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Advanced Glycation End Products (AGEs) in Food: Focusing on Mediterranean Pasta

Abate G[1], **Delbarba A**[2], **Marziano M**[1], **Memo M**[1] **and Uberti D**[1,2*]

[1]*Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy.*

[2]*Diadem Ltd, Spin Off of Brescia University, Brescia, Italy.*

[*]**Corresponding author:** Uberti D, Department of Molecular and Translational Medicine, University of Brescia, 25123 Brescia, Italy, Tel: +39-0303717509; E-mail: daniela.uberti@unibs.it

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Abstract

Advanced glycation end products, also known as glycotoxins, are a diverse group of highly oxidant compounds with pathogenic significance in aged-chronic disease, including diabetes, cardiovascular disease and neurodegenerative disease. They are produced physiologically in the body when reducing sugar binds to a free amino acid group of macromolecules. Thus conditions such as hyperglycemia and/or oxidative stress can favor AGE product formation, contributing to ageing processes and the exacerbation of pathological states. Beside endogenous AGEs, dietary AGE intake contributes significantly to the body AGE pool. It assumes that if dietary AGE intake gets lower, any chronic disease, such as diabetes and cardiovascular disease can be ameliorated, and even cured. For this reason, recently great attention has been made on the identification and quantification of AGE products in the consumed foods. Here we reviewed some knowledge, found in literature, concerning the formation of AGEs in food, their gastrointestinal absorption, and their toxic effects. In addition original data on AGE content in the Mediterranean pasta was discussed in relation to their production processes and cooking time.

Keywords: Dietary advanced glycation end products; Amadori products; Maillard reaction; Mediterranean pasta; Oxidative stress; Inflammation; Age-related disease

Abbreviations:

AGEs: Advanced Glycation End products; dAGEs: Dietary Advanced Glycation End products; FruLys: lactulosyllysine; GO: Glyoxal; MGO: MetylGlyoxal; CL: Carboxy-lysine; CML: N-carboxymethyllysine; ECM: Extracellular Matrix; ROS: Reactive Oxygen Species.

Introduction

Advanced glycation end products (AGEs) are a heterogeneous group of compounds formed by Maillard chemical reaction, which refers to a non-enzymatic glycation of free amino groups of proteins, lipids or nucleic acids by reducing sugars and reactive aldehydes [1]. In biological system the process of AGE formation begins under hyperglycemic and/or oxidative stress conditions, followed by the conversion of reversible formed Schiff-base adducted to covalently bound Amadori rearrangement products. Then Amadori products can undergo further chemical reactions that result in the AGE formation [2]. AGEs are formed continuously in the body, as a part of normal metabolism, but if excessively high, they reach tissue and circulation and can become pathological [3].

Their toxic effects are essentially related to their ability to promote oxidative stress and inflammation by binding to cell surface receptors or cross-linking with body proteins, altering their structure and function [3,4].

AGEs also exist in foods, and are named dietary AGEs (dAGEs). dAGEs can be already present in raw materials: different types of culturing, breeding and technical manipulation can affect their formation. Furthermore food processing, storage and cooking can contribute to increase dAGE content in final products [5-10].

Therefore, diet is a large source of dAGEs. Recently, different studies on mice and human have demonstrated that dAGEs can be absorbed at intestinal level, and be potentially toxic [1,3,4].

The notion that low-dAGE intake reduced markers of oxidative stress and inflammation, not only in patients with diabetes [11] or kidney disease [12,13], but also in healthy subjects [14], suggested that avoidance of dAGE-rich food could help in ameliorate chronic pathological conditions and in maintaining the healthy ageing status.

Here we reviewed some knowledge, found in literature, concerning the formation of AGEs in food, their gastrointestinal absorption, and the mechanisms at the base of their toxic effects. In addition original data on dAGE content in the Mediterranean pasta were discussed in relation to production processes and cooking times.

Dietary AGEs

It has been well known that factors affecting AGE formation in foods include their composition, temperature, exposure to air when, for example the natural protective covering is damaged, humidity, pH, and methods and duration of cooking [1,15,16]. Usually, foods high in lipid and protein content exhibit the highest dAGE levels. For example, fat and meat contain 30-and 12-fold higher AGE content than carbohydrate meal respectively [16]. Temperature and method of cooking appear to be more critical to AGE formation than cooking time. This is evidenced by the higher dAGE values of samples grilled at

temperatures of 230°C for shorter cooking times when compared to samples boiled in liquid media at 100°C for longer periods [1,16].

Clearly, meat and meat-derived products, processed at high, dry heat such as in broiling, grilling, frying, and roasting are major sources of dAGEs. Alternative cooking methods, such as boiling and stewing, allow daily dAGE ingestion to be reduced by up to 50%, keeping the same primary nutrients [17].

There are many strategies to reduce the dAGE intake. Some herbs, condiments and spices, have been reported to have intrinsic anti-glycation activity [6,18]. For example, pre-treatment of meats with lemon, vinegar or with any acidic marinade before cooking has a significant effect in preventing the excessive increase of dAGE content. Dearlove and colleagues [19] demonstrated that polyphenols found in culinary herbs like sage, marjoram, tarragon, and rosemary are potent inhibitors of fructose-mediated protein glycation. Spice extracts, such as cloves, ground Jamaican allspice, and cinnamon, were also found to be glycation inhibitors, even stronger than herb extracts [19]. Since foods mainly composed of carbohydrates (e.g., starches, fruits, vegetables, and milk) contain the lowest AGE concentrations, another strategy to reduce dAGE intake consists in implementing the use of these healthy foods instead to eat full-fat cheeses, meats, and highly processed foods.

It is well established that Maillard reactions modify the nutritional value of food, with loss of availability of essential amino acids, vitamin C as well as important metals such as copper, zinc and iron. In addition these reactions produce toxic final products affecting human health.

The cascade of reactions that begins with glycosylation at amino groups of Lysine or other amino acids, (arginine, histamine, tryptophan and cysteine) gives rise to a plethora of advanced end products, some of which have been well investigated in food. Pentosidine that forms by protein–bound crosslink during advanced stages of Maillard reaction occurs usually during heating and storage [10]. Glyoxal (GO) and MetylGlyoxal (MGO) work as precursors for more complex AGE crosslinks, such as pentosidine and glucosepane, and are well examined for example in bakery products and edible oil [7]. Carboxy-lysine (CL) and N-carboxymethyllysine (CML) are produced by multiple pathways, for example CML may be formed by oxidative cleavage of the Amadori product or by reaction with GO with Lysine residues [9]. CML is also formed during lipid peroxidation reactions and during auto-oxidation of ascorbate. CML adducts are accumulated over time during food production processes and this is considered a potential hazard to human health. Lipeng et al. [9] suggested that preventing the formation of CML through the addition of inhibitors or changing food processing conditions, could contribute in controlling food-derived AGEs. Semba et al. showed that the majority of urinary CML levels derived from food, even if CML can also be formed endogenously [20].

In the tentative to define a high or low AGE diet different authors measured AGE content in usual daily food intake. The average dietary AGE intake in a cohort of healthy adults from New York City area was found to be nearly 15000 KU/day [21]. In on other study, Goldberg et al. [1] analyzed 3-day food record from 34 healthy individuals and 40 type 2 diabetic patients. The mean daily AGE intake was around 16000 KU/day for healthy individuals and 18000 KU/day for diabetic patients. In these latter patients the increased AGE intake was principally due to the cooking methods, which included broiled, fried, grilled and roasted food.

dAGEs intestinal absorption

The potential biological role of exogenous AGEs has been ignored for long time because of the assumption that they undergo negligible gastrointestinal absorption [22]. Recently it has become clear that dAGEs contribute significantly to the body AGE pool. For the structural heterogeneity and the wide range of molecular weights of dAGEs, it is difficult to summarize their pharmacokinetics. Up today, limited studies have been conducted on few and selective compounds. For example fructoselysine, and lactulosyllysine (FruLys), mainly present in heated milk, are adsorbed passively through the intestinal mucosa [8,23]. Parts of them are degraded by microbiota, and a quote of 10% reaches the circulation, and they are mainly distributed in liver and muscle cells [8]. Also dietary ingested acrylamide is easily absorbed through the intestine tract, where it is rapidly metabolized and then excreted. However acrylamide and its metabolites can accumulate in the body when bounded to proteins in nervous system tissues or to hemoglobin in blood [24]. CML is widely measured as an index of AGEs in foods, although it can be also formed endogenously. Liardon et al. [25] assumed that the dietary CML is the main source of the urinary CML. Nearly its 10% is absorbed in the gastrointestinal tract and is delivered to liver and to other tissues. One third of this quote is excreted in the urine, and the remaining is accumulated in the body, leading to age-related damage [20]. Interestingly very recently Geissler et al. [26] showed that pyrraline, generated during the reaction of 3-deoxyglucosulose with lysine residues, was transported by H+–peptide co-transporter PEPT1 into intestinal cells. Also FruLys and CML have been demonstrated to bind to PEPT1, but with an inhibitory action [23].

Recent studies on human subjects have shown a significant increase in plasma AGE levels within two hours following the oral administration of a single AGE-rich meal [22]. Positive correlation between dAGE content and serum/tissue AGE levels have been also confirmed by several animal study [17,27,28]. For example Peppa et al. [29] to assess the role of dAGEs on type 1 diabetes, exposed the genetically susceptible NOD mice to a high-AGE diet and to a nutritionally similar diet with approximate fivefold-lower levels of CML and MG and demonstrated that after 44 weeks of treatment, NOD mice fed with Low-AGE diet showed almost half of serum AGE levels respect to High-AGE diet fed NOD mice. Moreover, Urribari et al. [30] demonstrated that dAGEs were correlated to the excess serum AGE levels found in diabetics and renal failure patients, contributing markedly to the total AGE pool in the body [11-13].

Circulating AGE levels reflect the equilibrium between exogenous/endogenous AGE accumulation, their degradation and renal elimination. At tissue level, macrophages and other cellular systems endocytose and degrade AGEs via both receptor or non-receptor pathways, resulting in the formation of low molecular weight AGE peptides [31-34]. These peptides undergo a variable degree of reabsorption in the proximal nephron, while the rest is excreted in the urine. Therefore, effective elimination is dependent on normal renal function [31].

Then, at cellular level, there are intracellular protective systems which also limit the accumulation of reactive AGE derivatives. For instance, MGO is first converted by glyoxalase-I to S-D-lactoylglutathione and then to D-lactate by glyoxalase-II [35].

The above homeostatic systems, however, can be overwhelmed in high AGE conditions such as diabetes and renal failure, especially when combined with increased dAGE intake [34].

Biological effects of AGEs

AGEs can exert their effects essentially by two different mechanisms. One is mediated by the interaction with specific receptors, and the other one is attributable to the direct cross-link to proteins, altering their structure and functions (Figure 1).

Among the AGE receptors the most studied is RAGE [36]. RAGE, a single trans-membrane multi-ligand receptor, belongs to the immunoglobulin superfamily, whose members include AGE-R, SR-A (macrophage scavenger receptor types I and II), and SR- B (SR-B type I and CD36) [3,37].

RAGE receptors are physiologically mainly expressed on vascular, endothelial and smooth muscle cells and on monocyte/macrophage membranes [36,37]. The ligands of RAGE a part from AGEs and CML include also amyloid-β peptide, members of the S100 protein family, proteins of the high mobility group box-1 (HMGB1) and prions [38].

The interaction of RAGE receptors with AGEs induced the activation of different intracellular cascades, which involve Nuclear Factor-kappa Beta (NF-κB) pathway and inflammatory mediators like the tumor necrosis factor-α (TNF-α), interleukin-6 and C-reactive protein (CRP) [39]. The interaction of AGEs with RAGE receptors can also induce the gene expressions of leptin and its receptor that in turn activates intracellular signaling such as JAK2 and PI3K pathways. All these pathways lead to a pro- inflammatory status and to an increased oxidative stress.

Differently to RAGE, two receptors AGE-R1 and R3, belonged to immunoglobulin superfamily, once bound to AGEs activate protective pathways, involved in preventing ROS formation and activating AGE degradation and urinary excretion [3,39].

Recently Cai et al. [40] showed that in mice fed with calorie-restricted diet, AGE-R1 receptor expression enhanced, while the level of RAGE was unchanged, thus resulting in a high AGE-R1/RAGE ratio. In contrast, RAGE levels were enhanced in mice fed with high-AGE diets and the AGE-R1/RAGE ratio was decreased with a corresponding increase in oxidative stress. Tang et al. [41] also demonstrated that AGEs could be directly involved in the divergent regulation of gene expression of RAGE and AGE-R1 in hepatic stellate cells, whose activation is fundamental for the development of hepatic fibrosis.

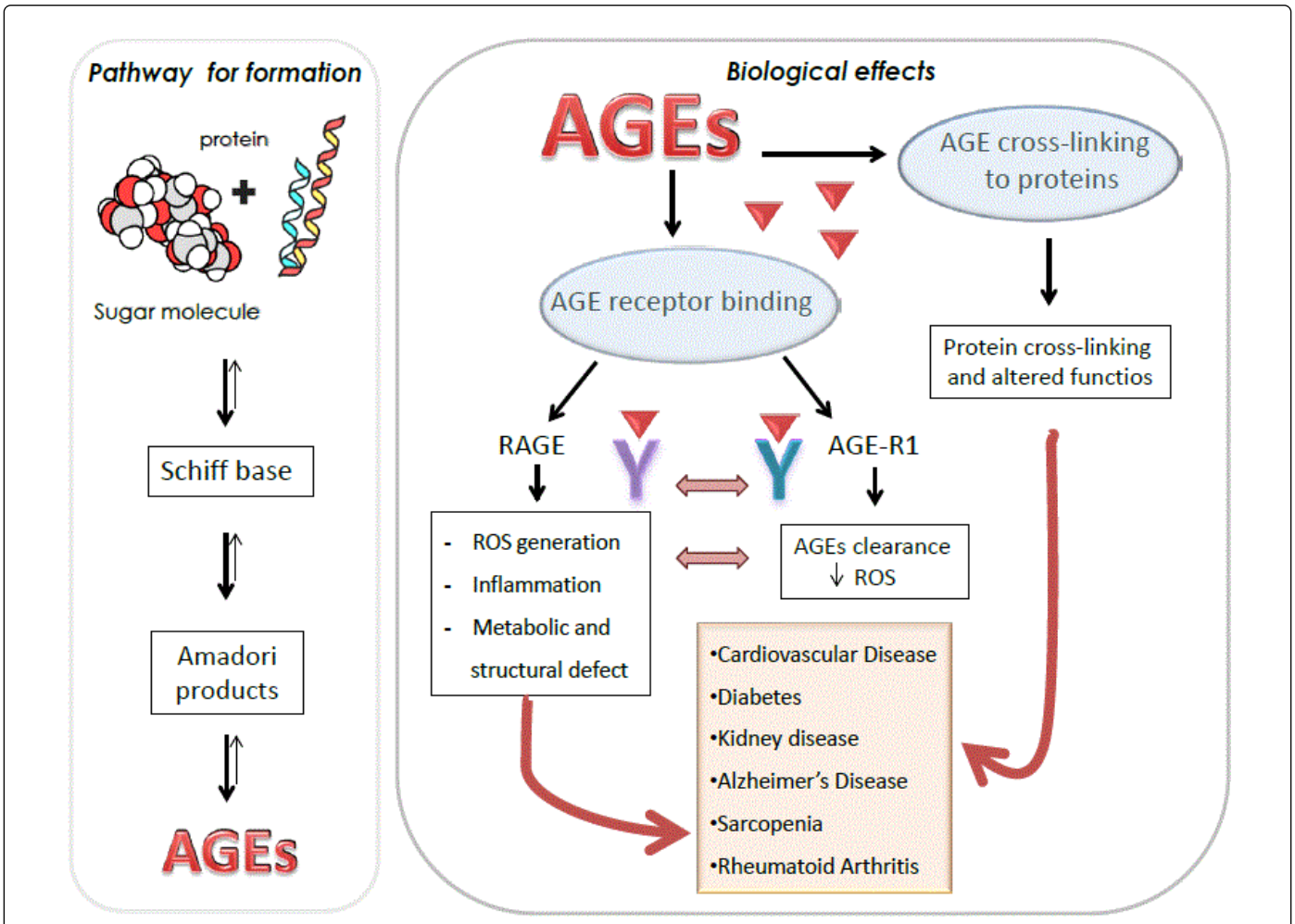

Figure 1: Schematic representation of AGEs formation and of their biological effects.

They hypothesized a vicious circle in which AGE-RAGE interactions activate the leptin intracellular signaling which leads to an increase of oxidative stress and that in turn facilitates the divergent regulation of gene expression of RAGE instead of AGE-R1.

Interestingly, they also showed that bioactive nutrients such as Curcumin could prevent AGE-mediated toxic effects by interrupting leptin signaling and regulating gene expression of RAGE and AGE-R1. This suggests that AGE effects can be determined by the delicate balance between the expression of different antithetical receptors, influenced not only by genetic or pathological conditions but also by eating habits.

A very strong expression of RAGE and high levels of AGEs have been found in inflammatory conditions including osteoarthritis [42], and rheumatoid diseases such as rheumatoid arthritis and fibromyalgia [43]. Such increase affects especially tissues with a slow turnover, including tendons, bones, cartilage, and skin and could lead to the tissue stiffness and fragility in these structures [44].

Moreover, a strong association between RAGE-expression and AGE levels and the severity of Alzheimer's disease has been proposed by different authors [44-47].

The toxic effects of endogenous and exogenous AGEs result also from structural and functional alterations in plasma and extracellular matrix (ECM) proteins, in particular, from crosslinking of proteins (Figure 1). For example glucose pane is the most important cross-link products formed with ECM, known in human skin [48], and the glycated-myosin mainly affects myosin velocity and directionality [49]. Furthermore, AGE accumulation in collagen leads to changes in the biochemical and structural property of the components of the basement membrane affecting for example its elasticity, ionic charge, and thickness [50]. Accordingly, has been postulated that accumulation of AGE–crosslinking formed with vessel-wall collagen and basement membrane proteins, can contribute to vascular dysfunction [4,5]. In addition, AGE deposits have been found in atherosclerotic plaques and myocardium of patients with diabetes [2,52]. Immunohistochemical studies using anti-AGE antibodies have revealed the presence of AGE-modified proteins in several tissues under pathological conditions, including the kidneys of patients with diabetic nephropathy [52,53], chronic renal failure [54], and amyloid fibroids in hemodialysis-related amyloidosis [55].

All these findings stressed that AGEs can be considered as previously unrecognized dietary risk factors and important pathogenic mediators, involved in many age-related disorders. The discovery of natural AGE inhibitors and the adoption of an AGE-restricted diet could be a further new challenge in order to promote a healthy status.

Mediterranean pasta

Pasta is a highly popular cereal-based food produced worldwide because of its taste, convenience of use, ease of cooking and storage properties. Its consumption is recommended by Mediterranean dietary guidelines.

Pasta is prevalently constituted of carbohydrates and proteins. Its quality depends by different factors [56]. Evaluation of good pasta making starts from grain, but also the production processes can influence the quality of the final product.

For example moisture, starch content and protein percentage influence the features of the wheat for good pasta. Durum wheat, such as triticum turgidum, one of the hardest varieties of wheat, is the best to use for pasta-making because of its good cooking performance and stability to overcooking. The composition and the amount of protein content influence the pasta quality.

Protein content of durum wheat is characterized by two fractions soluble in water and in salt solution (albumins and globulins respectively), and two quotes extractable in aqueous ethanol solution or in dilute acid (gliadins and glutenins respectively) [56,57]. Low protein level confers low firmness, while high-protein durum wheat reduces cooking loss and improves texture with better performance in overcooking. Also the structure and amylose content of starch granules were found to influence pasta features.

On the other hand, among the different steps of pasta processing cycle, drying is crucial for the quality of end product. The traditional dry methods use low temperature from 45° to 60°C for a long period of time, until 60 h. While, the on large scale production increases by double the temperature (reaching 90-100°C), shortening the drying process [58]. This technology brings benefit in term of productivity, cost, reliability, and reduction of microbial contamination. On the other hand, high temperature favors Maillard reactions with formation of stable Amadori compounds, which further evolved into stable AGE products. AGE product formation in pasta can be also favored by higher protein content and lower moisture in grain.

Thus, the AGE products can vary a lot depending by types of pasta (i.e., high or low protein amount, moisture, etc.) as well as by brand (i.e., production processes). Since especially CML has been used to commonly classify foods as an indicator of AGE burden in numerous animals and human studies, we measured CML content in 4 different pasta brands and in 3 different types of pasta: wheat, whole wheat and egg noodles. In details, different pasta samples were homogenized, dissolved in phosphate buffer saline and then tested for CML amount with an enzymatic-linked immuoassay based on monoclonal anti-CML 4G9 antibody [6].

Results were expressed as kilo units (KU)/100 g of pasta. The majority of different brands of the different types of pasta showed a similar AGEs content (Table 1). These values are in line with those reported in the dietary AGE database published by Uribbari et al. [6].

Samples	Wheat	Whole Wheat	Egg Noodles
	CML KU/100g		
Brand 1	123 ± 10,6	185 ± 11,2	125 ± 6,8
Brand 2	69 ± 5,3 **		72 ± 5,2**
Brand 3	65 ± 3,8**		68 ± 3,4**
Brand 4	128 ± 8,4		
Brand 5		152 ± 7,9	
Brand 6		154 ± 12,7	
Brand 7		230 ± 15,3	
Brand 8			123 ± 7,5

Table1: CML content expressed as KU/100g of raw pasta in wheat, whole wheat and egg noodles. Results were given as mean ± SEM values. Statistical significance of differences was determined by one-way ANOVA, followed by the Bonferroni test. **p<0,001 brand 2 and 3 vs the other ones.

However, there were two exceptions for two Italian brands (Table 1); whose wheat pasta and egg noodles expressed lower levels of CML content. Interestingly these products were dried at low temperature

with a traditional method as reported by the manufacturer in the packaging. Furthermore, the AGE content in pasta obtained from whole unrefined grains was basically higher in comparison with wheat and egg noodles (Table 1).

This is probably due because the bran and the germ of grains contain the highest protein to carbohydrate ratio. In addition cooking time can significantly modify the AGE content in pasta. We conducted a series of experiments where different types of pasta were cooked for 9-11 min (depending on the period of time reported on the package to obtain an "al dente" palatability) or for additional 30% of the advised cooking times (overcooking). As reported in Figure 2, cooking significantly increased the amount of CML in all examined types of pasta in comparison with respective raw samples.

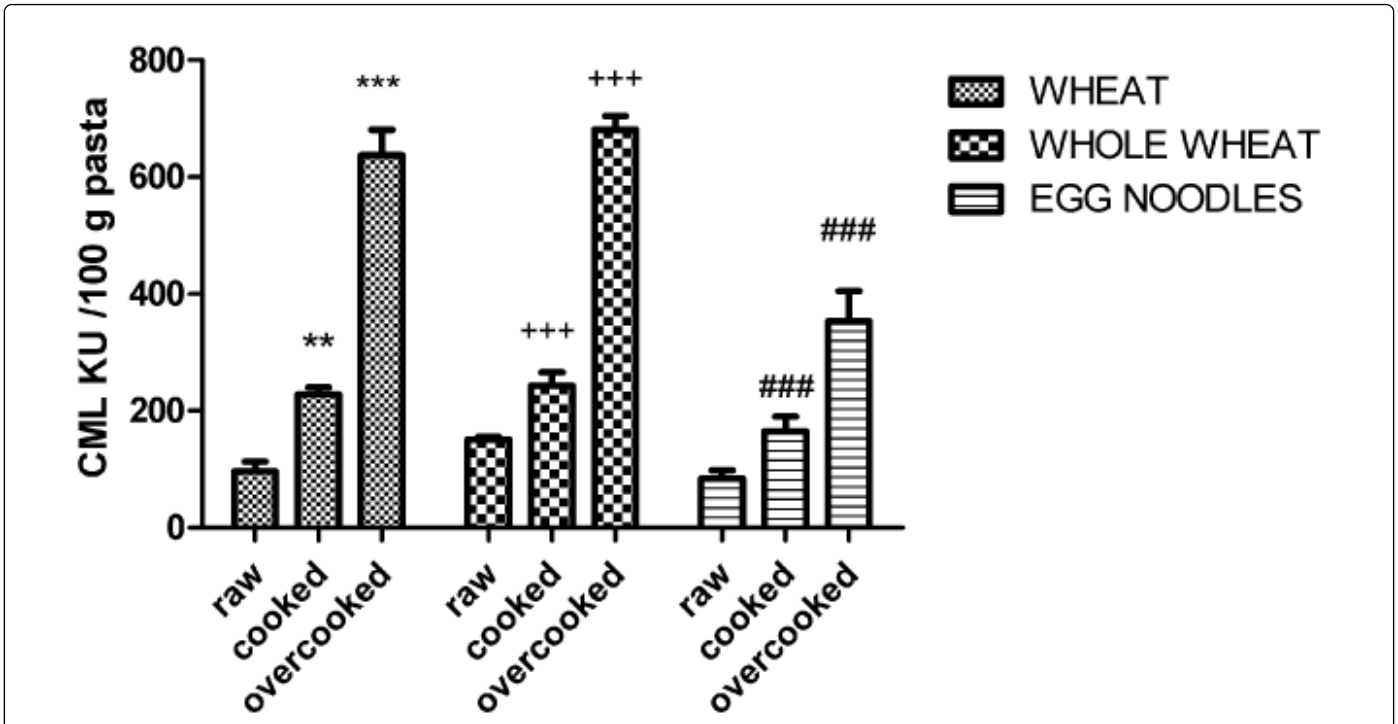

Figure 2: CML content analyzed in 3 different types of pasta at raw, cooked or overcooked. CML content was measured in 3 different types of pasta at raw, cooked or overcooked. Results were expressed as mean ± S.E.M values of 4 different pasta brands of three different experiments. Statistical significance of differences was determined by one-way ANOVA, followed by the Bonferroni test. **p<0,001 cooked and ***p<0, 0001 overcooked wheat vs raw wheat; +++p<0,0001 cooked and +++p<0,0001 overcooked whole wheat vs raw whole wheat; ###p<0,0001 cooked and ###p<0,0001 overcooked egg noodles vs raw egg noodles.

A dramatically increased of CML content was further observed with overcooking products. Among the overcooking products, egg noodles reported the lowest values of AGEs content in comparison with wheat and whole-wheat products, suggesting that the presence of egg nutrients might partially prevent AGE formation.

Especially fat soluble vitamin E and some minerals such as selenium present in eggs may exert an antioxidant effect, thus preventing oxidative degradation of sugar leading to AGEs formation. At this regards, it has been documented that antioxidant nutrient added to the base food can prevent the auto-oxidative pathways of AGE formation [52,59,60].

Different surveys, analyzing food records from healthy individuals, reported that the mean daily AGE intake was around 15,000 ± 5000 KU. These data could tentatively be used to define a high and low-AGE diet. Assuming that the mean consume of pasta per-capita in Italy is nearly 80 g/day; pasta can effectively be considered a low-AGE food. On the other hand cooking time can significantly modify its AGE content.

Some experiments conducted in our laboratory tried to highlight the biological relevance of pasta AGE content in function of cooking time, investigating its inflammatory and pro-oxidant effects. Initially to mimic the conditions at which food is exposed during the digestion, pasta extracts were incubated sequentially with different enzymes following the oral, then the gastric and finally the small intestinal digestion accordingly to Minekus et al. [61].

Human epithelial colorectal adenocarcinoma CACO2 cells were treated once a day for 3 consecutively days with different amount of digested protein extracts obtained from cooked or overcooked pasta. On the last day, cell cultures were processed for measuring IL-8 release and ROS production in conditioned medium and in cells respectively.

Cooked pasta did not modify IL-8 release and ROS production in cells at any examined concentration (Figure 3). Differently, when pasta was over-cooked its digested protein extracts induced an increase of ROS production and activated immune response with release of IL-8 at higher amounts (Figure 3).

Such effects were not of course comparable with those induced by LPS, but anyway are significant to note, taking into consideration the

repeated exposure that may induce potentially more toxic effects derived by AGEs accumulation.

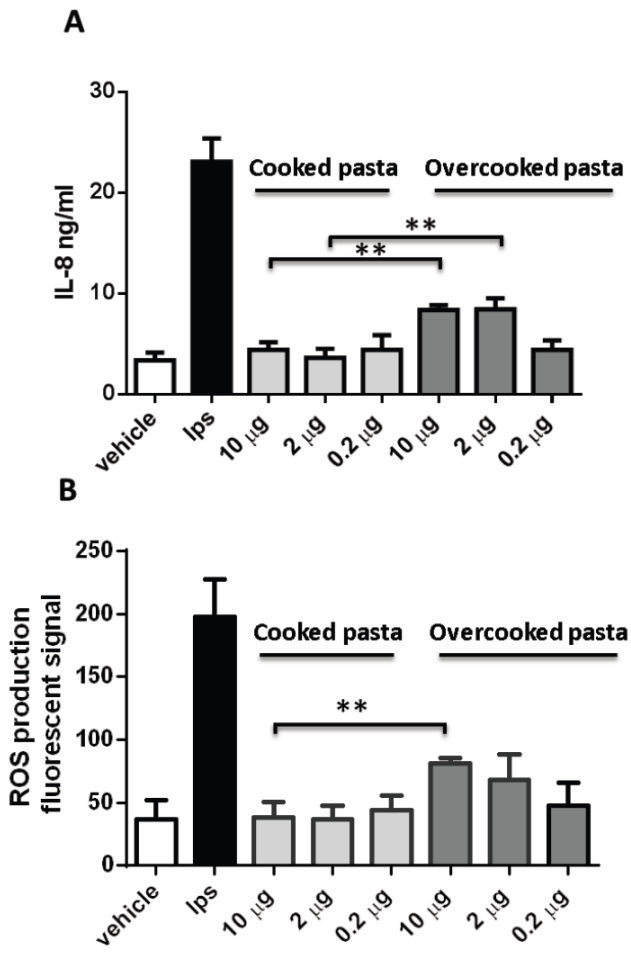

Figure 3: Effects of cooked and overcooked digested pasta extracts on IL-8 release and ROS production in CACO2 cells. Different amount of digested pasta extracts were added to confluent CACO2 cells ones a day for 3 days at different amounts. IL-8 release (A) and ROS production (B) were measured in the cells and conditioned media respectively. LPS was chosen as positive control, while digested solution without pasta protein extracts (vehicle) was the negative one. Statistical analysis was performed with one ANOVA test followed by Bonferroni test. IL-8 release: **p<0,001 10 µg and 2 µg cooked vs 10 µg and 2 µg overcooked, respectively. ROS production: **p<0,001 10 µg cooked vs 10 µg overcooked.

Strategies to limit new dAGE formation in food should be adopted in order to limit AGEs intake. Through a reduced consumption of highly processed heat-treated foods, dietary AGE restriction may represent a relatively simple strategy to preserve healthy status and possibly, in a synergic optic, support pharmacological treatments for certain age-related disease like diabetes and renal disease.

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