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Review

Parmigiano Reggiano cheese: general and metabolic/nutritional aspects from tradition to recent evidences

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Summary. Parmigiano Reggiano cheese is the oldest italian Protected Designation of Origin product, in accordance with Regulation (EU) No. 1151/2012 of the European Parliament and of the Council of 21 November 2012 on quality schemes for agricultural products and foodstuffs. It is produced in a strictly delimited territory, which includes the provinces of Parma, Reggio Emilia, Modena, Mantua to the right of the River Po and Bologna to the left of the River Reno; also the milk must come exclusively from this strictly delimited territory. It is a hard-textured, semi-fat cheese cooked and matured slowly. Additives are not allowed. The cheese must be matured for a minimum of 12 months, with significant variations between the fresh product and the aged one, especially in terms of protein digestibility. Cheese proteins essentially consist of casein, with traces of lactoglobulin and lactalbumin: the protein intake is approx. 33.0%, and the biological value of this nutritious substance is high. Parmigiano Reggiano is a semi-fat cheese with a fat content (29.7%), lower than the protein content. Conjugated isomers of linoleic acid are found in Parmigiano Reggiano cheese in quantities of approx. 3 mg/g of lipids. The amount of vitamins present in Parmigiano Reggiano cheese, while varying in relation to aging, is sufficient to cover a high percentage of the daily vitamin requirement in children and adults. A 100 g serving of Parmigiano Reggiano cheese covers also the entire daily requirement of calcium and phosphorus for an adult person with an extremely favourable calcium/phosphorus ratio. Lactose content ranges from below limit of detection to 0.39 mg/100 gr of cheese, thus allowing to classify Parmigiano Reggiano cheese among the "lactose-free" cheeses, according to the European Commission for the formulation of infant milk criteria. The absence of lactose means that it can be administered to patients with lactase deficiency. The energy value is, in any case, high (402 kcal per 100 g), so Parmigiano Reggiano cheese has not to be considered as a supplement to a normal meal, but a food in its own right. Thanks to its composition and its richness in protein substrates, in calcium, in trace nutrients and bioactive peptides, together with its excellent lipid profile, Parmigiano Reggiano cheese can be considered a "naturally" functional food, ideal for use in every age of life and in several disorders such as diabetes, ostheoporosis and dyslipidaemias.

Key words: Parmigiano Reggiano cheese, metabolic/nutritional aspects, PDO-certified

Introduction

Parmigiano Reggiano cheese is the oldest Italian PDO-certified cheese, which saw the production of 3 million wheels in 2014. This is equivalent to around 120,000 tons (1). Its production is governed by strict specifications, the last update of which has been in force since 29 August 2011 (2) and takes place exclusively in cheese factories located in a strictly delimited territory, the so-called "typical area", which includes the provinces of Parma, Reggio Emilia, Modena, Mantua to the right of the River Po and Bologna to the left of the River Reno; also the milk must come exclusively from this strictly delimited territory. This area provides the elements that make the production of this typical cheese possible: soil composition, forage types, specially selected cows and a tradition handed down by expert personnel.

General aspects

Parmigiano Reggiano cheese is a semi-fat, hard-textured cheese cooked and matured slowly. It is produced using raw cows' milk from livestock whose diet consists of at least 50% forage mainly produced in farm's own land and typical area because it is only within this area that the typical mesophilic lactic acid bacteria are found.

Traditionally, production used to stop during the winter season (running from St Martin's Day on 11 November to St Joseph's Day on 19 March): today production lasts all year long and is divided into three batches (1st batch January-April, 2nd batch May-August, 3rd batch September-December) (2).

Sixteen litres of milk are needed to make 1 kg of Parmigiano Reggiano cheese and the milk used is that from the previous evening's milking, partially skimmed, plus that from the next morning's milking. The milk must not be subjected to heat treatments prior to the cheese-making process and the use of additives is prohibited. The milk is delivered to the cheese factory within two hours of the end of each milking and while being kept in the cowshed, the temperature must never drop below 18°C, in order to avoid damage to the mesophilic lactic acid bacteria. Coagulation is obtained through the use of calf rennet after the adding of autochthonous whey starter, which brings about the complete transformation of the lactose into lactic acid within the first 72 hours of the cheese's life; after a period in brine of about 20 days, the aging process begins (minimum 12 months) during which the proteins are partially hydrolysed with the release of proteins of low molecular weight responsible for the aroma and endowed with important nutritional properties.

A brief history of Parmigiano Reggiano cheese

There is some controversy regarding the specific place and time in which Parmigiano Reggiano cheese was first produced. According to reliable historical evidence, a cheese with the same granular structure, straw-colour and fragrant aroma first appeared on the scene about half way through the 11th century in the mid-valley of the River Enza, straddling the current border between the provinces of Parma and Reggio Emilia, after which it spread towards the plain. In actual fact, the Benedictine monks living in the Po Valley, along the Via Emilia road, which has connected Milan with the Adriatic coast ever since Roman times, made a valuable contribution to the creation of this cheese, inasmuch as they played a fundamental role in the reclamation of the land (which had become marshy after the fall of the Roman Empire), in the development of crops that were indispensable for cattle forage and in the breeding of livestock. Thanks to the availability of large quantities of milk and the need to store it in one way or another, for the winter period, during which the cattle did not produce it due to lack of grass, a number of hard-textured cheeses were developed, among which Parmigiano Reggiano, already mentioned (under the title "caseus parmesanus") in a document regulating a bequest dating back to 1254 and filed in the State Archives of Genoa. The most famous quotation is, however, that of Boccaccio's Decameron, written around 1350, in which Maso describes the marvels of Bengodi to the gullible Calandrino, saying "and on a mountain, all of grated Parmigiano Reggiano cheese, dwell folk that do nought else but make macaroni and ravioli…" (3-5).

Characteristics of Parmigiano Reggiano cheese

Parmigiano Reggiano cheese is produced in cylindrical wheels that have a slightly convex heel between 20 and 26 cm in height, flat faces featuring slightly raised edges and a diameter of between 35 and 45 cm. The average weight of a wheel is around 40 kg at 12 months. The rind is around 6 mm thick and has a natural straw-coloured exterior. The cheese itself, which is a light-straw colour, has a texture made of tiny structured granules that when fractured breaks into scale-like fragments.

The cheese must be matured for a minimum of 12 months, but is most frequently used around 24 months and longer: It is important to remember that the "Parmigiano Reggiano" Protected Designation of Origin is only extended to the grated product if it is obtained from whole PDO certified cheeses, on condition that the grating process is carried out within the area of production of the cheese and the packaging is carried out immediately after without any kind of treatment and without adding any substances designed to change the preservability and original organoleptic characteristics of the product (2).

Parmigiano Reggiano cheese safety

Parmigiano Reggiano cheese has been made in substantially the same way for eight centuries, while the production process in its current form has been detailed and regulated by the Consortium since 1956.

While there are concerns about the safety of some soft and semi-hard raw milk cheeses, specific independent epidemiological studies and indeed time itself have clearly established that hard cheeses such as Parmigiano Reggiano are safe and, after decades (centuries, even…) of being eaten worldwide, no cases of any adverse effects have been reported.

What makes Parmigiano Reggiano cheese safe is:

- the synergy between the antimicrobial enzyme systems in raw milk and mesophilic milk flora (non-starter lactic acid bacteria - NSLAB),
- the addition of a natural whey starter (a culture of thermophilic lactic acid bacteria – SLAB) to the milk vat (approximately 3% v/v), and
- the subsequent fermentation of sugar substrates that lead to a sudden drop (5.1) in the pH during the first hours of the cheese making process,
- the high (55°C) temperature used for cooking the curds and the long time (at least 3 hours) for which the cheese is heated,
- the brine salting, responsible for the gradual decrease of water activity down to 0.90 and salt content in relation to water totalling around 4.2%,
- the consistency and thickness of the rind, which naturally protects the cheese from external agents and
- the long maturation (at least 12, usually 24 and often more than 30 months).

Every single cheese factory guarantees the application of appropriate productive practices by its own HACCP plan managed according to Regulation (EC) No. 852/2004.

The use of predictive microbiology models to study and state safety and hygiene parameters of foods is recognized and accepted at international level. A number of different predictive mathematical models have been used showing that, even if milk is raw at the beginning of the production process, the process itself guarantees heat treatment equivalent to pasteurization.

In order to validate the theoretical data described above from an empirical standpoint and to verify the effective ability of the Parmigiano Reggiano cheese-making process to reduce the potential presence of food-borne pathogens, various challenge tests have been carried out in the last years showing that this particular production process can eradicate (5-7 log reductions) pathogenic microbes potentially contained in milk, such as Salmonella spp., *Listeria monocytogenes*, E*scherichia coli* O157:H7, *Staphylococcus aureus* enterotoxigenic and even *Mycobacterium avium paratuberculosis* (CFPR, data on file).

Nutritional aspects

Parmigiano Reggiano cheese is one of the best cheeses from a nutritional perspective as it has characteristics that are particularly interesting for the human diet (Tab. 1).

The high protein intake (on average 32.4%) that Parmigiano Reggiano cheese can supply to the human diet is undoubtedly an important characteristic, asso-

Table 1. Parmigiano Reggiano cheese composition (100 g)

Water	31.4 g
Protein	32.4 g
Free aminoacids on total protein[1]	23.3%
Energy[2]	402 kcal 1671 kJ
Fat	29.7 g
Satured fatty acids	19.6 g
Monounsaturated fatty acids	9.3 g
Polyunsatured fatty acids	0.8 g
Fat in dry matter	43.3 % d.m.
Carbohydrates	0 g
of which sugars	0 g
Lactose	<1 mg
Fiber	0 g
Salt[3]	1.6 g
Lactic acid	1.6 g
Calcium	1155 mg
Phosphorus	691 mg
Sodium	650 mg
Potassium	100 mg
Magnesium	43 mg
Iron	0.2 mg
Copper	0.83 mg
Zinc	4 mg
Cholesterol	83 mg
Vitamin A	430 µg
Thiamine (Vitamin B1)	0.03 mg
Riboflavin (Vitamin B2)	0.35 mg
Vitamin B6	0.06 mg
Vitamin B12	1.7 µg
Vitamin C	0 mg
Niacin (Vitamin PP/B3)	0.06 mg
Vitamin E	0.55 mg
Vitamin K	1.6 µg
Pantothenic Acid (Vitamin B5)	0.320 mg
Choline	40 mg
Biotin	23 µg

Values, expressed per 100 g, are obtained from random samples of PDO-certified Parmigiano Reggiano cheese by the Consortium, not attributable to a specific manufacturer, production lot or geographical area.

[1] The percentage of free amino acids is referred to Parmigiano Reggiano 24 months ripened.

[2] Energy value is evaluated by the conversion coefficients as reported in All. XIV, EU Reg. 1169/2011 (11)

[3] Salt: salt equivalent content is evaluated by the formula Salt = sodium x 2.5 as reported in EU Reg. 1169/2011, Ann. 1. (11)

ciated moreover with the high biological value of this protein (Tab. 2) that is characterized by a very high utilization coefficient, having an index of 93, versus 69 for beef, 62 for meat of veal, 50 for bread (6-9). The proteolysis that takes place during the aging process gives rise to lighter polypeptide chains and to an amount of free amino acids equivalent to 7.5% of the edible part, much higher than that found in other types of cheese. This characterises the product from a nutritional perspective because these compounds can be assimilated rapidly and absorbed without the need for any digestive processes, making this a "digestion facilitated" food (an hectogram of this cheese is digested in 40 minutes against more than three hours of an hectogram of beef), that is very useful in the two extremes of age (children and elderly) (6, 7) as in sports. So, Parmigiano Reggiano cheese simultaneously contains an amount of whole casein, peptides of various lengths and free amino acids. During digestion, these three protein components have different speeds of absorption: slow, accelerated and fast, respectively, enabling modulation of the absorption of the protein substrate and a better use of the same in the diet (9). The bioactive peptides, which are released

Table 2. Amino acid composition of Parmigiano Reggiano cheese (6)

Amino acid	mg/100 g of product
glutamic acid	6030
proline	3560
leucine*	2880
lysine*	2460
aspartic acid	2260
serine	1860
tyrosine	1750
phenylalanine*	1610
valine*	1360
isoleucine*	1280
threonine*	1100
methionine*	1030
alanine	940
histidine*	920
arginine	810
glycine	700
tryptophan*	320
cysteine	200

** Essential amino acids*

Table 3. Overview of the main bioactive peptides and their physiological role (6)

Bioactive peptides	Precursor protein	Bioactivity
casomorphins	α-β-casein	Opioid agonist
α-lactorphin	α-lactalbumin	Opioid agonist and ACE-inhibitory
β-lactorphin	β-lactalbumin	Opioid agonist and ACE-inhibitory
lactoferroxins	lactoferrins	Opioid antagonist
casoxin C	κ-casein	Opioid antagonist
casoxin D	αS1-casein	Opioid antagonist
casokinins	α-β-casein	ACE-inhibitory and immunoregulatory
lactokinins	α-lactalbumin β-lactoglobulin seroalbumin	ACE-inhibitory
immunopeptides	α-β-casein α-lactalbumin β-lactoglobulin	Immunoregulatory
lactoferricin B	lactoferrin	Immunoregulatory and antimicrobial
casocidin	αs2-casein	Antimicrobial
isracidin	αs1-casein	Antimicrobial
casoplatelins	κ-casein	Antithrombotic
peptide inhibitorof thrombin	κ-casein	Antithrombotic
peptide inhibitor of thrombin	lactoferrin	Antithrombotic
casein phosphopeptides	αs1-casein αs2-casein β-casein	Bonding and transport of minerals

by the digestion of milk proteins, can exert many regulating effects: the intake of nutrients and the transport of minerals (calcium) in the intestine (phosphopeptides), the transport of amino acids, of intestinal fluid, gastrointestinal motility and the secretion of hormones (insulin, somatostatin) (beta-casomorphins), immunostimulation (fragments of alphaS1 and betacasein), anti-hypertensive effects (casokinins) (Tab. 3) (6-10). Of particular interest, moreover, is the presence of substances, with activities similar to opioids (morphine-like substances) also known as exorphins, which have an analgesic and calming effect, thereby inducing a feeling of well-being (6).

The fat content (on average 29.7%), lower than the protein content (Parmigiano Reggiano is a semi-fat cheese), is extremely precious from a nutritional standpoint (Tab. 4). The modifications of the lipid component during the aging phase release an amount of free fatty acids and facilitate their absorption. The saturated fatty acids are, for the most part, made up of short- and medium-chain fatty acids (from C4 to C10), compounds which are easily absorbable and which supply energy very rapidly, since they follow different utilisation pathways from long-chain fatty acids (8, 9). Among the compounds present in the lipid fraction of Parmigiano Reggiano cheese, it is important to highlight certain antioxidant phospholipids

Table 4. Fat partition

	% of total fat
Saturated fats	65.88*
Monounsaturated fats	31.31*
Polyunsaturated fats	2.81*

** from INRAN (Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione - National Institute Research Institute for Food and Nutrition)*

(7) such as phosphatidylserine, sphingomyelin and its catabolite sphingosine, conjugated isomers of linoleic acid (CLA), to which a great many beneficial effects are attributed as carcinogenesis inhibitors, antioxidants and modulators of the metabolism and the immune system (10).

Among the vitamins belonging to the B group, B2, B6 and B12 are found in considerable quantities, while among the liposoluble vitamins, vitamin A remains in substantial quantities (8, 9) (Tab. 1). The amount of vitamins present in Parmigiano Reggiano cheese, while varying in relation to the cheese aging process, is sufficient to cover a high percentage of the daily vitamin requirement in children and adults (Tab. 5) (6, 8, 9): a 100 g serving of Parmigiano Reggiano cheese covers over 25% of the adult's vitamin B2 requirement, 54% of the daily vitamin A requirement, and 68% of the vitamin B12 requirement according Regulation EU 1169/2011 (Tab. 5) (11) that are quite similar to 2014 LARN SINU (12), except for some differences for specific population groups, as shown in Table 5.

As far as minerals are concerned (8, 9), Parmigiano Reggiano cheese has a very high calcium content (1155 mg/100 g), which is in the form of lactate and hence, highly available also due to the presence of caseinophosphopeptides (CPP), which are released in the course of proteolytic aging by the casein in the milk and which play a key role in the stimulation of the intestinal absorption of calcium, a primary action for keeping the bones healthy. A 100 g serving of Parmigiano Reggiano cheese covers over the 100% of an adult's calcium requirement and up to 90-100% of that recommended for teenaged and 90% recommended for elderly women (12, 13).

The calcium/phosphorus ratio is extremely favourable, being around 1.7, making it possible to balance the mineral content of other protein foods, which generally contain more phosphorus than calcium. The salt content, which is not negligible (on average 1625 mg), is, in any case, around intermediate levels, between the 860-870 mg of cheeses such as provolone and taleggio, and the 1800 mg of pecorino. The considerable presence of zinc is not to be underestimated: a 100 g serving of the product supplies approximately 40% of the zinc requirement with important antioxidant effects.

The carbohydrate content of Parmigiano Reggiano cheese has been evaluated through high resolution chromatography on a variety of samples differing in terms of area of production and aging, and a lactose content ranging from "below limit of detection" to 0.39 mg/100 g of cheese was found, values that make it possible to class Parmigiano Reggiano among the "lactose-free" cheeses, on the basis of the criteria laid down by the European Commission for the formulation of infant milk (14).

The chromatographic characterisation of the oligosaccharides (highlighted in Figs. 1 and 2) confirmed also the presence in Parmigiano Reggiano cheese of

Table 5. Contribution of a 100 g intake of Parmigiano Reggiano cheese towards the main daily reference intakes referred to the Regulation EU 1169-2011 data (11) and LARN SINU data (12)

Nutrient	Adult (EU 1169-2011)	Adult (LARN-SINU) Male-Female	Adolescent (LARN-SINU) Male-Female
Protein	65%	55%-65%	60%-65%
Calcium	144%	100%-100%	90%-90%
Phosphorus	99%	100%-100%	55%-55%
Magnesium	11%	18%-18%	18%-18%
Zinc	40%	30%-45%	30%-45%
Copper	85%	95%-95%	100%-95%
Vit. B2	25%	22%-30%	22%-30%
Vit. B6	4%	4%-4%	4%-4%
Vit. B12	68%	70%-70%	75%-75%
Vit. A	54%	85%-110%	110%-110%

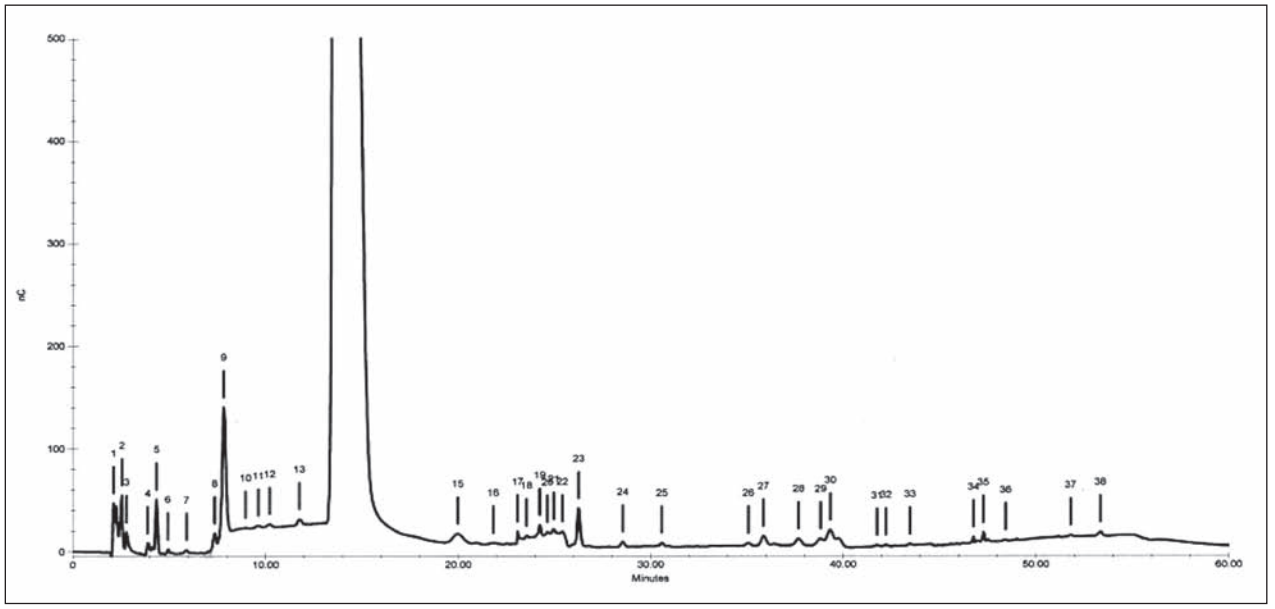

Figure 1. Chromatography of carbohydrates in cow's milk: the highest peak corresponds to the lactose whilst the other peaks to the oligosaccharides.

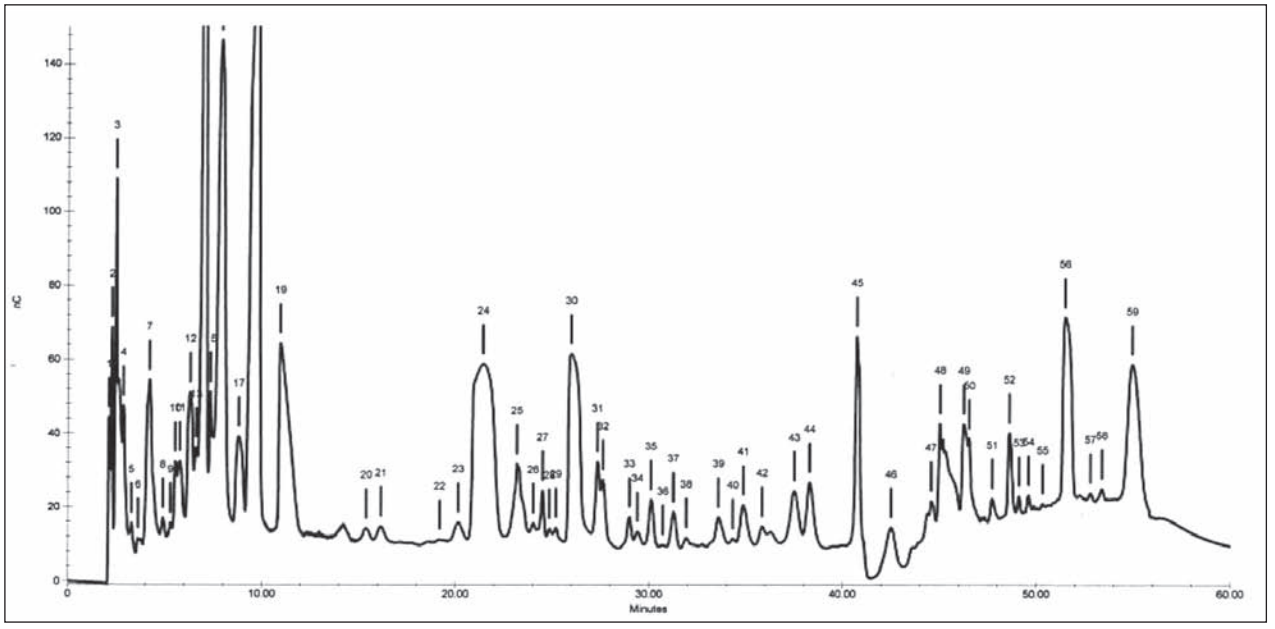

Figure 2. Chromatography of carbohydrates in Parmigiano Reggiano cheese: peak 21 corresponds to the lactose whilst the other peaks to the oligosaccharides.

numerous new oligosaccharide fractions, presumably responsible for the bifidogenic effect of the cheese, already confirmed some considerable time ago by *in vitro* studies, substantially different from those present in the base milk, so, probably, their presence in the finished product is attributable to the fermentation processes (14). This is the biochemical rationale behind the therapeutic use of Parmigiano Reggiano cheese in the treatment of enteritides (15), particularly viral forms (16), also in infants (17).

Use of Parmigiano Reggiano cheese in human nutrition

Parmigiano Reggiano cheese may be used as a topping, as an ingredient in the preparation of complex dishes, as a second course or as an ingredient in snacks (8, 9). When used as a topping in quantities of 10-15 g – the normal amount for a plate of pasta – it supplies approx. 4-5 g of protein, equivalent to the protein intake of 35 g from meat or fish. The amino acids contained in Parmigiano Reggiano cheese, moreover, "complement" the vegetable proteins which have a fairly unbalanced amino acid spectrum, because they are lacking in lysine, an essential amino acid that is particularly abundant in Parmigiano Reggiano cheese. Its use as a topping also improves the organoleptic characteristics and palatability of the dish stimulating the secretion of gastric juices and facilitating the digestive process. Parmigiano Reggiano cheese may be used in the form of slivers as a starter or dessert, or in association with other products. In this case, a portion of approximately 30 g supplies just over 120 kcal and 10-11 g of high biological value protein. The third possible use is to consume it as a meal. In this case, 50-60 g of the product supplies approximately 16 g of protein which is the same amount of protein contained in 100 g or more of fish or meat.

Given, therefore, that 50-60 g of Parmigiano Reggiano cheese is equivalent, from a nutritional standpoint, to 100 g of meat or fish, the quantity of cholesterol consumed using Parmigiano Reggiano cheese as a second course is around 40-45 mg, and therefore, less than that supplied by meat, the protein intake being equal.

The energy value is, in any case, high (402 kcal per 100 g), therefore, Parmigiano Reggiano cheese (like other cheeses) is not to be considered as a supplement to a normal meal, but a food in its own right, the daily intake of which should vary on the basis of the energy requirements of the person and a series of parameters such as, for example, age (usually a higher intake is recommended for infants/children and for the elderly), gender, weight, height, intensity and duration of physical exercise.

In any case, the huge volume of research conducted over the past ten years in the food sector has made it possible to radically correct the guidelines for a correct diet, expressly through the Food Pyramid. A comparison between the first Food Guide Pyramid formulated in the Seventies, and the latest version (18) has revealed an in-depth review of nutritional advice, among which - of particular importance - that relating to the role of milk and its derivatives. These foods have, in fact, gone up the pyramid, passing from the third to the fourth levels (foods not recommended, to be reduced) of the old Pyramid to the second of six levels (recommended foods, to be eaten every day) in the latest Pyramid (Fig. 3) (18).

The question of the relationship between Parmigiano Reggiano cheese and health forms part of the larger context of the connection with milk, dairy products and metabolic and atherosclerotic diseases, which over recent years have been subjected to a thorough review, with the discarding of preconceived and obsolete ideas. According to recent research, not only are these foods not atherogenic, as was believed in the past, but they actually seem to play a protective role. In 494 young people between the ages of 15-18 years, the cardiometabolic risk score was significantly lower in those who drank more milk (19). In a French population, a higher intake of milk and its derivatives, cheese and calcium was associated with a lower incidence at 9 years of metabolic syndrome and fasting hyperglycaemia/Type 2 diabetes: all 3 factors were associated with lower arterial diastolic pressure and a lower BMI; a higher consumption of cheese and calcium was associated with a lower increase in waist circumference and lower triglyceridemia; calcium with a lower arterial systolic pressure and lower triglyceridemia (20). Analogous results as regards dairy products and type 2 diabetes were found in a Chinese population (21). A study, presented at the recent European Congress of EASD 2014, on 26,930 Swedes between the ages of 45 and 74 years (60% women), confirms a protective role towards diabetes: 20% of the participants with high consumption of whole milk and dairy products had a 23% lower risk of Type 2 diabetes and cream, consumed daily in quantities of 30 ml, reduces this risk by 15%, while whole yoghurt reduces it by 20% (at least 180 ml/day). On the other hand, no association was observed between the consumption of light products and the risk of Type 2 diabetes. In conclusion, all

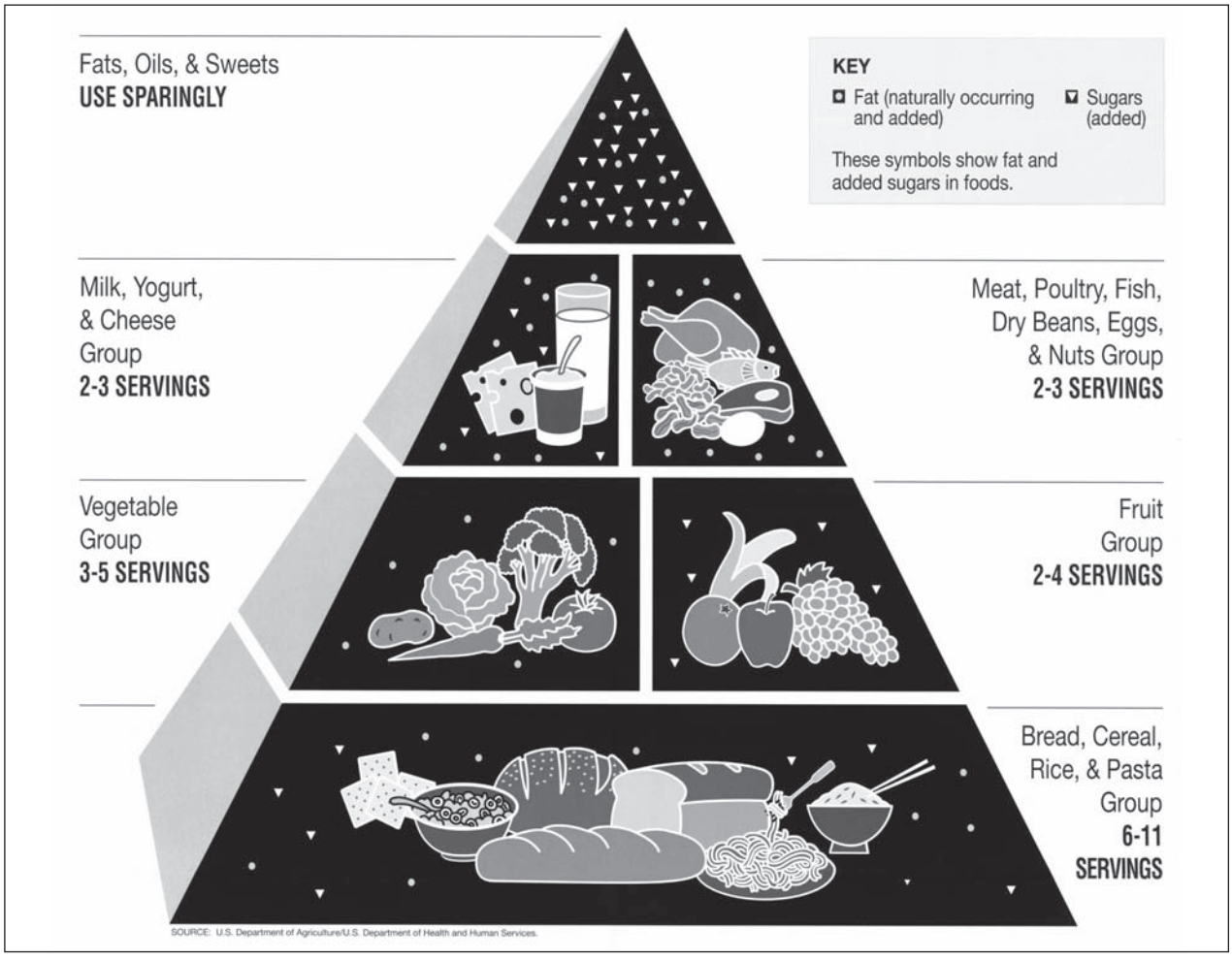

Figure 3. USDA Food Guide Piramid (18)

types of meat irrespective of their fat content, increased the risk of Type 2 diabetes, and indeed lean meats increased it more (24% against 9% in meats with a higher fat content) (22). Other research has confirmed that the consumption of milk and its derivatives is inversely associated with the risk of obesity (23, 24). The mechanism by means of which milk and its derivatives allegedly combat obesity is not very clear and has led to the formulation of a variety of hypotheses, probably due to the fact that it is difficult to identify a single factor, given the great nutritional richness of these foodstuffs. The first factor taken into consideration was the calcium content. The mechanism is allegedly linked to an alteration in the intestinal absorption of fats, with the formation of fatty acid and calcium soaps (25-28). In fact, diets enriched with milk and cheese, are alleged to have brought about a reduced increase in total and LDL blood cholesterol, notwithstanding the high content of saturated fats (identical in all 3 cases and equivalent to 60% of total lipids), due to an increase in the faecal excretion of fats (29). Another hypothesis concerns hormonal interference (oestrogens, cortisol) with calcium (30). Other studies have suggested stimulation of thermogenesis in order to uncouple oxidative phosphorylation (31). Moreover, the protein component of milk was found to be inversely related with adiposity (32-36) and, particularly the amino acids in milk are allegedly responsible for modifications in incretin secretion leading to a reduction in appetite and with an insulin response that is markedly greater with respect to the glycemic curve (37-40), to such an extent that the effect is comparable to that of sulpho-

nylureas (41). Other researchers, on the other hand, have reassessed the dangerousness of fats of animal origin, confirming that it is not saturated fats but trans fats (i.e. those of fast foods, margarine, crisps, crackers and biscuits) that have an oxidative effect, fuelling inflammatory and degenerative processes, increasing the risk of heart disease, increasing LDL and decreasing HDL cholesterol (42). The fermented products of milk contain bioactive peptides derived from the native proteins through a microbial action during the digestive process, with anti-hypertensive properties (43). All this has led researchers to conjecture that the "French paradox" might be a phenomenon due, not only to the moderate intake by the French population during meals of red wine, as traditionally believed, but also to the abundant intake of milk and its derivatives (44). Last but not least, there is thought to be an inverse relationship between diabetes and the intake of cheese and fermented products (45, 46).

The rich content of milk enzymes in Parmigiano Reggiano cheese, due to its area of production and to the specific processing techniques employed, which ensure an optimal temperatures and exclude the use of antibacterial substances, have led researchers to a better understanding of its positive effects on health. In fact, the relationship between our body and the gut microbiota represents a new scientific frontier, shifting the attention of researchers to relationships not yet fully explained, but undoubtedly important, between metabolic diseases and gut microbiota (47-50). The human intestine has been colonised by thousands of species of bacteria during the coevolution of humans and microbes; there are 3.3 million microbial genes compared to only 23,000 human genes. The majority of these bacterial genes encode enzymes and structural proteins with the power to influence immune system function, modify the epigenome of mammals and change the regulation of the metabolism. It is this very alteration in the gut microbiota that is thought to lead to chronic and immunological diseases, cancer of the colon, gastric ulcers, cardiovascular diseases, intestinal diseases and especially obesity (51, 52). The products of the intestinal microbes, such as butyrate, can induce positive metabolic effects by boosting mitochondrial activity, preventing metabolic endotoxemia and activating intestinal gluconeogenesis through different methods of gene expression and hormonal regulation (53). Some of the recent research studies are particularly interesting: the weekly consumption of three portions of yoghurt brings about an increase in weight which is more than halved compared to the consumption of a half portion (54); the microbiota plays a role in childhood obesity (55). A microbiota transplant from the intestine of monozygotic twins, one brother being thin and the other obese, brings about different metabolic consequences in the receivers of the bacterial flora of the thin twins, which protects against obesity (56); a family of bacteria (Christensenellaceae), which has been identified very recently, is much more present in thin people and rare in obese people and the administration to a group of mice of colonies of bacteria from this family, showed that the mice treated in this way acquired less weight in comparison to the mice in the control group which were subjected to the same diet but not treated (57).

The use of Parmigiano Reggiano cheese in special diets

Thanks to its excellent nutritional qualities and especially to its digestibility and high protein and calcium content, Parmigiano Reggiano cheese appears to be a valuable food for all ages but particularly during the age of development (6), pregnancy, old age as well as during convalescence subsequent to debilitating clinical conditions (8, 9). Its almost total absence of carbohydrates, its richness in highly digestible protein substrates, in trace elements, trace nutrients and biofunctional peptides, together with its excellent lipid profile, make it a "naturally" functional food in the real sense of the term (7), ideal for use in numerous metabolic disorders such as obesity, diabetes, hypertension (taking care to monitor the daily intake of NaCl) and dyslipidaemias, disorders for which ever increasing evidence confirms the beneficial effect of the regular consumption of dairy products, also in terms of reduced incidence of cardiovascular complications (58-64).

As regards nutrition applied to sport, Parmigiano Reggiano cheese can be an interesting resource, both during the training phase and during the post-exercise recovery phase, as an important "recovery meal" i.e. consisting of that mixture of nutrients which, thanks

to their properties, can rapidly activate muscle recovery mechanisms. In the hours after fairly heavy physical exercise there is a "metabolic window" thanks to which the intake of carbohydrates with a high glycaemic index (GI) and proteins makes it possible to improve the glycogen re-synthesis process and facilitate protein synthesis. Although the best proteins are found in the whey, the casein can also stimulate protein synthesis and for a very long time (1 hour for the whey against 5-7 hours for the casein). If then, in addition to whole proteins and to peptones or peptides, recovery meals also contain FAAs (Free Amino Acids, as per aged Parmigiano Reggiano cheese), the effect on protein synthesis is particularly accentuated. Even more so if BCAAs (Branched Chain Amino Acids) are also available: these have the special property of being absorbed directly by the muscles and used, both for the construction of new proteins as well as a source of energy. Supplementation with BCAAs and essential amino acids has been under investigation for some time now. Their effects have been studied first and foremost in the post-exercise phase in which maximum priority is given to the stimulus of the mechanisms responsible for repairing the damaged muscle cells and restoring the integrity of the muscle protein chains. A substantial volume of scientific papers have demonstrated how an intake of essential amino acids, BCAAs, and leucine in particular, in the initial post-exercise phases (within one hour) can improve and substantially quicken muscle recovery processes, reducing protein degradation phenomena and increasing protein synthesis.

The considerable presence of these amino acids in Parmigiano Reggiano cheese makes this product ideal as a snack for post-exercise recovery, as well as being an ideal food for consumption during normal meals as a contribution to the overall protein requirement needed for the type of physical energy involved.

Another interesting fact is that, along with post-exercise metabolic recovery, the body also has to restore its sodium/water balance, given the losses it has suffered during exercise, both through sweating and even through breathing. It is important to remember that sweat causes the loss of large quantities of sodium. Therefore, imagining a recovery meal that provides water, sodium, carbohydrates and protein (particularly essential AAs), the combination of water, bread (or other high GI carbohydrates) and Parmigiano Reggiano cheese (proteins + essential AAs + sodium) can offer a simple and appetising solution. In general, the use of dairy products in sport is supported by recent clinical observations (58) and – with particular reference to Parmigiano Reggiano cheese – by field studies conducted on various types of sport, including those practised in extreme environmental conditions, such as mountain sports (65, 66).

As regards allergies to egg proteins, often associated in early infancy with cow's milk protein allergies, it is important to remember that people who are allergic to eggs can usually consume milk and its derivatives, provided that they do not contain lysozyme (67-71). From this perspective, the consumption of Parmigiano Reggiano cheese cheese is not a problem as it is totally free from lysozyme, the egg protein which is, on the other hand, present in numerous other cheeses, having been used in place of formaldehyde over the course of recent years as an anti-fermentation agent (72). A recent study conducted on a paediatric population of 70 children allergic to cow's milk proteins demonstrated that 58% of the patients were tolerant to the consumption of aged Parmigiano Reggiano cheese (24-40 months), probably thanks to the digestion of the casein, which takes place during the cheese's aging process. The absence of β-lactoglobulin-specific IgE appears to be an efficient tolerance marker (73). On this basis, Berni Canani et al. suggested the use of Parmigiano Reggiano cheese as an effective immunonutrient, i.e. as a food with the power to modulate the immune system function, either directly or by exerting an action on the composition and function of the gut microbiota (74): it is, in fact, possible to stimulate a more rapid acquisition of immunological tolerance in children allergic to cow's milk protein by administering extensive hydrolysate of casein containing the probiotic *L. rhamnosus* GG (LGG) (75). This effect seems induced by the combination of a direct immunomodulating action exerted by peptides deriving from the beta-casein and the action of the LGG (76), which the same Authors have demonstrated to be able to regulate the composition and functions of the microbiota in children affected by cow's milk allergy and regulate directly some immunological mechanisms involved in the pathogenesis of this condition (75). At the same time, other groups have dem-

onstrated the likelihood that a high number of people affected by IgE-mediated cow's milk allergy can tolerate foods containing cow's milk proteins hydrolysed through various techniques (77). Moreover, it has been hypothesised that these strategies might facilitate the acquisition of immunological tolerance in patients with cow's milk allergy (78). One of these foods is Parmigiano Reggiano cheese, which in the course of its aging process is subject to extensive hydrolysis of the cow's milk proteins with degradation of its caseins and production of a high quantity of peptides and free amino acids (79). At the same time, in samples aged for longer periods, there is an appreciable quantity of *L. rhamnosus* (80). A prospective, multicentre case-control study lasting 12 months is currently underway. Its aim is to evaluate the efficacy of a regular Parmigiano Reggiano cheese intake as a nutritional strategy for stimulating the acquisition of immunological tolerance in children allergic to cow's milk (81).

As in the pediatric field, the studies conducted at the University of Modena by professor O. Olivi in the '70s on the utility, for the treatment of enteric problems in neonates, of a not yet identified "bifidogenic factor" existing in Parmigiano Reggiano cheese, have been continued also in recent years (16). Since it is well-known that, as Parmigiano Reggiano cheese ages, proteolytic processes take place, due to which a variety of peptides with positive biofunctional activities are formed, it has been hypothesised that these peptides might exert an action on the intestine, modulating the composition of the commensal microbiota. Prebiotics are food supplements that stimulate growth and the bifidobacterium and lactobacillus metabolism: although some hydrolysed proteins have been proven to be bifidogenic, most of the prebiotics used are fibres and oligo- and polysaccharide carbohydrates, while the prebiotic/bifidogenic potential of the peptides contained in Parmigiano Reggiano cheese has not yet been explored. Recently, it was suggested that the development of bifidobacterium and lactobacillus stimulated by these prebiotics might have positive effects on the treatment of paediatric enteropathies: this theory is currently under study both *in vitro* and *in vivo* (82) with the aim of investigating the previously documented nutritional aspects of Parmigiano Reggiano cheese, providing scientific evidence in terms of the bifidogenic and/or prebiotic effect of the peptides that form from the hydrolysis of the milk proteins during the aging of Parmigiano Reggiano cheese.

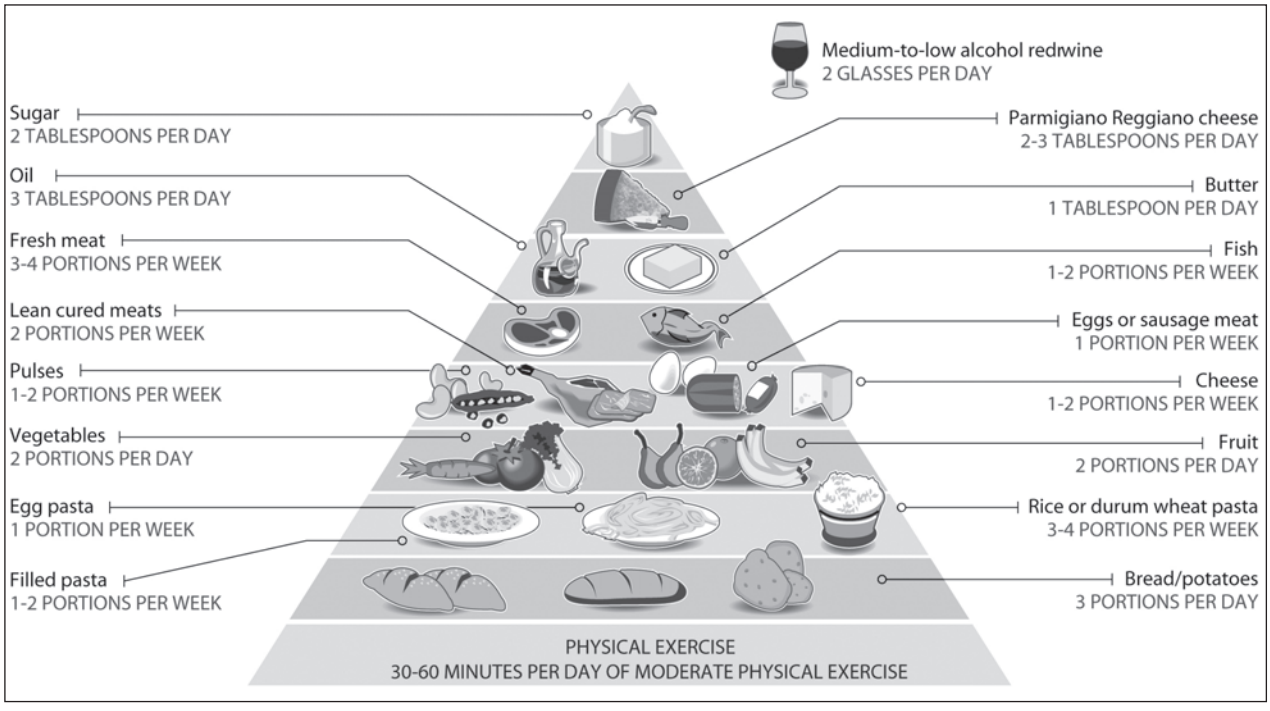

Figure 4. The Pyramid diet (83)

The absence of lactose means that it can be administered to patients with lactase deficiency, for whom it could be used as an element to "re-educate" them to consume milk or dairy products.

Conclusions

Nutrition should not be considered as a mere replenishment of nutrients because it also involves psycho-emotional, socio-cultural, relational and symbolic aspects. This multi-disciplinary approach to nutritional science seems to be the most effective in promoting healthy lifestyles, possibly also thanks to the use of educational/information models that are well-known in literature, such as the classic food pyramids, for which versions deeply-rooted in the local culinary tradition of the various Italian regions have recently been proposed (Fig. 4) (83).

Parmigiano Reggiano cheese is perhaps the most famous PDO product in the world and unquestionably one of the most important ingredients of the Italian culinary tradition; but although it has eight centuries of history behind it, it is nonetheless totally modern from a nutritional standpoint, able to fit into the most recent dietary models, also in the light of ever newer evidence capable of clarifying scientifically why Parmigiano Reggiano cheese has always been considered a "functional" food, even before this term was actually coined.

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