopenia can be classified in two categories: i) primary sarcopenia that is age-related; ii) secondary sarcopenia that occurs in the context of systemic diseases, especially those involving inflammatory processes, malignancy or organ failure. Physical inactivity and low protein intake contribute to sarcopenia [33]. In our study we did not assess the prevalence of sarcopenia based on the EWGSOP2 criteria, but we used the malnutrition diagnosis criteria recently published by the GLIM and the HAS. These latter criteria propose to use separately of the other, the assessment of fat-free mass or muscle mass, and the muscle strength.

In 2020, a meta-analysis reviews and synthesizes the available evidence regarding the association between diabetes mellitus and sarcopenia [34]. The authors showed that the risk of sarcopenia was significantly increased in type 2 diabetic patients compared with euglycemic subjects (n=15 studies, OR 1.55, 95% CI 1.25–1.91, p<0.001; I² 34.6%). The diabetic patients presented lower values of handgrip strength (n=6 studies (standardized mean difference (SMD) – 0.24, 95% CI – 0.39 to – 0.09, p=0.002)), but no difference in skeletal mass index was observed (SMD 0.018, 95% CI 0.047 to – 0.075, p=0.11; I² 25.6%), which is consistent with our study. However, a large study including 746 diabetic non-obese patients and 2067 controls showed that the frequency of sarcopenia increased linearly with the HbA1c level. HbA1c level was specifically associated with low skeletal mass index [35].

3. Loss of skeletal muscle mass

The EWGSOP2 suggest several methods to evaluate the loss of skeletal muscle mass. Magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) are considered gold standards, but the equipment costs and their lack of portability makes difficult their use in clinical routine. They are mostly used in research [33]. We choose to evaluate the loss of skeletal muscle mass by BIA as it offers a simple, high feasible, easy, cheap, and fast method to assess muscle mass at patient's bed. Decreased of muscle mass measured by BIA is known to be associated to higher risk of malnutrition in hospitalized patients. In 2017, the EMPOWER study, including 378 hospitalized patients aged 70 years or older in Amsterdam studied the association between the risk of malnutrition at admission and the muscle mass. The authors showed that high risk of malnutrition, determined by the Short Nutritional Assessment Questionnaire (SNAQ), was significantly associated with lower muscle mass, assessed by BIA (Odds Ratio, 95% CI, 0.90, 0.85-0.96), and lower appendicular lean mass assessed by DXA (Odds Ration, 95% CI, 0.89, 0.83–0.96) [36]. Moreover, low FFMI has already been described as a risk factor of mortality [37]. In our study, we report that 64.4 % of malnourished patients had a low FFMI. A Danish study has shown that the association between FFMI and mortality is reverse J-shaped with high mortality for low FFMI and a tendency to level off for high values [38]. In our study, we were unable to show a relation between FFMI and mortality, as we included almost no control patients, i.e. without malnutrition. This is due to our study design leading to the recruitment of malnourished patients mostly.

We showed that diabetic patients had higher FFMI than the non-diabetic patients. This result was not expected. As shown above, diabetes is mainly associated with low muscle mass. Park *et al.* [22] described in older type 2 diabetic patients an excessive loss of appendicular lean mass by DXA but the study has only included an older sarcopenic population.

To our knowledge, only some studies have used the BIA to assess the muscle mass of diabetic patients. Shah *et al.* have performed BIA in 78 type 2 diabetic patients and an equal number of controls. They found lower values of skeletal muscle mass in diabetic patients compared to controls (23.4%±4.5 vs $30.7\%\pm6.6$, p<0.0001). They did not use the FFMI as we did. As their study was published before the GLIM criteria were, the authors did not use thresholds to define a low muscle mass, making the comparison with our results difficult. Using BIA, Sugimoto *et al.* [23] showed that higher HbA1c level (>6,5%) was associated with lower skeletal mass index. The mean HbA1c of our diabetic population was $6.4\pm1.9\%$, which may explain why we did not find any association between the FFMI and diabetes.

Our diabetic patients were more often over-weighed or obese than the non-diabetic patients. A German study conducted in 2019 in 175 healthy subjects showed that overweight and obesity were associated with more errors in BIA interpretation. Fat-free mass (FFM) and muscle mass were especially overestimated in obesity [39], so that we need specific equations to evaluate fat-free mass in obese patients. We did not use specific equations for obese patients to estimate FFM in our study. The BIA equations we used are not known as the manufacturer keep them secret. Thus, the FFM variable was automatically calculated. These equations may not be appropriate for obese and overweight population,

explaining a higher FFMI in the diabetic patients of our study. In addition, we could not completely exclude that the presence of edema could have made overestimating fat-free mass in our hospitalized patients.

4. Loss of muscle strength

The measurement of handgrip strength by dynamometer is another easy method to diagnose malnutrition that could be performed at bedside after a short training. In our study, handgrip strength had a very good negative predictive value to predict survival. Some studies suggested that handgrip strength could have a better performance than the measurement of muscle mass to assess outcome. For example, a meta-analysis conducted in 2012 and including seven articles showed an overall association between low muscle strength and functional decline (pooled OR=1.86, 95% CI: 1.32, 2.64; I²=91%), whereas low muscle mass was not [40]. Moreover, the Prospective Urban-Rural Epidemiology (PURE) study, a large longitudinal study conducted in 17 countries and enrolling 142 861 participants has shown that handgrip strength was inversely associated with all-cause mortality (hazard ratio per 5 kg reduction in grip strength 1.16, 95% CI 1.13–1.20; p<0.0001) [41]. In our study, despite a greater fat-free mass, diabetic patients had a lower handgrip strength. The same result was found by Park et al. in the Health ABC study [42]. They evaluated handgrip and knee extensor strength in 3075 well-functioning older adults of whom 80.2% were diabetics. In men, diabetics showed significantly lower muscle strength in both upper and lower extremities although muscle mass was significantly greater, assessing by DXA. No difference in muscle strength was found in women, despite their muscle mass was also higher. In a younger population, aged 30 to 79 years with a mean age of 50,7 years, Bo Kyung Koo [43] has also studied the muscle strength of diabetic patients. They included 13149 participants from Korea National Health and Nutrition Examination Survey of which 13.5% were diabetics. They showed that diabetes was significantly associated with low muscle strength even after adjustment (OR, 1.328; 95% CI, 1.133–1.558). After stratification according to obesity status, low muscle strength remains significantly associated with diabetes mellitus only in non-obese patients (OR, 1.513; 95% CI, 1.224-1.870; p<0.001 in non-obese and OR, 1.124; 95% CI, 0.879-1.437; p=0.351 in obese participants, respectively).

Several explanations are proposed in literature to explain this poor muscle function in diabetes. Neuropathic processes might be involved as Oh *et al.* [44] have found that handgrip strength was significantly lower in men with diabetic peripheral neuropathy compared with men without $(27.0\pm9.4 \text{ vs. } 29.7\pm8.4 \text{ kg}, p=0.036)$. This finding was consistent with Andersen *et al.*'s electrophysiological study [45] that showed that loss of muscle strength in diabetic patients is due to incomplete reinnervation following axonal loss. However, this finding does not explain our results as only a few diabetic patients had peripheral neuropathy. Another explanation might be the inflammation associated with diabetes mellitus. Poor glycemic control is associated with increased systemic inflammatory cytokines, such as tumor necrosis factor-alpha [46] and interleukin-6 [47]. High level of these cytokines are reported to be associated with lower muscle mass and lower muscle strength [48].

Decrease of food intake is a good indicator of malnutrition and is known to be a risk factor for mortality. A large cross-sectional study, the NutritionDay® survey, has audited the food intake of 16'455 patients treated in 748 wards from 256 hospitals in 25 countries. The authors showed that the incidence of death increased from less than 1% for those eating all their meals to nearly 9% for those eating nothing despite being allowed to eat (p < 0.001). The mortality increased with decreased of food intake and was dramatically high in older patients [49]. By improving the presentation meal of patients hospitalized, Navarro *et al.* [50] has shown that increased food intake reduces readmission rate to hospital. They included 206 newly hospitalized adults in Internal Medicine Departments in a prospective open non-randomized controlled study. They worked with the Paul Bocuse Institute to improve the presentation of meal, without changing the ingredients. The experimental group left on their plate less starch (0.19±0.30 vs. 0.52±0.41, p<0.05) and less from the main course than the control group (0.18±0.31 vs. 0.46±0.41, p<0.05). Readmission rate decreased significantly in the study group (p<0.02), from 31.5% to 13.5%.

In diabetic population, food intake is also associated with mortality. Omura *et al.* [51] evaluated data from 756 older patients with diabetes mellitus and the association between baseline food intake and mortality. Food intake was assessed using a Yoshimura's food frequency questionnaire based on food groups. They observed a U-shaped relationship between energy intake adjusted on body weight and mortality during a 6-year follow-up period: the patients who eat less are at increased risk for mortality. This study shows the importance of an optimal food intake in diabetic patients, particularly in the older patients already fragile and at risk of poor outcomes.

The assessment of food intake is a key part of nutritional assessment, corresponding to an etiological criterion of the GLIM and HAS criteria of malnutrition [4]. We chose to evaluate food intake with the SEFI®, since it is easy to use and offers a standardized measure of malnutrition risk based on food intake. It has shown in general practice primary care population an excellent negative predictive value (99%), a 76% sensitivity and 87% specificity for the diagnosis of malnutrition [52]. Thibault et al. [53] have shown that this analogue scale is also well correlated with energy intake (p=0.82, P<0.0001) in hospitalized population, with an excellent feasibility in 114 malnourished patients or at risk of malnutrition. Accuracy for assessing malnutrition was calculated over 98 malnourished patients or at risk of malnutrition. They showed good specificity and positive predictive value (81% and 86% respectively); whereas sensitivity and negative predictive value were lower (57% and 46% respectively). These results were confirmed by Guerdoux-Ninot et al. [26] in 1762 medical oncology hospitalized patients. They showed that patients with a SEFI® score <7 had 12-fold higher probability of being at nutritional risk (OR 12.3; 95% CI (8.7-17.4); p < .001) than those with a score \geq 7. Our study is the first to evaluate the accuracy of SEFI® to evaluate the risk of mortality in a subgroup of malnourished or at risk for malnutrition patients. We did not show that SEFI ® <7 was a good predictor of mortality risk, probably because our study includes a majority of severe malnourished patients. We should reevaluate whether another cut-off of SEFI® could predict the risk for mortality.

6. Diabetes, infections and mortality

In our study, abdominal infection and bacteremia were more often detected in diabetic than in non-diabetic patients. The association between diabetes and infection is well known. Old in vitro studies have shown that the increase of infection is related to neutrophil dysfunction: deficiency in the chemotaxis of polynuclear leukocyte [54], reduction in phagocytic property [55] and defective bactericidal capability [56]. The first study that have explored the risk of developing an infection in a diabetic population was a performed in Canada in 1999. It has retrospectively compared all the diabetic people in Ontario, Canada with matched people without diabetes (n=513,749 in each group). It has shown a significant higher rate of infection in people with diabetes (1.21 [99% CI 1.20 - 1.22]), p<0.0001). Rate was especially high for sepsis (2.45 [2.23–2.68], p<0.0001), post-operative infection (2.02 [1.80–2.27], p < 0.0001) and peritonitis (1.94 [1.58–2.37], p<0.0001). Risk of death attributable to infection was increased with a risk ratio of 1.92 ([1.79 - 2.05], p < 0.0001) [57]. In 2016, a large observational study based on the Royal College of General Practitioners Research and Surveillance Centre database in UK has investigated the impact of type 2 diabetes on presentation with infection, and the effect of glycemic control, including 34'278 people with type 2 diabetes and 613'052 people without [58]. They found that poor glycemic control (HbA1c>8.5%) increased adjusted odds ratio for all type of infection (1.35 | 1.25 - 1.45], p < 0,001 vs 1.11 [1.05 - 1.18] p < 0,001 for moderate glycemic control). However, even if the risk for intestinal infectious disease was higher in the diabetic population, there was no association with glycemic control. The latter is consistent with our results that our diabetic patients had a good glycemic control, with mean HbA1c of 6.4±1.9 %, with an increased risk for GI infection.

Although not statistically significant, the increased risk for infections reported in the diabetic patients of our study may partly explain the association between diabetes and mortality. Diabetes mellitus is a well-known factor of all-cause hospital mortality [59–62]. Wu *et al.* [62] conducted in 2007 an observational study including 1792 hospitalized diabetic patients, with the aim to identify the predictive factors of mortality. These factors were an age greater than 65 years, a duration of hypertension more than 5 years, 24 h proteinuria greater than 0.3 g, and an estimated creatinine clearance less than 60 mL/min. Age apart, we did not investigate any of these latter factors in our analyses. Truly, the presence of diabetes complications may explain the higher mortality risk of diabetic patients.

7. Practice analysis

Our data constitute an evaluation of the CHU Rennes NST practices. We have shown the importance of doing a systematic multimodal assessment of the nutritional status of hospitalized patients with the use of BIA, handgrip dynamometer and SEFI®, in addition to weight measurement at admission and during the hospitalization, in accordance with the GLIM and HAS recommendations. These tools are easy to use and the measurements are quick to perform. They should be part of the clinical examination of all hospitalized patients at their admission, in order to detect malnutrition as early as

possible. To achieve this goal, the education and the training of the health caregivers are highly warranted. Moreover, with the creation of the new 'DES Endocrinology-Diabetology-Nutrition (EDN)', the EDN residents have become the cornerstone of the management of malnutrition in diabetic patients. The screening of malnutrition in this population should be as important as the screening of diabetes complications in every patient assessment. Furthermore, the EDN resident is the best placed to manage the complications of nutritional support. Indeed, enteral nutrition and even more parenteral nutrition are associated with increased glycaemia, and the EDN resident is the one who knows how to manage the oral anti-diabetic drugs and insulin when artificial nutrition is introduced.

8. Study limitations

We suffer from a selection bias, as our study patients were mostly malnourished, with a large prevalence of severe malnutrition. It could explain why we could not show that diabetes was a risk factor for severe malnutrition. We could also speculate that the number of diabetic patients included was not enough to have sufficient power to found significant associations, especially with complications, mortality and 1-month hospital readmission. Particularly, the diabetic patients included in our study had few complications and half of them had a well-controlled diabetes.

Conclusion

To our knowledge, our study is the first to characterize the phenotype of malnourished diabetic patients based on the newly published HAS criteria. Twenty per cent of the patients followed by the NST are diabetic. Diabetes mellitus was not associated with a higher risk of severe malnutrition. Diabetic patients had poorer outcomes, especially mortality, unless it fell to reach the statistical level of significance in the multivariate analysis. The diagnosis and management of malnutrition in the clinical practice at hospital is essential to prevent complications, mortality and to reduce hospital length of stay. Diabetic patients are more susceptible to malnutrition, especially if they are older people. As they are more vulnerable, future studies should assess whether malnutrition should be evaluated with specific thresholds of fat-free mass or muscle strength in diabetic patients. The malnutrition in diabetic patients is a transversal topic that should bring together the endocrinologist and the nutritionist communities, as they are now in the newly created 'DES Endocrinology-Diabetology-Nutrition' diploma.

Glossary

- BIA = Bioimpedance analysis
- BFMI = Body Fat Mass Index
- BMI = Body Mass Index
- CHU = Centre Hospitalo-Universitaire
- CI = Confidence Interval
- DXA = Dual energy X-ray absorptiometry
- EDN = Endocrinology Diabetology Nutrition
- EN = Enteral Nutrition
- FFM = Fat-Free Mass
- FFMI = Fat-Free Mass Index
- GI = Gastro-intestinal
- GLIM = Global Leadership Initiative on Malnutrition
- HAS = Haute Autorité de Santé
- HbA1c = Glycated Hemoglobin
- MNA = Mini Nutritional Assessment
- NPV = Negative Predictive Value
- NST = Nutritional Support Team
- ONS = Oral Nutritional Supplements
- OR = Odds Ratio
- PN = Parenteral Nutrition
- PPV = Positive Predictive Value
- ROC = Receiver Operating Characteristic
- SEFI = Simple Evaluation of Food Intake
- SMD = Standardized Mean Difference

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U.F.R. DE MÉDECINE DE RENNES

BARRALLIER Mathilde - Impact of type 2 diabetes on the clinical outcome of malnourished hospitalized patients managed by the Nutrition Support Team at Rennes University Hospital

Thèse : Endocrinologie-Diabétologie-Nutrition ; Université de Rennes 1; 2021 Résumé :

Introduction : La dénutrition hospitalière est fréquente, car elle est associée à plus de complications et à une mortalité augmentée. Les patients diabétiques sont à plus haut risque de dénutrition. Pourtant, peu d'études ont étudié le phénotype de la dénutrition dans cette population.

Méthodes : Nous avons mené une étude observationnelle rétrospective incluant les patients suivis par l'Unité Transverse de Nutrition du CHU de Rennes.

Résultats : 231 patients ont été inclus, dont 20,3% de patients diabétiques et 83,5% de patients dénutris. Les patients diabétiques n'étaient pas plus sévèrement dénutris que le reste de la population (83,0 % vs 83,7%, p = 0,91) mais ils avaient un indice de masse maigre mesuré par bioimpédancemétrie augmenté (15.5±4.1 vs 17.9±3.4 kg/m², p < 0.0001) mais une force musculaire diminuée (64.3% vs 45.6%, p=0.03). En analyse multivariée le diabète était associé à une mortalité plus élevée (OR = 2.33 [0.96 ; 5.62], p=0,06).

Discussion : La dénutrition est fréquente chez les patients diabétiques. Le phénotype de leur dénutrition étant particulier, la définition de seuils spécifiques pourrait permettre une meilleure prise en charge.

Abstract :

Introduction: Malnutrition is a major health issue in hospitals because it is associated with more complications and increased mortality. Diabetic patients are at increased risk for malnutrition. However, few studies have investigated the phenotype of malnutrition in this population.

Methods: We conducted a retrospective observational study including patients followed by the Nutritional Support Team of CHU Rennes.

Results: 231 patients were included, of whom 20.3% were diabetic patients and 83.5% were undernourished patients. Diabetic patients were not more severely undernourished than the rest of the population (83.0 % vs 83.7%, p = 0,91) but had increased muscle mass (15.5±4.1 vs 17.9±3.4 kg/m², p < 0.0001) but decreased strength (64.3% vs 45.6%, p=0.03). In multivariate analysis, diabetes was associated with increased mortality (odds ratio = 2.33 [0.96 ; 5.62], P=0,06).

Discussion: Malnutrition in frequent in diabetic patients. The phenotype of malnutrition being particular, the definition of specific thresholds could allow a better management.

Rubrique de c	classement :	Endocrinologie-Diabétologie-Nutrition				
Mots-clés français :Dénutrition,diabète,compositioncorporelimpedancemétrie		corporelle,	bio-			
Mots-clés anglais		Malnutrition, diabetes, body composition, bioimpedance analysis				
	Président :	Pr Fabrice BON	NET			
JURY :		Pr Ronan THIB	AULT direct	teur de thèse		
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N°