Pharmacological Research 76 (2013) 28–33

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

"The enemy within". How to identify chronic diseases induced-protein metabolism impairment and its possible pharmacological treatment☆

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ARTICLE INFO

Article history:
Received 16 June 2013
Accepted 24 June 2013

Keywords:
Sarcopenia
Protein metabolism
Chronic diseases
Rehabilitation
Nutrition
Amino acid

ABSTRACT

Recent clinical and experimental data show that considerable impairment of protein metabolism occurs in patients with chronic diseases such as heart failure. However, too often the extent of impairment is under-estimated or ignored by most clinicians and no therapy is considered leading to progressive loss of body proteins, increase morbidity, hospital stay and mortality. This paper illustrates the possible biological markers to evaluate general protein metabolism, including quantification of related damage and possible improvement of the metabolism using specific therapeutical metabolic strategies recently studied in a clinical setting.

1. Protein metabolism impairment: the bodies fifth column

Every living being adapts its own metabolism to acute external and/or internal needs through acute changes of their metabolic fluxes. Indeed, the proteins of sarcomeres, mitochondria, membranes, cytosoles, nuclei and the blood are in a constant state of flux [1]. However, the concept of a 'dynamic state of body constituents including proteins' has received relatively little attention in cardiovascular research as Taegtmeyer et al. recently pointed out [1]. For example, under normal conditions, heart proteins turn over at an average rate that would replace themselves in the entire heart within 30 days.

Protein metabolic impairment may be due to the following: (1) reduced intake, digestion and (2) absorption of nutrients including those containing proteins which cause quantitative and qualitative alterations and/or (3) elevated body protein catabolism (hypercatabolism) due to increased circulating catabolic hormones and/or inflammatory cytokines and decreased anabolic stimuli [2,3]. The complex cross-talk between inflammation and skeletal muscle after acute damage and in chronic degenerative diseases has been recently reviewed [4]. Clinically, impaired-proteins metabolism may become evident by: (1) fewer muscular proteins leading to muscular wasting and sarcopenia and (2) reduced circulating serum and cell proteins [5].

Interestingly, muscular wasting and hypercatabolism are often found together in chronic diseases such as chronic heart failure (CHF) and are more pronounced in elderly patients (>65 years), who nowadays make up the majority of hospitalised patients. Both past and recent data show that malnutrition and muscular wasting are present in 45% ± 5 of elderly patients hospitalized from a variety of chronic diseases [6].

In addition, Anker *et al.* demonstrated that when muscular wasting is associated with cachexia the morbility, hospital stay and mortality increase independent of the primary disease and age [6,7]. This finding is not surprising. The importance of the metabolic properties of skeletal muscle has recently been described in detail by Wolfe, who illustrated the fundamental biochemical role of muscles in both healthy and diseased subjects [8].

Skeletal muscle is an important reservoir of proteins, so in order to maintain whole-body metabolism in response to stress, muscular proteins are digested. The resulting amino acids are released into the blood and are used by the liver to produce glucose, and/or in other organs to support cellular energy production and/or fundamental intermediates for global metabolism [9]. The clinical consequences of this metabolic condition are a significant loss of muscle protein and mass with significant impairment of whole-body metabolism and energy availability. Wolfe therefore concludes that it is imperative to maintain muscle protein content and consequently muscular mass and metabolism. This aspect should be included in future studies and considered as an

☆ Perspective articles contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

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http://dx.doi.org/10.1016/j.phrs.2013.06.006

Table 1
5th percentile of upper-arm muscle area (cm^2) by age for male and female of 18–75 years.

Age	5th percentile
18–24.9	34.2
25–29.9	36.6
30–34.9	37.9
35–39.9	38.5
40–44.9	38.4
45–49.9	37.7
50–54.9	36.0
55–59.9	36.5
60.0–64.9	34.5
65–69.9	31.4
70–74.9	29.7

inclusion criteria of clinical trials on CHF or used for sub-group analyses [8].

Data from recent research suggest that identifying and evaluating protein metabolic impairment early is a fundamental step for better care of patients with chronic diseases, avoiding additional independent damage and allowing traditional therapy to work properly. As a result, assessment of early changes in protein metabolism is an important biomarker to individualize high risk CHF patients who should be followed more closely and treated with specific therapy before metabolic abnormalities become irreversible [10].

2. What we can measure?

Here, we have suggested several clinical biomarkers to evaluate both general metabolic and nutritional status and any related damage to protein metabolism. Since the ideal marker does not exist, we believe that an understanding of the advantages and disadvantages of each evaluation (illustrated in Table 1 and discussed below), integrated with patients' clinical information, could allow doctors to achieve an overall idea of the patient, fundamental for better patient care.

It is important to stress that a simple evaluation of body mass index (BMI) is a good first step in assessing metabolic impairment, because 85% of ideal body weight is an index of protein-calorie malnutrition. However, BMI is only partially useful because it cannot distinguish lean muscular from fatty tissues. Furthermore, BMI is influenced by fluid retention, which is a major concern in protein malnutrition due to hormonal and cytokine impairment in CHF patients.

Therefore, global and protein metabolism of the body can be measured by the following biomarkers:

(1) anthropometric measurements, which allow us to perform a qualitative analysis of body composition, distinguishing muscular lean mass from fatty mass,
(2) quantification of the visceral proteins in the blood such as: albumin, transferrin, prealbumin, retinol binding protein which provide information on visceral protein synthesis, and
(3) evaluation of total lymphocyte blood count which is a functional index of global and protein impairment.

Furthermore, the dynamic metabolism of protein can be measured by nitrogen balance and serum or urinary excretion of 3-metil histidine.

However, we should also bear in mind that protein assessment in patients with chronic diseases such as CHF with excess extra-cellular fluid (ECF) can be challenging because ECF could mask weight loss and dilution of serum protein concentrations. In addition, fluid retention also influences body composition due to bioelectrical interference, e.g., from impedentiometry rendering this technique less reliable when identifying fatty and lean mass in these patients [11,12].

2.1. Anthropometric measurements

Body anthropometric measurements have been described in detail in the Anthropometric Indicator Measurements Guide by Food and Nutritional Technical Assistance Project Academy and elsewhere [13,14]. The high degree of body composition can be performed with Dual-energy X-Ray Absorptiometry (DEXA or DXA). DXA is most widely used to study bone density. First, two X-ray beams with different energy levels are aimed at the patient. When the bone tissue absorption is subtracted, the soft tissue absorption can be determined and lean mass measured. However, DXA scanners are expensive and also require specific medical skill to manage and interpret. In addition, although DXA use low energy X-ray, patients are still exposed to radiation.

Simpler, less expensive and non-invasive methods of estimating body composition as indirect evaluation of general protein metabolism include the development of *skinfold thickness* as an index of fatty mass (measured by a plicometer) and *arm muscle area* as an index of lean muscular mass (measured in centimetres). These can be routinely evaluated at the patient's bedside.

Skinfold thickness should be measured in specific body sites such as:

- *triceps* (TSF): measuring along the midline on the back of the triceps of the right arm pinching the skin so that the fold is running vertically. This measurement is the easiest and simplest to collect and is most commonly used,
- *pectoral*: using a line from the fold of the axillary to the nipple, determining the midpoint,
- *abdominal*: measuring about 1 in. lateral the right side from 0.5 in. below the umbilicus lifting a horizontal fold of skin,
- *suprailiac*: measuring the top of the iliac crest,
- *thigh*: using a midline of the front of the thigh and measuring midway between the inguinal crest.

Skinfold thickness is measured by a calliper by lifting the skin up from the muscle and waiting 4 s before reading the plicometer as the fat is compressible and measurements before or after 4 s may distort the results.

Arm muscle area (*AMA*) is relatively easy to measure and is also used for rapid screening of protein catabolism and muscle loss. It can be measured from the mid-points of the left upper arm, straightening the patient's arm and wrapping the tape around the arm at its midpoint, making sure that the tape is properly taut and then reading the measurement. AMA can be calculated from the mid-arm muscle circumference (MAMC) also using the TSF according to the following formula:

$$\text{MAMC (cm)} = \text{MAC (cm)} - 3.14 \times \frac{\text{TSF (mm)}}{10} - \left[3.14 \times \frac{\text{TSF (mm)}}{10}\right]$$

TSF and AMA are not influenced by excessive extra-cellular fluids and can be used in patients with fluid retention. However, adult and elderly anthropometric measurements have not been standardized in terms of reference data, so reference standards should be developed locally. Table 1 shows data corresponding to the 5th percentile of AMA found in subjects by age and gender [15].

When the impairment of global and protein metabolism and/or sarcopenia has been found with these simple anthropometric measurements, additional evaluations are needed to study and identify the evolution of the problem better.