Review

Clinical assessment for diet prescription

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Keywords

Nutritional Assessment • Micronutrients deficiency • Malnutrition • Dietary Intake Assessment • Physical Activity Assessment

Summary

Accurate nutritional assessment based on dietary intake, physical activity, genetic makeup, and metabolites is required to prevent from developing and/or to treat people suffering from malnutrition as well as other nutrition related health issues. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare setups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected. In this review we have explored different techniques used for nutritional and physical activity assessment. Dietary Intake (DI) assessment is a multidimensional and complex process. Traditionally, dietary intake is assessed through self-report techniques, but due to limitations like biases, random errors, misestimations, and nutrient databases-linked errors, questions arise about the adequacy of self-reporting dietary intake procedures. Despite the limitations in assessing dietary intake (DI) and physical activity (PA), new methods and improved technologies such as biomarkers analysis, blood tests, genetic assessments, metabolomic analysis, DEXA (Dual-energy X-ray absorptiometry), MRI (Magnetic resonance imaging), and CT (computed tomography) scanning procedures have made much progress in the improvement of these measures. Genes also plays a crucial role in dietary intake and physical activity. Similarly, metabolites are also involved in different nutritional pathways. This is why integrating knowledge about the genetic and metabolic markers along with the latest technologies for dietary intake (DI) and physical activity (PA) assessment holds the key for accurately assessing one's nutritional status and prevent malnutrition and its related complications.

Introduction

In the present advanced world, nutritional research mainly focuses on improving individual as well as population health through diet management. Health- and Nutrition-linked researcher have established that, along with their essential functions, both the nutrients and the non-nutrient food components interact with various metabolic pathways, thus influencing health and increasing or decreasing the risk of various diseases [1].

The precise assessment of the dietary intake (DI) as well as of physical activity (PA) is crucial for quality research in the areas of nutrition, public health, and exercise science [2]. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare setups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected. However, the differentiation between such procedures is quite subtle, especially because of the identification of significant prognostic clinical processes that are interlinked both with each other as well as to the nutritional status, like sarcopenia and frailty [3].

Several nutritional assessment and screening tools have been proposed, but none of them are truly comprehensive. However, among those assessment tools, the multidimensional ones seem to be more informative. Some of these tools are age-specific; like certain assessment tools that have been tailored specifically for older people. Moreover, in certain cases applying biochemical parameters (i.e. blood tests, genetic assessments and metabolomic analysis) might be considered significant and their extra costs should be compensated by the useful information they provide as nutrition marker for different perspectives, like nutritional status assessment, malnutrition grading, prognosis and refeeding effectiveness (Tab. I) [4].

Dietary Intake (DI) assessment in healthy adult population is a multidimensional and complex process that makes an accurate quantification somewhat challenging. Traditionally, DI is assessed via self-report techniques including diet records, FFQs (food frequency questionnaires), and recalls [5]. These self-assessment or self-reporting techniques have been known to underestimate the caloric intake by almost 11 to 35% (mostly in obese people) as compared to direct measuring techniques, such as doubly labeled water [6]. Reporting er-

https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2753

Tab. I. Biochemical values to detect malnutrition and monitor nutritional status [8].

Biochemical values	Nutrition Independent Factors	Half-Life	Appropriateness to Detect Malnutrition
Albumin	Increased dehydration, Decreased inflammation, Infections, Trauma, Heart failure, Edema, Liver dysfunction, Nephrotic syndrome	20 d	+/++ Not appropriate in case of anorexia and acute illness
Transferrin	Increased renal failure, Iron status, Acute hepatitis, Hypoxia	10 d	+
Prealbumin/Transthyretin (TTR)	Increased renal dysfunction, Dehydration, Corticosteroid therapy Decreased inflammation, Hyperthyreosis, Liver disease, Overhydration	2 d	Not appropriate to detect anorexia Subnormal values within one week when fasting
Retinol bindingprotein (RBP)	Increased kidney failure, Alcohol abuse, Decreased hyperthyreosis, Chronic liver diseases, Vitamin A deficiency, Selenium deficiency	12 h	Idem prealbumin
Insulin-like growth factor 1 (IGF-1)	Increased kidney failure, Decreased liver diseases, Severe catabolic status, Age	24 h	++ Rapid decrease in fasting periods
Urinary creatinine	Increased collection time > 24h, Infection, Trauma, Decreased and insufficient collection time, Acute kidney failure	-	1 mmol of creatinine is derived from 1.9 kg of skeletal muscle mass
Lymphocytes	Increased healing phase after infection, Hematologic diseases, Decreased sepsis, Immune suppressants, Steroids	-	+ Very unspecific

rors including biases (also called "systematic errors"), random errors, mis-estimations, and nutrient databases-linked errors are the source of some of the current criticisms, which leads to questioning the adequacy of self-reporting dietary intake procedures for scientific conclusions about the relationship between dietary intake and health [7]. Additionally, the Malnutrition Universal Screening Tool (MUST) (Tab. IIa, IIb) was developed to identify malnourished individuals within all care settings (like nursing homes, hospitals, home care, etc.). MUST was the basis of the NRS-2002; however, since it did not include the last food intake, the weight loss percentage calculations might be tedious and create an obstacle for the busy staff of healthcare wards [8]. The most recent studies have thus suggested that dietary intake should be assessed using novel and improved methods, suitable to apply in independently living individuals (like biomarkers, digital photography, or remote sensing devices), instead of solely relying on self-reporting methods [2].

Tab. IIa. The Malnutrition Universal Screening Tool (MUST).

BMI (kg/m^2)	Unintentional weight loss in the past 3–6 months	Acute illness with reduced food intake (estimated) for ≥ 5 days
≥ 20 0	≤ 5% 0	No = 0
18.5-20.0 1	5-10% 1	Yes = 2
≤ 18.5 2	≥ 10% 2	

Tab. IIb. Overall Risk for Malnutrition.

Total	Risk	Procedure	Implementation
0	Low	Routine clinical care	**Clinic:** weekly **Nursing home:** monthly **Outpatient:** yearly in at-risk patient groups, e.g., age > 75 years
1	Medium	Observe	**Clinic, nursing home, and outpatient:** Document dietary intake for 3 days. If adequate: little concern and repeat screening (hospital weekly, care home at least monthly, community at least every 2-3 months). If inadequate: clinical concern. Follow local policy, set goals, improve and increase overall nutritional intake, monitor and review care plan regularly.
≥ 2	High	Treat	**Clinic, nursing home, and outpatient:** Refer to dietitian, Nutritional Support Team, or implement local policy. Set goals, improve and increase overall nutritional intake. Monitor and review care plan (hospital weekly, care home monthly, community monthly).

Additionally, the availability of various diagnostic tools is another important issue or limiting factor to overcome in clinical practice. Particularly for muscle mass assessment, in spite of the precise result of DEXA (Dual-energy X-ray absorptiometry), MRI (Magnetic resonance imaging), and CT (computed tomography) scanning procedures, noninvasive, bed-side and low-cost techniques like BIA (bioelectric impedance analysis) are still considered as an ideal solution for the routine usage and extensively used. Besides, in the absence of these instrumental methods, anthropometric measurements like calf or mid upper-arm circumference could be adequate substitutes [9].

Moreover, many subjective as well as objective methods of dietary intake (DI) and physical activity (PA) assessment exist, each of which has its own biases and limitations (Fig. 1) [2]. Besides, even though nutritional assessment and screening should be easy and quick procedures, increasing evidences are suggesting that more time should be devoted to them [3].

Assessment of nutritional status by dietary intake

Dietary intake assessment has been performed using several objective as well as subjective tools, each having its own inherent limitations and strengths. Hence, the selection of the appropriate tool for the research mostly depends upon nutrients of interest, study design, target population, availability of time and economic resources. Some limitations hinder the capability of self-report dietary intake (DI) measures to reach scientific conclusions about the relationship between dietary intake (DI) and the health outcomes. However, the traditional DI assessment methods like diet records, FFQs and recalls remain the main choice because of their familiarity, cost efficiency and the lack of consensus upon other objective methods that are capable of producing the complex required outcomes [10].

Latest advancements in technology have resulted in the development of many automated tools for dietary assessment that can overcome some of the limitations of traditional subjective tools, in addition to strive for time and cost efficiency. Such advanced assessment methods include automated self-administered 24-hour dietary assessment tool (ASA24) and food records [11], photo-assisted dietary assessments (PADAs) [12], image-based dietary assessments (IBDAs), and graphic and automated food frequency questionnaires (FFQs) [2, 13].

Automated Self-Administered 24-hour (ASA24)

The National Cancer Institute (NCI) introduced an upgraded version of the USDA's (U.S. Department of Agriculture) Multiple-Pass 24-Hour Recall Method that enables automated self-administered 24-hour recalls (ASA24) by the respondent and could be used for several days to maintain food record. Automated self-administered 24-hour recalls (ASA24) overcome the limitations of traditional 24-hour recalls like reduced time, independence from trained interviewers, reduced respondent burden and reduced economic burden for researchers. In order to automate the ASA24 tool, several novel self-administered web-based food frequency questionnaires (FFQs) have been developed, like Nutrition Quest's NCIB lock questionnaire, Fred Hutchinson Cancer Research Center FFQs, and NCI's Diet History Questionnaire (DHQ) III. All of these are web-based

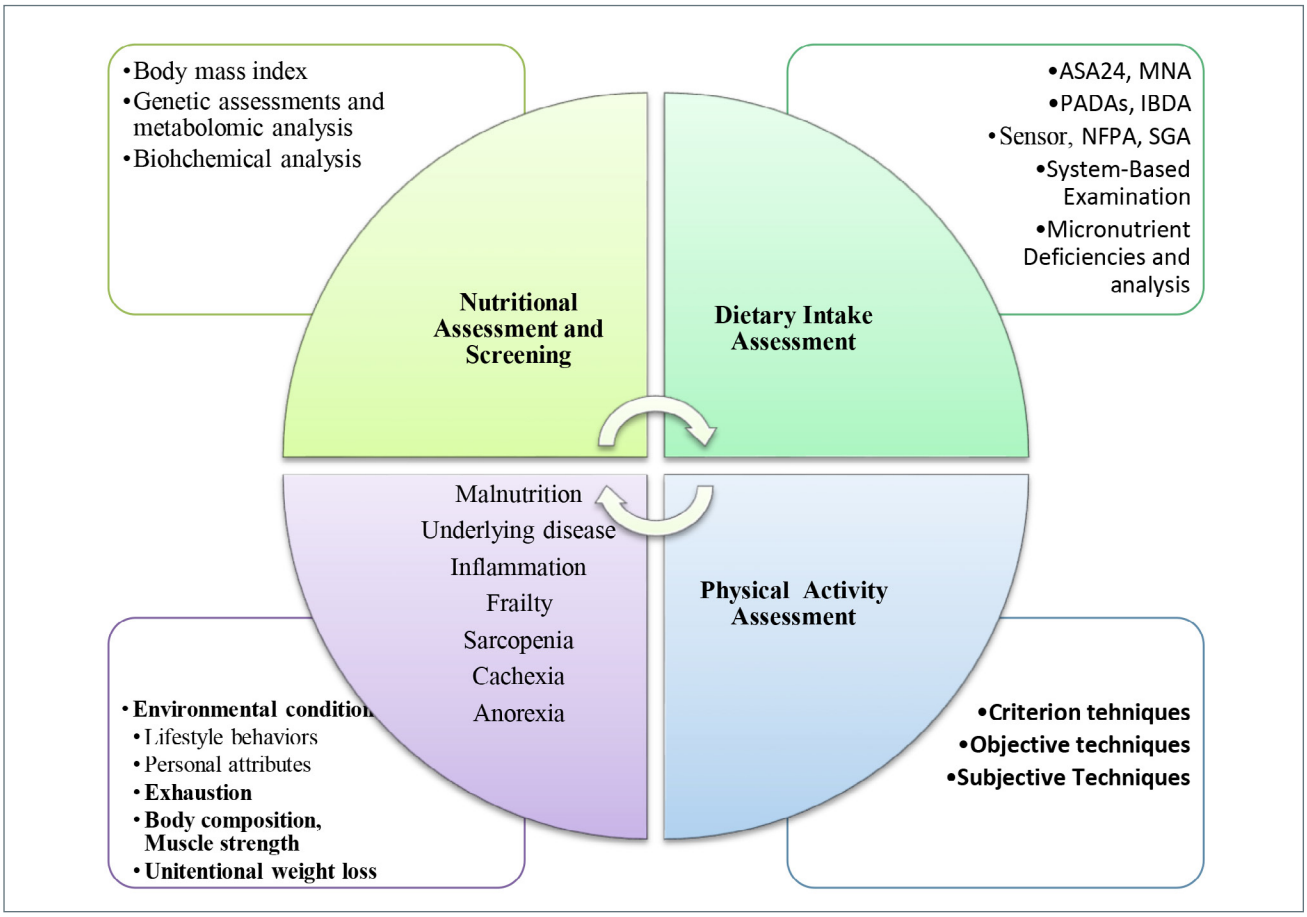

Fig. 1. Steps and Factors involved in Nutritional Assessment and Screening.

questionnaires and comprise over 100 questions concerning food items and their purchasing and preparation, with different layout designs and analytical techniques. Some of these, like NCI's Diet History Questionnaire (DHQ) III, are also freely available for researchers. Another novel alternative, VioScreen, provides a graphical FFQ option, hence addressing the limitations of the traditional FFQs [2, 14, 15].

Nutritional risk screening (NRS 2002)

Globally, one of the most commonly used nutritional risk screening and evaluating tools for hospitals is the NRS-2002 (Tab. III), developed by Kondrup et al. as a generic tool for the hospital setup to be used for detecting patients who could benefit from nutritional therapy [16]. Recently, NRS-2002 was presented in large multi-centric randomized controlled study involving medical inpatient population; the results of the study established a decrease of significant clinical outcomes like mortality in patients that were evaluated by NRS-2002 and found to be at malnutrition risk. NRS-2002 is a well-validated and simple tool, incorporating the preliminary screening via four questions. If the answer to any of these questions is positive, the patient will undergo a complete screening that includes alternate measures of their nutritional status, with static as well as dynamic parameters along with data about the severity of the disease [8].

Mini Nutritional Assessment (MNA)

For other care settings – such as outpatient, community, institutions, rehabilitation and subacute – their evaluation should be carried out using Mini Nutritional Assessment (MNA), on the bases of the amount of data collected. Even the short-version MNA has been validated and optimized as full-assessment procedures, that identifies three categories of nutritional status even in patients without possibility of BMI measurement (measuring circumference of calf as an alternative) (Tab. IV). Hence, this nutritional assessment tool is designed to be faster and easier to complete, minimizing the requirement of patient's participation as well as the quantity of unanswered questions, also enabling a wider distribution between healthcare professionals. Thus, all at-risk patients must undergo a complete nutritional assessment to evaluate the presence of any malnutrition [3, 17].

Photo-Assisted Dietary Assessments (PADAs)

Photo-Assisted Dietary Assessments (PADAs) involve images of the food selections and any remaining food after the meal for dietary intake estimation and might be an efficient and unobtrusive method of DI assessment among large groups of independent individuals. Mostly, they have been used to assess the DI of military recruits during their basic training, younger adults, disabled individuals, and overweight or obese females.

Tab. III. Nutritional Risk Screening (NRS-2002).

Sr. No	Preliminary Screening	Yes	No
1	Is the BMI of the patient < 20.5 kg/m^2	-	-
2	Did the patient lose weight in the past 3 months?	-	-
3	Was the patient's food intake reduced in the past week?	-	-
4	Is the patient critically ill?	-	-

If yes to one of those questions, proceed to screening. If no for all answers, the patient should be re-screened weekly.

Screening					
Impaired nutritional status		Score	Severity of the disease		Score
Normal nutritional status	Absent	0	Normal nutritional requirements	Absent	0
Weight loss > 5% in 3 months OR 50-75% of the normal food intake in the last week	Mild	1	Patient is mobile Increased protein requirement can be covered with oral nutrition Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*, chronic hemodialysis, diabetes, oncology	Mild	1
Weight loss > 5% in 2 months OR BMI 18.5-20.5 kg/m^2 AND reduced general condition OR 25-50% of the normal food intake in the last week	Moderate	2	Patient is bedridden due to illness Highly increased protein requirement, may be covered with ONS Major abdominal surgery* Stroke* Severe pneumonia Hematologic malignancy	Moderate	2
Weight loss > 5% in 1 month OR BMI < 18.5 kg/m^2 AND reduced general condition OR 0-25% of the normal food intake in the last week	Severe	3	Patient is critically ill (intensive care unit) Very strongly increased protein requirement can only be achieved with (par)enteral nutrition Head injury* Bone marrow transplantation* Intensive care patients (APACHE > 10)	Severe	3
-		Total A	-		Total B

Age: < 70 years: 0 pt; ≥ 70 years: 1 pt

Grand Total = (A) + (B) + Age
≥ 3 points: patient is at nutritional risk, a nutritional care plan should be set up.
< 3 points: repeat screening weekly.
NRS-2002 is based on an interpretation of available randomized clinical trials.
* indicates that a trial directly supports the categorization of patients with that diagnosis.

PADAs methods include both the traditional methods as well as advanced technologies of digital photography and remote food photography plus recalls, both of which validate direct energy measurement in different population and environment extremities. Their major limitations include lack of the fully automated nutrient analysis after capturing the photo as well as the nutrient database quality used for analysis [2, 18, 19].

Image-based dietary assessment (IBDA)

Image-based dietary assessment (IBDA) is a technique that also uses images of the food selections as well as any remaining food after the meal to estimate the patient's dietary intake (DI) but, unlike PADAs, IBDA captures the image passively (i.e. the images, automatically captured by the device, are the main information source the user provides for verification). IBDA's updated versions have combined the automated food identification, a software for portion size estimation, and user prompts for accurate DI assessment. Some examples of these assessment techniques include the Technology-Assisted Dietary Assessment system, the Nutricam Dietary Assessment Method, and the eButton [13, 20].

Sensors and informatics research tools

Early studies have observed the use of smart kitchen equipment, like tables, plates, and bowls that can measure and record the weight of the food (either with or without the plates) before as well as after the consumption of the meal. Similarly, wearable sensors provide an automated record of food consumption by hand-to-mouth gestures or chewing modality (like microphones that detect the crushing of food), electro-myographic sensors for the detection of muscle activation or acceleration, and strain sensors to

Tab. IV. The Mini Nutritional Assessment (MNA) Screening Short-Form.

A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, or chewing or swallowing difficulties?	0 = severe loss of appetite 1 = moderate loss of appetite 2 = no loss of appetite
B	Weight loss during the last 3 months	0 = weight loss over 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
C	Mobility	0 = bedridden or chairbound 1 = able to get out of bed/chair but does not go out 2 = goes out
D	Has the patient suffered psychological stress or acute disease in the past 3 months?	0 = yes 2 = no
E	Neuropsychological problems	0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems
F1	Body mass index (BMI)	0 = BMI under 19 1 = BMI 19 to under 21 2 = BMI 21 to under 23 3 = BMI 23 or higher
If BMI is not available, replace question F1 with F2. Do not answer F2 if F1 is already completed.		
F2	Calf circumference (CC) in cm	0 = CC less than 31 3 = CC 31 or greater

12-14 points: normal nutritional status. 8-11 points: at risk of malnutrition. 0-7 points: malnourished

detect the chewing motion or the frequency of swallowing [21, 22]. Chewing monitors are considered as reliable ingestion indicators for people that live in the community. Interestingly, chew counts present a significant correlation with ingested food mass. Still, these chewing monitors might also lead to false detections, for example due to gum-chewing movements, or they might be unable to detect liquids consumption, even though the intake of some liquids also cause jaw motions that are similar to chewing movements (like sucking through a straw) and therefore they might possibly be detected. On the other hand, swallowing is considered a reliable DI indicator, as all food needs swallowing to be a part of nutrition. Moreover, the intake of solid as well as liquid food could be detected as an increased swallowing frequency over spontaneous non-nutritive swallowing. Swallowing sensors are made up of microphones, motion and electrical sensors. [23]
Other informatics- and sensor-based assessment tools have been developed to determine the food type as well as its nutritional composition, such as food classification based on acoustic sensors, miniaturized portable (near infrared) spectrometers that can scan food items and determine their matrix characteristics, miniaturized tooth mounted sensor that can detect nutrients as well as wirelessly communicate to the user's mobile. Research and developmental studies are still going on these technologies and devices, several of these require comprehensive nutrient databases to support their mechanism and technology to assess accurately the portion size [24].

Nutrition-focused physical assessment (NFPA)

The application and utility of the nutrition-focused physical assessment (NFPA) could cover various settings for supporting the best practice in patient care. Moreover, NFPA is a part of the nutrition care process and model (NCPM), which is a framework of the nutritional care planning in four distinct and consecutive steps, including nutrition assessment, diagnosis, intervention, as well as monitoring and evaluation. Nutrition-focused physical assessment (NFPA) is considered as an essential part of nutritional assessment, as it could be used to identify the physical outcomes linked to micronutrient deficiencies. Historically, interest in using physical assessment skills within clinical settings is higher when an increased morbidity as well as mortality rate is reported in the hospitalized patients of surgical and medical intensive care units (ICUs), linked with poor nutritional status either prior to or during hospitalization [25].

Subjective Global Assessment (SGA)

The awareness of the harmful effects of "malnutrition" led to the requirement of assessment and screening tools in order to identify patients at risk or suffering from malnutrition. Thus, this medical challenge brought to the development of the bedside nutrition assessment tool, the Subjective Global Assessment (SGA), which was among the first assessment tools that included a patient-generated subjective scoring system, calculating the nutrition status on the basis of physical examination as well as patient history. Unlike other traditional assessment techniques that are solely based on anthropometric and biochemical markers, SGA outlines a rating scale that is based upon the variations in dietary intake (DI), in gastrointestinal signs linked with nutrition, weight, functional capacity, subcutaneous fat loss assessment, disease severity, edema, and muscle wasting. SGA has

been endorsed in several diseases due to its sensitivity and specificity in detecting nutrient deficiencies as well as malnutrition risk [25, 26].

System-Based examination

Surrogate biochemical markers, formerly used for nutrition status assessment, are found to be unreliable nutrition markers; however, they indicate disease severity, inflammation, morbidity as well as mortality risks (this is the case of serum albumin, prealbumin, and transferrin, for example). Besides, according to the latest etiology-based definition of malnutrition, physical parameters depicting changes in body composition – like subcutaneous fat loss, fluid accumulation, and muscle mass wasting – are included in the six malnutrition characteristics. Clinicians are therefore required to do a brief physical examination of their patients to identify body regions that are linked to macronutrient deficiencies; the findings should be rated as normal, mild to moderate depletion, or severe depletion. These physical indicators could be integrated into the nutrition-focused physical assessment (NFPA) by performing the full head-to-toe assessment by the clinicians, along with the thorough evaluation and examination of all body systems for those physical findings associated with nutrition-linked problems. Moreover, micronutrient deficiencies could have a multifactorial etiology, including inadequate intake, enhanced nutrient requirement, malabsorption, disease processes, natural disasters (e.g. famine), or drug interaction/shortage [25, 27, 28].

According to the Academy of Nutrition and Dietetics, nutrition assessment requires critical observational and analytical skills to identify physical indications through system-based examination. The main constituents of system-based examination and evaluation of the whole body involve the general inspection of vitals, nails, skin, eyes, nose, head, hair, neck, chest, mouth, musculoskeletal, and abdomen. Different inspection techniques are used to carry out the basic examination, involving both critical eye – to observe the shape, color, texture, size of the individual – as well as palpation – that requires touching with the pads and fingertips for the evaluation and assessment of texture, tenderness, size, temperature and mobility. Consequently, data obtained from all these examinations along with other parameters could be used for nutrition assessment as well as for critical interpretation and identification of nutrition-related problems [25].

Micronutrient Deficiencies and analysis

Often micronutrients deficiencies are stated as a single nutrient or multiple nutrients deficiency, on the bases of the region, phase of life cycle, or disease state. Micronutrient deficiencies universally affect over 2 million people worldwide; the predominant single-nutrient deficiencies include iodine, iron, and vitamin A. Vitamins are the essential organic micronutrient and only a small amount is required in the diet for them to play their role in many specific chemical reactions, such as growth, metabolism, and the preservation of cellular integrity [29].

Moreover, micronutrient deficiencies could also play a significant role in the development and progression of certain acute and chronic disorders, and they also could be linked to harmful changes in overall health [30]. Today the percentage of elderly individuals is much higher than in the past, thanks to the advancement in medical technology (like organ transplantation, noninvasive surgeries, obesity treatments, cancer treatment options, nutrition support modalities, etc.) and to the wider possibilities to have access to it [31]. Howeverm in spite of all these medical advances, micronutrient deficiencies are still predominant, even in the absence of malnutrition and insufficient caloric intake. Biochemical lab tests could be used to assess micronutrient status through the evaluation of metabolites or nutrient levels in urine, blood, or body tissues. However, biochemical lab tests only provides a quantitative and qualitative measurement of the micronutrient in a specific tissue or in some fluid sample like blood, urine, or plasma, but these results might fail to reveal the overall storage of that micronutrient in the body in terms of deficiency or excess [25].

Changes in skin color are mostly related to deficiencies of iron or B-complex vitamins or both, as these micronutrients are involved in several hematologic processes. Vitamin A deficiency (VAD) causes impairment of cell differentiation and maturation, leading to changes in the mucosal membranes and skin. Furthermore, protein and/or iron deficiencies could result in pallor, spoon-shape, clubbing, transverse banding, or ridging of nails. Whereas vitamin C deficiency leads to coiled and corkscrew hair, vitamin A deficiency affects the vision and can cause night blindness. The depletion of iodine, protein, and energy causes thyroid enlargement as well as fat and muscle wasting, with noticeably bony chest [25].

Nutrition-Focused Physical Assessment (NFPA) techniques analyze the obvious physical signs to assess macro- or micronutrients deficiencies during a head-to-toe physical examination and assessment. Thus, identifying the physical and clinical changes in different regions of the body caused by the unavailability of nutrient could be a cost-effective alternative approach to recognize micronutrient deficiencies (Tab. V) [25].

Nutritional assessment in older people

In older people, another significant aspect to be considered is the functional status impairment, evaluated by analyzing muscle strength and physical performance. Various factors are involved in functional status evaluation via screening procedures in older people; specifically, the relationship between muscle atrophy and decreased physical functioning acts as an independent diagnostic factor. Certainly, impaired functioning mostly results from muscle loss that is linked to disease-related malnutrition or immobility [32].

To maximize general health with aging, older individuals should undergo a complete geriatric assessment, including multidisciplinary diagnostics as well as treatment processes that identify medical, functional, and psychosocial capabilities. Similarly, nutrition status is mostly assessed due to its associations with functional status and disabilities. Therefore, the evaluation of

Tab. V. Clinical signs and symptoms of micronutrient deficiencies [8].

Affected organs	Symptoms	Micronutrient deficiencies
Skin	Petechiae Purpura Pigmentation Edema Pallor Decubitus Seborrheic dermatitis Unhealed wounds	Vitamins A and C Vitamins C and K Niacin Protein, vitamin B1 Folic acid, iron, biotin, vitamins B12 and B6 Protein, energy Vitamin B6, biotin, zinc, essential fatty acids Vitamin C, protein, zinc
Nails	Pallor or white coloring, Clubbing, Spoon-shape, Transverse ridging/banding, Excessive dryness, Darkness in nails, Curved ends	Iron, protein, vitamin B12
Head/Hair	Dull/lackluster, Banding/sparse, Alopecia, Hair depigmentation, Scaly/flaky scalp	Protein and energy, biotin, copper, essential fatty acids
Eyes	Pallor conjunctiva Night vision impairment Photophobia	Vitamin B12, folic acid, iron Vitamin A Zinc
Oral cavity	Glossitis Gingivitis Fissures, stomatitis Cheilosis Pale tongue Atrophied papillae	Vitamins B2, B6, B12, niacin, iron, folic acid Vitamin C Vitamin B2, iron, protein Niacin, vitamins B2 and B6, protein Iron, vitamin B12 Vitamin B2, niacin, iron
Nervous system	Mental confusion Depression, lethargy Weakness, leg paralysis Peripheral neuropathy Ataxia Hyporeflexia Muscle cramps Fatigue	Vitamins B1, B2 and B12, water Biotin, folic acid, vitamin C Vitamins B1, B6 and B12, pantothenic acid Vitamins B2, B6 and B12 Vitamin B12 Vitamin B1 Vitamin B6, calcium, magnesium Energy, biotin, magnesium, iron

body composition in screening phase, particularly muscle mass and its functioning, appears to be mandatory. While considering the problems related to muscle mass and its functioning, systematic estimation of inflammation, vitamin D status, and protein intake should be included in nutritional assessment [33].

Older people are often unable to cooperate with the assessment, thus sometimes limiting the extent of collected information. Malnutrition in older people is not always related to a disease condition, but it could also be caused by psychological or socioeconomic problems. Besides, older people also usually have the so-called "inflammaging" (also spelled "inflamm-aging"), a chronic condition with low-grade inflammation mostly prevalent in the elderly and frequently overlapping with disease-linked inflammation. The key element in this situation is therefore the presence of an already established disease, even though older people are likely to have co-occurrence of many aging-related diseases [34, 35].

Moreover, age-related factors cause muscle mass loss and conditions like sarcopenia, that recently has been recognized by the International Classification of Disease-10 (ICD-10) as an independent condition, which is clinically significant and identified via systemic screening [36]. Additionally, vitamin D deficiency is quite prevalent in older people. Vitamin D levels decrease with aging because of multiple factors, such as sun exposure, decreased synthetic activity of the skin, reduced gastrointestinal absorption, and reduced dietary intake. It is known that vitamin D also has anti-inflammatory characteristic and an increasing amount of literature supports the involvement of vitamin deficiencies in the reduced synthesis of muscle protein and muscle strength. In order to age healthily, it is essential to begin implementing effective strategies early on, so that any additional functional decline or disability could be prevented, especially in healthy older people [3, 37].

Assessment of nutritional status by physical activity

Physical activity (PA) can be defined as the bodily movements that are produced by the skeletal muscles and results in caloric expenditure. According to this comprehensive concept, the amount of energy expenditure (EE) is directly proportional to the size of the muscle mass involved. In the last few decades, technology usage for the personalized dietary intake (DI) assessment along with PA has been expanding rapidly. Typically, both self-report techniques and mechanical devices are used for PA assessment. Self-report measures for PA assessment include usage of questionnaires and completion of comprehensive diaries and logs. On the other hand, device-based techniques include motion sensors like accelerometers, heart rate monitors, pedometers, and other multisensory devices. Although these novel technologies have exhibited some advantages in the methodology of dietary intake and physical activity assessment, there are still many challenges and limitations [2, 38].

PA-related energy expenditure of an individual is affected by their body weight as well as their movement efficiency. Evidently, activity energy expenditure (AEE) involves a broad range of activities, including physical activity during leisure time, occupation, sports, household activities, transportation, home and personal care. In 1992, the American Heart Association published a report identifying physical inactivity as the fourth most significant and treatable risk factor of coronary heart disease (CHD) [39, 40].

Therefore, an accurate quantification of PA becomes essential in determining how much PA is of importance for a specific health outcome, in monitoring temporal events of PA, in evaluating the effectiveness of intervention programs, and in studying dose-response relationships. There are three main types of physical activity assessment methods/techniques, namely criterion, objective, and subjective [39].

Criterion techniques

Calorimetry

Physical activity is defined as the body movement that results in the expenditure of energy. The so-called "direct calorimetry", which measures energy expenditure (EE) by quantifying the heat production or heat loss, is considered as the gold standard of the physical activity measurement and other methods should be validated against it. However, its feasibility is not likely because of practical reasons. Hence, the mostly used criterion for assessment validation is by indirect calorimetric method, which involves the quantification of energy expenditure or heat production by calculating oxygen consumption or carbon dioxide production [39].

Direct behavioral observation

The initial methods for physical activity assessment include direct behavioral observation of motor activities by some skilled observers. Although now there are many assessment techniques to evaluate different physical activity (PA) settings, like sport classes, physical education, or independent living conditions, the main goal is to classify PA behaviors into separate categories that can be analyzed and quantified using different codes. However, the strength of this technique mostly relies on its access to contextual information.

Another important factor that influences physical activity is environmental conditions. This relationship is very significant for cognitive behavior research, as it could suggest change in sedentary behavior. The direct behavioral observation method is mostly used to assess children's physical activity patterns, while other assessment techniques like questionnaires or pedometers are not useful for them. Unfortunately, this method is a very time-consuming and tiresome method and therefore it is not suitable for larger studies [39, 41].

Doubly labelled water method (DLW)

The doubly labelled water method (DLW) is an isotope-based technique for the assessment of daily energy expenditure and average daily metabolic rate of an organism over a period of time and could be used for both field and lab studies. DLW measures metabolic processes that are directly linked to physical activity. The DLW principle involves the ingestion of two stable isotopes, i.e. 2H and 18O, in the form of water (2H2 18O) in standard amount. These isotopes are then evenly distributed in the body water, as observed from urine samples. Elimination of Deuterium (2H) from the body takes place in the form of water (2H2O), whereas 18O is removed from the body in the form of water (H2 18O) as well as carbon dioxide (C18O2). The elimination rates difference (over 5 to 14 days) between isotopes presents the quantity of CO2 produced, which leads to the assessment of energy expenditure (EE) [42]. In adults, the accuracy of this method is almost 3-10% of the calorimeter values and the variation of DLW within a subject is 8%; moreover, DLW is also applicable in children and provides precise measurements for free living conditions because it is does not influence PA patterns [43]. Still, DLW also has some limitations. The production as well as the analysis of isotopes is quite expensive, which is why this method is not suitable for larger studies; also, it could only calculate the TEE, therefore not distinguishing between physical activity energy expenditure (AEE), diet-induced energy expenditure (DEE), and basal metabolic rate (BMR) [39, 44].

Objective techniques

Pedometers

Motion sensors can register body motion. Pedometers are small electromechanical devices that have a spring mechanism to register the vertical movements and are generally worn on the waist. They are used for counting steps during a certain time period, mostly from morning to night. Then, these steps are converted into distance by entering the individual's average stride length. As a result, pedometers can only register physical activities related to running or walking, but it cannot monitor correctly movements of the upper body, cycling, carrying a load, swimming, or even movements on land or soft surfaces. Yet, as walking and running is a major part of our physical activity pattern, pedometer use remains highly valuable for estimating total daily movements. Hence, pedometers are considered as very helpful instruments for various health campaigns, such as "10,000 steps a day". In his study, Crouter et al. assessed the validity of 10 different pedometers and found out that the accuracy of pedometers is excellent for step counts, whereas they are less accurate for the assessment of distance and the accuracy of kilocalories assessment is even less [39, 45].

Accelerometers

An accelerometer is a sophisticated monitor that records the person's movements on several different planes. Instead of through a mechanical lever, as in pedometers, accelerometers function with piezoelectric transducers, along with microprocessors for the quantification of the magnitude as well as the direction of acceleration, which

is also considered as the dimensionless "counts". Tri-axial accelerometers are considered the best available accelerometer to date because, theoretically, they have the ability to record all movements; however, like pedometers, they still have some limitations in recognizing complex movements, such as upper body movements, cycling, graded terrain, etc. Also, studies have showed that there is a linear relationship between accelerometer counts and energy expenditure (EE). Subsequently, the EE of physical activities could be estimated by using linear regression equations along with body weight, height, gender, and age as co-variables. However, most studies have revealed that accelerometers provide a sufficiently accurate estimation of the overall PA, but its accuracy level for EE is relatively low, specifically for the point estimation of specific activities. Still, accelerometry is one of the most popular techniques used in PA research [46, 47].

Heart Rate monitoring (HR)

Another objective PA assessment method is the heart rate monitoring (HR). The heart rate indicates the intensity of the relative stress applied to the cardio-respiratory system by the movement, therefore indirectly measuring physical activity. This method basically relies upon the linear relationship of heart rate with oxygen consumption during moderate to intense PA range. While in resting state or during low-intensity physical activities, this heart rate/oxygen consumption relationship might not be linear and it is also affected by many other factors in addition to energy demands, like smoking, stress, caffeine, and body position. After establishing this relationship, the heart rate calculation could lead to the estimation of oxygen consumption, which in turn helps estimating energy expenditure in free living conditions. The heart rate records are usually maintained minute-by-minute and can be stored for many hours or even for days, hence providing information about the frequency, duration, and intensity of certain activity in addition to total energy expenditure (TEE). For the estimation of energy expenditure (EE) from the heart rate values, the FLEX HR methodology is a comprehensively examined approach. The HR data can show a great variability because of many confounding factors, thus making the EE estimation quite unreliable at individual level; still, this method shows significant epidemiological validity [39, 48, 49].
The next generation assessment PA in free-living conditions combines both HR monitoring and movement sensor, which might improve the precision an accuracy of activity energy expenditure (AEE) assessment [50].

Subjective techniques

Questionnaires/Surveys

Traditionally, physical activity questionnaires and surveys are an inexpensive tool of PA assessment that can be used efficiently for larger populations. However, this technique mostly depends on subjective analysis of the questions as well as observation related to the PA behavior of the individual. When dealing with very young or elderly people, extra care and attention should be taken, because their memory could be compromised [51]. Over- or under-estimation of the physical activity could be influenced by various factors like age, social desirability, questionnaire complexity, seasonal variation, as well as the span of the surveyed period [52]. Surveying techniques can be divided into four categories: interviewer-assisted questionnaires, self-report questionnaires, diaries, and proxy-report questionnaires. All of these questionnaires must undergo validation against the criterion methods (direct observation, DLW, or indirect calorimetry) or against objective techniques (HR, pedometers, or accelerometers). During their research, Philippaerts et al. evaluated the reliability as well as the validity of the three most frequently used PA questionnaires against doubly labelled water method (DLW) [53] and established that the Baecke Questionnaire [54], the Tecumseh Community Health Study Questionnaire [55], and the Five City Project Questionnaire [56] provided the most valid as well as reliable physical activity data. Whereas, Racette and colleagues [57] made the comparison of seven-day physical activity recall questionnaire for obese women against DLW, as well as two other physical activity questionnaires, like PA scale for elderly and Zutphen physical activity questionnaire, and their results validated that method against DLW in elderly people. Also, the results of these validation studies have shown that in general questionnaires classify the population into various distinctive categories of physical activity behavior such as low, moderate or highly active categories, but they are still not suitable for EE assessment at individual level [39, 58].
The latest developments in information technology (IT) – like computer networking, internet, and multimedia software – leads to the development of electronic surveys that are useful for PA research. Information technology facilitates the researcher in simultaneously administering the questionnaires to great number of people. In addition, in electronic surveys the subjects directly enter their answers or response on the computer, eliminating all the coding errors that could occur in interviews or traditional paper-pencil surveys. Moreover, in electronic surveys the subjects could not omit any question. Additionally, depending upon the subject's answers, the computer program could skip the unnecessary questions, which results in brief administration time. Lastly, certain studies have also indicated that people might be relatively more honest about any objectionable behavior to a computer rather than a researcher or paper-pencil questionnaires [39, 59].

Assessment of nutritional status by metabolomics

To overcome the limitations of self-reporting dietary assessment methods, nutritional epidemiologists have started to examine the biomarkers as measures of the nutritional status and dietary intake. Dietary biomarkers

were proven to be a more accurate and objective measure for DI in comparison with traditional questionnaires because they also consider the nutrient bioavailability as well as its metabolism [1].

The human genome initiative has introduced new visions for biological research as well as its translation into human health [1], and metabolomics is one of the most significant tools for its implementation [60]. Metabolomics uses different approaches than analytical chemistry and provides a comprehensive picture of all the metabolites that are present in the bio-fluids at a certain time [61]. The analysis of metabolites in blood – like glucose, cholesterol, and triglycerides – is already employed to diagnose monitor diabetes risk and heart diseases. Metabolomics provides the potential to magnify the intrinsic capability of urine and plasma metabolites to evaluate the human health status (Tab. VI) [60]. Researchers strongly believe that metabolites are highly sensitive to dietary exposure because diet is not only a significant source of the variation in metabolites, but it also induces metabolic responses. The two major approaches applied in metabolomics are MS (mass spectroscopy) and NMR (nuclear magnetic resonance) spectroscopy. The use of metabolomics in characterizing habitual dietary exposure as well as in identifying nutritypes have proven it to be a very exciting and emerging field that has many potential applications in the field of nutrition epidemiology [61].

The mechanisms that drive these metabolic and nutritional pathways are intricate and multi-factorial. The latest advancements of the large-scale metabolite profiling for larger epidemiological studies not only provide insights of molecular mechanisms causing age-linked diseases, but they also help in the assessment of metabolites that could predict the risk factors for cardio-metabolic disorders [61]. Metabolite profiling might identify and estimate such metabolites, like acylcarnitines, sphingolipids, and glycerophospholipids, that could not be estimated by the HDI (Healthy Diet Indicator) score. Moreover, these metabolites are known to be associated with greater risks of insulin resistance, fatty acid oxidation, cardiovascular diseases (CVD), and type 2 diabetes (T2D) [31, 32]. Several metabolites, like phosphatidylcholine and acylcarnitines, are associated with gut microbial-dependent pathways that are involved in the hepatic production of TMAO (trimethylamine-N-oxide) from choline; TMAO is subsequently converted into trimethylamine (TMA) within the microbiota, which might increase atherosclerosis risk [37] as well as glucose metabolism [36, 38]. TMAO plays a role in cardiovascular disease, as it promotes accumulation of macrophage foam cells that lead to reverse cholesterol transport inhibition and affect bile as well as sterol metabolism, which subsequently enhances the hyperactivity of platelets along with the initiation of atherosclerotic plaque formation [39, 40] (M2).

Several studies have investigated the association of overall diet with metabolites and mostly these investigations have evaluated the metabolites through mass spectrometry. For instance, in a large prospective cohort study like The European Prospective Investigation into Cancer and Nutrition (EPIC-Potsdam), which included 2,380 adults, the dietary intake patterns were analyzed by the methods of reduced rank regression, and the results showed maximum metabolites variations as well as the weak association of habitual diet with serum metabolites [62]. Similarly, in the ARIC (Atherosclerosis Risk in Communities) study, 1,977 participants samples were assessed for 336 metabolites; the results have revealed an association between a high-sugar (both in food and beverages) dietary pattern and seven long-chain unsaturated fatty acids, two sex steroids, five 2-hydroxybutyrate-linked metabolites, five γ-glutamyl dipeptides, as well as 4 metabolites involved in other pathways [63]. Likewise, the Women's Health Initiative study exhibited the association of Prudent dietary pattern with 85 metabolites (most of them are lipids). Another study examined 502 participants from a Lung, Prostate, Ovarian and Colorectal Cancer Screening Trial and established the correlations of 412 metabolites with food groups as well as the Healthy Eating Index score [64]. The researchers established the association of 39 metabolites with 13 different dietary groups, thus confirming the usefulness of metabolomics in identifying biomarkers and thus endorsing the nutritional intake effects on human metabolic system [61].

Identifying the strong associations of dietary habits with metabolites might thus provide a better prospect to understand the pathways through which nutritional intake mediates the protection against various chronic diseases, like CVDs [61].

Tab. VI. Metabolites, their Function and associated Disease Condition.

Disease Condition	Metabolites	Sample type	Function	Analyzing Technique
Dysbiosis	Skatole	Urine Plasma	Pulmonary toxin that induces the expression of AhR regulated genes	HPLC
	Indican	Urine	Stimulated vascular smooth muscle cell proliferation in vitro	Liquid chromatography/ electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS)
	Propionate	Serum	Lower lipogenesis, serum cholesterol levels, and carcinogenesis	HPLC

Tab. VI. *Continues.*

Disease Condition	Metabolites	Sample type	Function	Analyzing Technique
Oxydative stress	Homocysteine	Blood	Lipid peroxidation, free radical formation, inflammation, and endothelial dysfunction	HPLC
	Vitamin D	Blood	Promotes calcium absorption in the gut	Liquid chromatography (LC), Liquid chromatography-mass spectrometry (LC-MS), Tandem mass spectrometry, Radioimmunoassays (RIA), Chemiluminescence immunoassays (CLIA)
	Thioglycolic acid	Urine	Present as cysteine-thioglycolic acid	HPLC, Gas chromatography
Amino acid profile	Histidine	Serum Urine		NMR spectroscopy
	Isoleucine	Plasma Urine	Associated with both lower AHEI score and increased incident CVDs risk	Mass spectrometry
	Leucine	Plasma Urine	Protein synthesis stimulation and reduction of muscle protein breakdown after a physical trauma	Mass spectrometry
	Lysine	Serum Plasma Urine	Calcium absorption and collagen formation	Mass spectrometry
	Methyonine	Plasma	Angiogenesis, overconsumption is related to cancer growth	High performance liquid chromatography
	Cysteine	Plasma Urine	Antioxidant	Mass spectrometry
	Phenylalanine	Blood Plasma Urine	Gluconeogenesis, lower chronic inflammation	HPL, Tandem mass spectrometry
	Tyrosine	Urine Plasma	Production of neurotransmitters	Mass spectrometry
	Threonine	Serum Plasma	Keeping connective tissues and muscles throughout the body strong and elastic	Peptide microarray technology
	Tryptophan	Urine Serum	Part of melatonin and serotonin production	HPLC, Liquid chromatography- tandem mass spectrometry
	Valine	Plasma	Muscle growth and tissue repair	NMR spectroscopy, Mass spectrometry
	Alanine	Plasma Urine	Source of energy for muscles and central nervous system	NMR spectroscopy Mass spectrometry,
	Aspartic acid	Urine Plasma	Fatigue, athletic performance, and muscle strength	Mass spectrometry
	Glutamic acid	Urine Plasma	Sugars and fats metabolism, neurotransmitter	Mass spectrometry
	Glycine	Urine Plasma	Acts as neurotransmitter, proteins production	NMR spectroscopy
	Asparagine	Urine Plasma	Production of body's proteins, enzymes and muscle tissue	Mass spectrometry
	Proline	Urine Plasma	Role in protein synthesis, metabolism, nutrition, wound healing, antioxidative reactions, and immune responses	NMR spectroscopy
	Glutamine	Urine Plasma	Substrate for protein synthesis, anabolic precursor for muscle growth, acid-base balance in the kidneys	Mass spectrometry
	Arginine	Urine Plasma	Important role in cell division, wound healing, removing ammonia from the body, immune function, and hormone release	Mass spectrometry
	Serine	Urine Plasma	Biosynthesis of proteins, purines pyrimidines, enzymes, and muscle tissue	Mass spectrometry

Tab. VI. *Continues.*

Disease Condition	Metabolites	Sample type	Function	Analyzing Technique
Non-protein amino acid	Carnitine	Urine	Energy production support, general brain function maintenance	NMR spectroscopy
	Taurine	Urine Plasma	Nerve growth support, blood pressure lowering, calming the nervous system	Mass spectrometry
	Glutathione	Urine Plasma	Antioxidant, involved in nutrient metabolism, cellular events regulation	Mass spectrometry NMR spectroscopy
Inflammation and lipidomics	Fatty acid amides	Urine Plasma	Signaling lipids, modulation of neurobehavioral processes in mammals, including pain, sleep, feeding, and locomotor activity	Gas chromatography, Mass spectrometry
	Leukotrienes	Urine Plasma	Potent inflammatory mediator	Liquid chromatography, Mass spectrometry
	Prostaglandin	Blood Serum Urine	Regulation of smooth muscle tissue contraction and relaxation	Liquid chromatography, Mass spectrometry
	Thromboxane	Blood	Blood clotting and constriction of blood vessels	Liquid chromatography, Mass spectrometry, Thin layer radio-chromatography
Steroids	Aldosterone	Serum Urine	Increased sodium and water retention, increased potassium excretion, blood pressure regulation	Liquid chromatography/ tandem mass spectrometry
	Cortisol	Blood Urine Saliva	Metabolism and immune response regulation	Liquid chromatography/ tandem mass spectrometry
	Corticosterone	Blood	Involved in metabolism, energy balance, stress and adaptation	Mass spectrometry HPLC ELISA Radioimmunoassays
	Dehydroepiandrosterone sulfate	Blood Plasma	Involved in the development of male sexual characteristics at puberty	Liquid chromatography/ tandem mass spectrometry
	11-Deoxycortisol	Serum Plasma	Metabolic intermediate within the glucocorticoid pathway	Mass spectrometry
	21- Deoxycortisol	Blood Plasma Urine	Marker of congenital adrenal hyperplasia due to 21-hydroxylase deficiency	Liquid chromatography/ tandem mass spectrometry, HPLC
	Androstenedione	Serum Urine	Increasing the production of the hormone testosterone to enhance athletic performance, build muscle, reduce body fat, increase energy	Liquid chromatography/ tandem mass spectrometry
	Testosterone	Blood	Sexual development regulation, muscle mass, and red blood cells production	Liquid chromatography/ tandem mass spectrometry
	17-OH-Progesterone	Blood	Marker for congenital adrenal hyperplasia (CAH)	Liquid chromatography/ tandem mass spectrometry
	Dehydroepiandrosterone	Blood	Endothelial function modulation, inflammation reduction, improvement of insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism,...	Gas chromatography-mass spectrometry (GC-MS), Liquid chromatography-mass spectrometry (LC-MS)
	Progesterone	Serum Plasma Urine	Menstruation regulation and pregnancy support	Liquid chromatography-mass spectrometry (LC-MS)
	Estradiol	Blood Saliva	Development and maintenance of female reproductive system	HPLC, Liquid chromatography-mass spectrometry (LC-MS)
	Estrone	Serum Urine	Involved in female sexual development and function	Gas chromatography-mass spectrometry (GC-MS), Liquid chromatography-mass spectrometry (LC-MS)
Toxoma	More than 5,000 toxins	-	-	-

Assessment of nutritional status by genetic biomarkers

Genetic biomarkers play a crucial role in determining the association between intermediate biomarkers like fasting glucose, inflammation markers, plasma lipids, oxidative markers, etc. and the occurrence of diseases like type 2 diabetes, cardiovascular diseases, neurodegenerative diseases, cancer, etc. Currently, hundreds of SNPs are known to be persistently associated with various phenotypes of nutrition-linked diseases (Tab. VII); hence, nutritional epidemiological studies require the knowledge of most pf the genetic polymorphisms that are linked to the phenotypes of interest to establish reliable associations between the diet and the disease. This phenomenon is especially relevant to understand individual variations associated with certain gene variants that might influence the correct evaluation of the nutritional status [65].

Lactase 13910C>T polymorphism /rs4988235 located on MCM6 gene is one example of the effect of genetic polymorphism on nutritional status, as it effects the lactase gene (LCT). It strongly affects the persistence of lactase synthesis, which in turn influences the individual's intolerance or tolerance to lactose [66]. Usually, those who have a CC genotype exhibit a physiological decrease of lactase activity within the intestinal cells because of the difficulty in lactose metabolism. Therefore, CC genotype variant of Lactase 13910C>T polymorphism has been proposed to act as proxy for the low consumption of milk [67]. Similarly, genetic variants also affect the intake biomarkers concentration, like phylloquinone/vitamin K1, which is the major circulating vitamin K form and reflects the intake of vitamin from plants. Circulating phylloquinone acts as a biomarker associated with a healthy lifestyle, while its lower concentrations are considered to be associated with an enhanced risk of different chronic diseases. Thus, understanding the gene variants that might affect phylloquinone concentration might explain the individual variability in the response of phylloquinone intake from the diet or supplements [68].

Additionally, genetic variability also plays significant role in accurately assessing the micronutrient status, which might have a small safety range between the toxic and safe dosage, as well as regulate the bioavailability of these micronutrients. For instance, zinc homeostasis is usually regulated by the zinc transporter genes, and the zinc transporter SLC-30A8 polymorphism is found to be associated with an increased risk of type 2 diabetes, as zinc is required for insulin metabolism within the pancreatic beta-cells. Empirically, the total zinc intake is inversely related with the level of fasting plasma glucose in people having the glucose increasing A allele. Moreover, many studies have evidently proposed that zinc levels might be considered at individual basis [65, 69].

In addition to dietary intake (DI), genes also affect physical activity (PA). Since physical activity is one of the major factors contributing to the total energy expenditure (TEE), it plays a vital role in regulating energy balance. It is commonly established that the training-associated metabolic changes are mostly influenced by the individual's genetic background. Moreover, identifying the genetic markers that enhance the beneficial effects of training might be helpful in assessing various training programs that, along with dietary intervention, could improve the body weight reduction among obese individuals. Therefore, personalized interventions for obesity reduction would be significant in the clinical management of obesity and obesity-related diseases, such as lymphedema [70-73].

In the last two decades, genome-wide association studies (GWAS) and the development of new technologies in the fields of molecular biology and human genetics have enable scientists to easily perform hundreds of genomic analyses, as well as high throughput DNA sequencing techniques. Such broad-range techniques have facilitated the identification of novel genes and established the correlations between different SNPs related with training capabilities (collectively, such genetic factors are known as performance-enhancing gene polymorphisms, or PEPs) [74]. Recently, a scientific review has identified the association of 5,147 genes with training and physical activity (PA). However, 51% of these genes have up-regulatory effect by training and PA, while 42% of the genes have shown down-regulatory effects by PA [74,75].

For instance, MYBPH gene encodes the structural component of the muscle sarcomeres, which is a myosin-binding protein that might be involved in myosin interaction with the thick A-band myofilaments [76]. Similarly, PDK4 gene encodes the protein kinase (PTK) enzymes, which are located in the mitochondrial matrix and are involved in the inhibition of pyruvate dehydrogenase complex (PDC), which reduces glucose usage and increases free fatty acid (FFA) catabolism [77]. Likewise, ACE (angiotensin-converting enzyme) gene is a reliable candidate for the genetic predisposition to athletic physical activity. Several studies have shown that insertion (allele I) or deletion (allele D) polymorphism of 287bp Alu repetitive sequence located in intron 16 have an association with increased performance as well as duration of exercise in many subjects [78]. A common single nucleotide polymorphism (SNP) rs1801282 C>G (Pro12Ala) in PPARG (Peroxisome Proliferator Activated Receptor Gamma) gene is known to be associated with various muscle changes linked with exercise. Also, the Ala variant of the SNP rs1801282 could enhance the positive effects on increased muscle mass related with training resistance [70, 79].

Conclusion

Food is required to maintain activities of life. The nutrients and the non-nutrient food components interact with various metabolic pathways, thus influencing health. Nutrient deficiencies could play a significant role in the development and progression of several acute and chronic disorders, and they also could be linked to harmful changes in overall health. For nutritional assessment or screen-

Tab. VII. Genes and SNPs involved in Nutritional Assessment.

Sr. No.	Gene	SNP	Alleles	Gene function
1	*LTB4R2*	rs1950504	A/G	Chemotaxis mediation of granulocytes and macrophages
2	*ALOX5*	rs4987105,	C/T	Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes
		rs59439148	del$(GGGGGC)_{4/3/2}$ /del$(G)_5C$ /dup$(G)_5C$ /dup$(GGGGGC)_{2/3}$	
		rs4769874	G/A	
3	*LTA4H*	rs17525495	C/T	Epoxide hydrolase that catalyzes the final step in the biosynthesis of leukotriene B4
		rs1978331	C/T	
4	*MMP2*	rs1030868	G/A	Metalloproteinase involved in vasculature remodeling, angiogenesis, tissue repair, inflammation
		rs2241145	G/C	
5	*CEACAM1*	rs8110904	G/A	Cell-cell adhesion molecule with roles in angiogenesis and immune response modulation, reduction of inflammasome activity, blood vessel remodeling through endothelial cell differentiation and migration, vascular permeability regulation
		rs8111171	G/T	
6	*FOXC2*	rs199772307,	G/A	Transcriptional activator. Involved in mesenchymal tissue formation
		rs34221221,	A/G	
7	*TNF*	rs1800629	G/A	Cellular responses to cytokines and stress, regulates the immunological response to infections
8	*TLR2*	rs121917864	C/T	Key role in the innate immune system. It is expressed in macrophages, B lymphocytes, mast cells
9	*TLR4*	rs4986791	C/T	Key role in the innate immune system. It is expressed in macrophages, B lymphocytes, mast cells
10	*VEGFA*	rs699947	C/A	Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization
		-1154	G>A	
		-460	C>T	
		+405	G>C	
		+936	C>T	
11	*HGF*	rs5745652	C/T	Role in angiogenesis, tumorigenesis, tissue regeneration
		rs2074725	C/A	
12	*CYP26B1*	rs2241057	A/G	Involved in the retinoic acid metabolism
13	*PROX1*	rs340874	T/C	Critical role in neurogenesis and in the development of the heart, eye lens, liver, pancreas, and lymphatic system
14	*RORC*	rs11801866	A/T	Essential for lymphoid organogenesis
		rs12128071	G/A	
		rs12045886,	A/G	
15	*LCP2*	rs572192	C/T	T-cell antigen receptor-mediated signaling
		rs6866733	C/G,T	
		rs315721	A/G	
16	*NRP2*	rs849530	G/T	Interaction with vascular endothelial growth factor (VEGF)
		rs849563	T/A,G	
		rs16837641	G/A,C,T	
17	*SYK*	rs158689	T/A	Regulation of innate and adaptive immunity, vascular development. Crucial role in the innate immune response to fungal, bacterial and viral pathogens. Activates the inflammasome and NF-kappa-B-mediated transcription of chemokines and cytokines in presence of pathogens. Involved in vascular development, where it may regulate blood and lymphatic vascular separation
18	*VCAM1*	rs3176861	C/T	Pathophysiologic role in immune responses and leukocyte emigration to inflammation sites

Tab. VII. *Continues.*

Sr. No.	Gene	SNP	Alleles	Gene function
19	*miR499*	rs3746444	A/C,G	miR-499 gene targets are involved in remodeling and inflammation-related signaling pathways, including fibrogenic and immune-modulator pathways
20	*CDKN2B-AS1*	rs1333048	A/C,G	Interacts with polycomb repressive complex-1 and -2, leading to epigenetic silencing
21	*CALCRL*	rs185008808	C/T	Receptor for calcitonin-gene-related peptide together with RAMP1 and receptor for adrenomedullin together with RAMP3 and RAMP2
		rs61739909	A/G	
		rs10177093	G/C,T	
22	*VEGFC*	rs2333496	C/T	Growth factor active in angiogenesis of veins and lymphatic vessels, and in endothelial cell growth, stimulating their proliferation and migration, and permeability of blood vessels
		rs7664413	C/T	
23	*EPHB4*	rs314313	T/A,C,G	Cell adhesion and migration regulation, angiogenesis, blood vessel remodeling and permeability
		rs314311	T/G	
24	*PLA2G4A*	rs10798069	G/T	Hydrolyzes arachidonyl phospholipids for releasing arachidonic acid. Implicated in the initiation of the inflammatory response
25	*IL1R1*	rs949963	C/T	Mediator involved in cytokine-induced immune and inflammatory responses
26	*IL4*	rs2227284	T/C,G	B-cell activation, DNA synthesis stimulation, expression induction of MHC-II on resting B-cells, secretion enhancement and cell surface expression of IgE and IgG, expression regulation of CD23 IgE receptor on lymphocytes and monocytes, expression induction of IL31RA in macrophages, autophagy stimulation in dendritic cells
27	*IL6*	rs2066992	G/A,C,T	Inducer of the acute phase response, final differentiation of B cells into Ig-secreting cells, lymphocyte and monocyte differentiation, generation of Th17 cells, myokine, increased fats breakdown, improved insulin resistance
28	*IL10*	rs1518111	T/C	Cytokine produced by monocytes, lymphocytes, pleiotropic effects in immunoregulation, inflammation, down-regulation of Th1 cytokines expression, MHC-II, macrophages stimulator, B cell survival enhancement, proliferation, antibody production
		rs1518110	A/C,G,T	
29	*NFKB2*	rs1056890	G/A,C	Pleiotropic transcription factor ubiquitously expressed involved in inflammation, immunity, differentiation, cell growth, tumorigenesis, apoptosis
30	*ANGPT2*	rs6990020	C/A,T	Endothelial cell migration and proliferation
31	*SOX17*	rs12541742	C/G,T	Embryonic vascular development, postnatal angiogenesis
32	*FLT4*	rs75614493	C/T	Lymphangiogenesis and lymphatic endothelium maintenance
		rs10464063	A/G	
		rs307814	G/A	
		rs307811	C/T	
		rs11960332	C/T	
		rs11739214	G/C	
33	*KDR*	rs2239702	G/A	Endothelial proliferation, survival, migration, tubular morphogenesis, sprouting
		rs4576072	A/G	
		rs10020464	C/A,T	
		rs11133360	C/T	
34	*CYP2A6*	rs1801272	T/A	High coumarin 7-hydroxylase activity

Tab. VII. *Continues.*

Sr. No.	Gene	SNP	Alleles	Gene function
35	*PLIN1*	rs228948	A>G/A>T	Modulators of lipolysis and triglyceride levels; protection of lipid storage droplets from hormone-sensitive lipases
		rs894160	C>T	
		rs230479	A>C	
		rs105270	-	
		rs2304794	T>A	
36	*ADRB2*	rs1042713	G>A	Induction of thermogenesis in response to cold and diet, lipolysis induction
		rs1042714	G>A	
37	*ADRB3*	rs4994	A>G	Induction of thermogenesis in response to cold and diet; induction of lipolysis
38	*PPARGC1A*	rs8192678	C>T	Transcriptional regulation of white adipocyte differentiation, insulin, and adipocytokine pathways
39	*TFAM*	rs1937	G>C	Maintenance of normal levels of mitochondrial DNA
40	*PPARA*	rs4253778	G>C	Stimulating the expression of genes required for fatty acid oxidation in mitochondria
41	*PPARD*	rs2016520	C>A/T	Regulation of the peroxisomal beta-oxidation pathway of fatty acids in mitochondria
42	*GABPB1*	rs7181866	A>G	Activation of cytochrome oxidase expression and nuclear control of mitochondrial function
		rs12594956	C>A/G	
		rs8031031	C>T	
		rs12594956	C>A/G	
43	*ACE*	rs4646994	-	Regulation of energy expenditure, lipolysis and glucose incorporation into lipids in adipocytes
44	*AMPD1*	rs17602729	-	Critical role in energy metabolism
45	*CKM*	rs8111989	-	Central role in energy transduction in tissues with large fluctuating energy demands (skeletal muscles, heart)
46	*ADRB2*	rs1042713	-	Induction of thermogenesis in response to cold and diet, lipolysis induction
47	*IL6*	rs1800795	-	Increase in fat breakdown, insulin resistance improvement
48	*UCP3*	rs1800849	-	Uncoupling of oxidative phosphorylation, thermogenesis
49	*AGT*	rs699	-	Activation of lipogenic enzymes, induction of lipid transport into adipocytes, increase in delivery of fatty acids to adipocytes
50	*KCNJ11*	rs5219	-	Insulin secretion
51	*COL5A1*	rs12722	-	Ubiquitous connective tissue component that also binds insulin
52	*HIF1A*	rs11549465	-	Activation of glucose transporter transcription under hypoxic conditions, encodes glycolytic enzymes
53	*PPARG*	rs1801282	-	Regulator of adipocyte differentiation
54	*GABPB1*	rs12594956	-	Activation of cytochrome oxidase expression and nuclear control of mitochondrial function
		rs7181866	-	
55	*SOD2*	rs4880	-	Destroys toxic superoxide anion radicals normally produced in cells
56	*ACTN3*	rs1815739	-	Structural component of sarcomeric Z line in skeletal muscle
57	*BDKRB2*	rs1799722	-	Mediators of pain and inflammation
58	*AQP1*	rs1049305	-	Passive transport of water across osmotic gradient
59	*MTHFR*	rs1801131	-	Conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
60	*NOS3*	rs2070744	-	Vasodilation in response to training
61	*FTO*	rs9939609	-	Stimulation of food consumption
		rs1558902	-	
		rs8050136	-	

Tab. VII. *Continues.*

Sr. No.	Gene	SNP	Alleles	Gene function
62	*ADIPOQ*	rs1501299	-	Energy expenditure
63	*LEP*	164160	-	Appetite regulation
64	*LEPR*	rs1805094	-	
65	*INSIG2*	rs7566605	-	Regulation of cholesterol and fatty acid synthesis
66	*MC4R*	rs17782313	-	Energy homeostasis, appetite regulation
		rs17066866	-	
		rs1943226	-	
		rs11875096	-	
		rs1943224	-	
		rs7235242	-	
		rs11872992	-	
		rs8093815	-	
		rs17066856	-	
		rs17066836	-	
		rs1943227	-	
		rs1943218	-	
		rs17066829	-	
		rs9966412	-	
		rs17066859	-	
		rs9965495	-	
		rs12970134	-	
		rs17700633	-	
		rs11873305	-	
		rs8091237	-	
		rs7240064	-	
67	*PCSK1*	rs236918	-	Insulin resistance
68	*PPARG*	rs1801282	-	Increased BMI
69	*ADBR2*	rs1042714	-	Adaptive thermogenesis
		rs1042713	-	
70	*ADBR3*	rs4994	-	
71	*GHRL*	rs696217	-	Appetite regulation
72	*FABP2*	Ala54Thr-polymorphism	-	Fatty acid uptake
73	*APOA5*	rs964184	-	Lipoprotein metabolism
		rs662799	-	
74	*APOA1*	rs670	-	
75	*LIPC*	rs2070895	-	
76	*CETP*	rs3764261	-	
77	*MTNR1B*	rs10830963	-	Appetite regulation
78	*NPY*	rs16147	-	
79	*GIPR*	rs2287019	-	Insulin signaling
80	*IRS1*	rs1522813	G>A/G>C	
		rs2943641	T>A/T>C	
81	*TCF7L2*	rs12255372	G/T	Blood glucose homeostasis
		rs7903146	C>G/C>T	
82	*PCSK1*	rs6232	T>C	Energy metabolism
		rs6234	G>C	
83	*MCM6 (*601806)*	rs4988235	C>T (C)	Lactose intolerance, adult type (#223100)
		rs182549	G>A (G)	
		rs145946881	G>C (G)	
84	*HLA-DQA1 (*146880)*	rs2187668	C>T (C)	Susceptibility to celiac disease 1 (#212750)
		rs2395182	G>T (G)	
		rs4639334	G>A (G)	
		rs4713586	A>G (G)	
		rs7454108	T>C (C)	
85	*HLA-DQB1 (*604305)*	rs7775228	T>C (C)	

Tab. VII. *Continues.*

Sr. No.	Gene	SNP	Alleles	Gene function
86	*HJV (*608374)*	rs74315323	C>A	Hemochromatosis, type 2A (#602390)
		rs74315324	G>A	
		rs74315325	A>T	
		rs74315326	A>G	
		rs28940586	A>C,G	
		rs74315327	A>G	
		rs121434374	G>C,T	
		rs786205063	$(GA)_3G>GAG$	
		rs121434375	T>A	
87	*SLC40A1 (OMIM *604653)*	rs104893662	T>A,G	Hemochromatosis, type 4
		rs28939076	G>T	
		rs878854984	$(CAA)_4>(CAA)_3$, $(CAA)_5$	
		rs104893663	T>A,C	
		rs104893670	C>A,T	
		rs104893671	C>A	
		rs104893672	T>A	
		rs104893673	C>A	
		rs104893664	C>T	
88	*HFE (*613609)*	rs1800562	G>A	Hemochromatosis
		rs1799945	C>G,T	
		rs1800730	A>T	
		rs1800758	G>A	
		rs28934889	G>A	
		rs111033557	G>A	
		rs28934595	A>C	
		rs111033558	G>C,T	
		rs28934596	T>C	
		rs28934597	G>C	
		rs111033563	A>C	
89	*TFR2*	rs80338880	G>C	Hemochromatosis, type 3
		rs80338877	$(G)_5>(G)_6$	
		rs80338879	A>T	
		rs41303501	C>T	
		rs80338889	T>C,G	
90	*FTH1*	rs387906549	T>A	Hemochromatosis, type 5
91	*ADH1B (*103720)*	rs1229984	A>G	G/C, higher alcohol consumption
		rs2066702	C>T	A/T, acetaldehyde accumulation
92	*ADH1C (*103730)*	rs1693482	C>T (T)	Type II alcoholism
		rs698	T>A,C (C)	
93	*ALDH2 (*100650)*	rs671	G>A (A)	Acute alcohol sensitivity (#610251)
94	*CYP1A2 (+124060)*	rs762551	C>A (C)	Higher risk of nonfatal myocardial infarction
95	*ADORA2A (*102776)*	rs5751876	T>C (C)	Greater caffeine sensitivity, sleep impairment, increased beta activity during non-REM sleep
		rs35320474	delT (T)	Greater caffeine-induced anxiety
96	*DRD2*	rs1110976	T>G (G)	Greater caffeine-induced anxiety
97	*COMT*	rs4680	G>A (A)	Higher risk of acute myocardial infarction
98	*ALDOB (*612724)*	rs1800546	C>G (G)	Fructose intolerance (#229600)
		rs76917243	G>T (T)	
		rs118204425	AAGdel (del)	
99	*UGT1A1 (*191740)*	rs6742078	G>T (T)	Bilirubin serum level (#601816)
100	*G6PD (*305900)*	rs1050829	T>A,C (A)	Nonspherocytic hemolytic anemia (#300908)
		rs1050828	C>T (T)	
101	*BCO1*	rs12934922	A>T (T)	Reduced conversion of beta-carotene to retinol
		rs7501331	C>T (T)	

Tab. VII. *Continues.*

Sr. No.	Gene	SNP	Alleles	Gene function
102	*GC*	rs2282679	T>G (G)	Lower vitamin D levels
		rs4588	G>T (T)	
		rs842999	C>G (C)	
103	*SLC23A1*	rs33972313	C>T (T)	Reduction of circulating levels of vitamin C
104	*SLC30A8*	rs11558471	A>G (G)	Susceptibility to diabetes mellitus
105	*SLC5A6*	rs1395	G>A (A)	Reduced intestinal uptake, cellular delivery, and transplacental transport of pantothenate and biotin
106	*TCN2*	rs1801198	C>G (G)	Decreased serum vitamin B12, increased homocysteine
107	*TTPA*	rs4501570	G>A (A)	Vitamin E deficiency
		rs4587328	T>C (C)	
		rs4606052	C>T (T)	
108	*VDR*	rs731236	A>G (G)	Immune weakness, increased cancer risk, early bone loss, increased cognitive decline risk, mood disorders
109	*CYP2R1*	rs10741657	A>G (G)	Lower vitamin D levels
		rs10766197	A>G (A)	
110	*LPA*	rs10455872	A>G (G)	Coronary artery disease
		rs3798220	C>T (C)	Cardiovascular events risk
111	*CDKN2B-AS1*	rs10757274	A>G (G)	Heart disease risk
		rs2383206	A>G (G)	
		rs2383207	A>G (G)	
112	*Intergenic*	rs10757278	A>G (G)	Heart attack risk
113	*MC4R*	rs17782313	C>T (C)	Increased BMI
114	*APOA2*	rs5082	C>T (C)	Higher total energy, fat, protein intake
115	*PCSK1*	rs6232	A>G (G)	Higher risk of obesity and insulin sensitivity
116	*APOA5*	rs662799	A>G (G)	Higher risk of early heart attack, less weight gain on high-fat diets
117	*SH2B1*	rs7498665	A>G (G)	Obesity, type-2 diabetes
118	*SLC2A2*	rs5400	C>T (T)	Higher sugar consumption
119	*F2*	rs1799963	A>G (A)	Higher risk of thrombosis and cerebral stroke
120	*F5*	rs6025	A>G (A)	Higher risk of thrombosis
121	*FUT2*	rs602662	A>G (G)	Lower vitamin B12 levels
122	*ALPL*	rs4654748	C>T (C)	Lower Vitamin B6 blood concentration
123	*CYP2R1*	rs10741657	A>G (G)	Lower vitamin D levels
		rs10766197	A>G (A)	
124	*GC*	rs4588	G>T (T)	
		rs842999	C>G (C)	
125	*MTHFR (*607093)*	rs1801133	G>A (A)	Homocystinuria (#236250)
126	*CBS (*613381)*	rs121964962	C>T (T)	Homocystinuria (#236200)
127	*FOXO3*	rs2802292	C>T (T)	Longer lifespan
		rs2802288	A>G (A)	
		rs2802292	T>G (G)	
128	*SIRT1*	rs3740051	-	Higher basal energy expenditure
		rs2236319	-	
		rs2272773	-	
129	*PEMT*	rs12325817	G>C (C)	Low choline
130	*CHDH*	rs12676	G>T (T)	

ing, precise evaluation of the dietary intake (DI) as well as of physical activity (PA) is crucial. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare setups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected. Dietary Intake (DI) assessment is a multidimensional and complex process. Traditionally, DI is assessed through self-report techniques including diet records, FFQs (food frequency questionnaires), and recalls. But due to reporting errors such as biases, random errors, misestimations, and nutrient databases-linked errors, questions arise about the adequacy of self-reporting dietary intake

procedures for scientific conclusions. Therefore many objective methods are proposed for dietary intake (DI) and physical activity (PA) assessment such as biomarkers analysis, blood tests, genetic assessments, metabolomic analysis, DEXA (Dual-energy X-ray absorptiometry), MRI (Magnetic resonance imaging), and CT (computed tomography) scanning procedures as well as bed-side and low-cost techniques like BIA (bioelectric impedance analysis). Although most of these methods have their own biases and limitations.

In the future, thanks to the presence of such nutritional, genetic, and metabolic status indicators along with intelligent interventions, like healthier and more aware choices in food and supplements and lifestyle modifications, the individual metabolic phenotype will be developed in a beneficial and individually designed direction. Such vision will bring a deeply different prospect to the management of human diet and will enable a very interactive, detailed, and significantly valuable system to provide health.

Acknowledgements

This research was funded by the Provincia Autonoma di Bolzano in the framework of LP 15/2020 (dgp 3174/2021).

Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; AKK, MCM, Kristjana D, Kevin D, PC, FF, MAP, MRC, PM, SN, MC, TB: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript

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How to cite this article: Kiani AK, Medori MC, Dhuli K, Donato K, Caruso P, Fioretti F, Perrone MA, Ceccarini MR, Manganotti P, Nodari S, Codini M, Beccari T, Bertelli M. Clinical assessment for diet prescription. J Prev Med Hyg 2022;63(suppl.3):E102-E124. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2753