Ultra-processed Food, Carboxymethyl-lysine and Pubertal Development in Girls

A Narrative Review

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Abstract

Introduction

Puberty marks a significant developmental milestone in an individual's life. Understanding the factors that influence the timing and progression of puberty is crucial. Nutrition plays a vital role in shaping puberty's onset and progression. This paper proposes future research directions to delve into the specific effects of toxins present in ultra-processed food, such as advanced glycated end products (AGEs) and its most prominent marker, Carboxymethyl lysine (CML), on pubertal changes in the modern world.

Methods

The search was conducted in three databases (ScienceDirect, PubMed and Scopus) and one central register (The Cochrane Central Register of Controlled Trials) from 2019 to 2024. The search was tailored for each database to construct the searches. We excluded articles involving participants with medical conditions capable of influencing sexual development. Humans, not automation tools, removed ineligible articles. Five reviewers performed the full-text screening independently.

Results

This initial search resulted in 567 unique entries. Additional sources were discovered by searching these articles for other potential references. Ultimately, 170 articles were included in the review. The final sources are listed in the References section.

Conclusions

In conclusion, this review emphasises the importance of food processing on pubertal timing. Demonstrating a direct association between Carboxymethyl lysine (CML) and pubertal timing is essential in highlighting the significance of modifiable factors such as diet. Acknowledging that numerous compounding factors influence the population and database studies, further research on preclinical models will offer valuable insights for educating physicians/parents about cooking methods affecting CML formation.

Keywords: *Pubertal Development, Nutrition, Carboxymethyl-lysine, AGEs, Ultra-processed Food.*

ულტრა- პროცესირებული საკვები პროდუქტები, კარბოქსიმეთილ-ლიზინი და სქესობრივი მომწიფება გოგონებში

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შესავალი

ბავშვებში სქესობრივ მომწიფების ინიცირებასა და მიმდინარეობაზე ზეგავლენის მრავალი ფაქტორია აღწერილი სამეცნიერო ლიტერატურაში.თუმცა, ნაადრევი სქესობრივი მომწიფების ინსიდენსის ზრდამ აქტუალური გახადა კითხვა - აქვს თუ

არა კლინიკურად მნიშვნელოვანი გავლენა ულტრა-პროცესირებული საკვების მოხმარებას გოგონებში სქესობრივი განვითარების ინცირებასა და მიმდინარეობაზე?
ენდოკრინოლოგიის ეროვნული ინსტიტუტის სამეცნიერო გუნდმა ჩაატარა ლიტერატურული მიმოხილვა იმისათვის რომ გამოევლინა -
რამდენად მჭიდროა კორელაცია საკვების პროცესირების მარკერ კარბოქსიმეთილ-ლიზინსა (CML) და პუბერტატულო განვითარების თავისებურებებს შორის.

მეთოდოლოგია

კვლევის ფარგლებში მოძიებულ იქნა 2019- 2024 (დღემდე) პერიოდში გამოქვეყნებული სამეცნიერო მასალები მონაცემთა სამი ბაზიდან: ScienceDirect, PubMed and Scopus და ერთი ცენტრალური რეესტრიდან - The Cochrane Central Register of Controlled Trials.
საძიებო მეთოდოლოგია მორგებულ იქნა თითოეულ მონაცემთა ბაზას. გამორიცხვის კრიტერიუმად მიღებულ იქნა სამედიცინო მდგომარეობები, რომელიც გავლენას ახდენს სქესობრივ მომწიფებაზე.
სტატიები რომლებიც სცდებოდა კვლევის არეალს, ან არ აკმაყოფილებდა ჩართვა/გამორიცხვის კრიტერიუმებს, შეფასდა და გამოირიცხა ენდოკრინოლოგიის ეროვნული ინსტიტუტის სამეცნიერო ჯგუფის მიერ და არა კომპიუტერული პროგრამის დახმარებით. სტატიების სრული ტექსტი შეამოწმა და მიმოიხილა ხუთმა მკვლევარმა დამოუკიდებლად.

შედეგები

თავდაპირველი ძიებით მოპოვებულ იქნა 567 სტატია. ამ სტატიების სრული მიმოხილვის საფუძველზე შეფასდა დამატებითი წყაროები.
საბოლოოდ, წარმოდგენილი მიმოხილვა მოიცავს 170 სტატიას (კვლევით სტატიებსა და ლიტერატურულ მიმოხილვებს). წყაროების სრული ჩამონათვალი წარმოდგენილია ბიბლიოგრაფიის ნუსხით.

დასკვნა

ლიტერატურის მიმოხილვა ხაზს უსვამს საკვების ულტრა-პროცესირების შედეგად მასში წარმოქმნილი პოტენციური ტოქსინების გავლენას სქესობრივი მომწიფებაზე. შედეგად, გამოიკვეთა კვლევის აუცილებლობა შეფასდეს კარბოქსიმეთილ-ლიზინსა (CML) და სქესობრივ მომწიფებას შორის პირდაპირი დამოკიდებულება. ამ კორელაციის დემონსტრირება გააძლიერებს კვების ფაქტორს, როგორც მარტივად მოდიფიცირებად კომპონენტს მკურნალობის გეგმაში.
იმ ფაქტის გათვალისწინებით, რომ პოპულაციურ და კლინიკურ კვლევებში მონაცემთა შდეგებზე გავლენა აქვს მრავალი ფაქტორის ერთობლივ მოქმედებას, ჩვენი სამეცნიერო გუნდი შეაფასებს პრეკლინიკურ მოდელებში საკვების ულტრა-პროცესირების მარკერის კარბოქსიმეთილ-ლიზინის კუმულაციური ეფექტს, დამოუკიდებლად სხვა ენდოკრინული დისრაპტორებისგან.

საძიებო სიტყვები: სქესობრივი მომწიფება, კვება, კარბოქსიმეთილ-ლიზინი, პუბერტატი, პროცესირებული საკვები.

Introduction

Over the past few decades, there has been a noticeable increase in body mass index (BMI) and obesity rates among children and adolescents worldwide[1]. Secular trends towards obesity among children coincide with the trend towards earlier pubertal timing [2]. Girls are more likely to experience an earlier onset of puberty when they are obese. Conversely, boys with severe obesity may often experience a delayed onset of puberty [3]. The accelerated increase in pediatric puberty with the rise in sexual precocity in girls has prompted inquiries into the interrelated mechanisms: Is nutrition the fundamental factor contributing to this phenomenon? If so, what specific alterations in nutritional patterns may account for the observed changes?
The practice of food production and processing is an age-old tradition of humanity. Humans cultivated, harvested, and transformed raw ingredients into nourishing meals from ancient times. As we delve into the complexities of the modern food industry, we must recognise that the reaction to growing, preparing, and consuming food has been an integral part of our cultural and culinary heritage.

As the food industry continues to evolve and expand, the processes involved in food production have undergone significant changes. These advancements have brought about a range of damaging factors that affect not only the quality of our food but also the environment and human health.

Nutrition is an essential source of exogenous advanced glycation end products (AGEs) where thermally processed foods, especially lipid and protein-rich foods typical of Western-style diets, contain many toxicant AGEs. Advanced glycation end products (AGEs) are created when protein reacts with reducing sugar during food processing, cooking, and storage [4][5]. There is controversy about whether dietary AGEs play a role in secular trends to earlier pubertal development. Recognising the factors that impact puberty [6], our study seeks to specifically explore the impact of food toxins, including advanced glycation end products and their primary marker, Carboxymethyl lysine (CML), on this physiological process.

Methods

The search was conducted in three databases (ScienceDirect, PubMed and Scopus) and one central register (The Cochrane Central Register of Controlled Trials) from 2019 to 2024. The search was tailored for each database to construct the searches. We began our search with the following terms: "Advanced glycation end product", "carboxymethyl-lysine", "carboxymethyl lysine", "precocious puberty", and "precocious pubarche". We used Mesh "Dietary Advanced Glycation End Products"[Mesh], "N(6)carboxymethyllysine" [Supplementary Concept], "Puberty, Precocious"[Mesh].

These terms were combined with boolean operators “OR” and “AND” to ensure a thorough literature search. We also examined the references of the articles we included to find related literature. We did not consider studies involving subjects with medical conditions or diseases that could lead to early puberty, like adrenal dysfunction, pituitary tumours, hypothyroidism, and congenital disorders.

Literature screening and Data Extraction

The research papers identified in the search were checked for duplicate entries, and then their titles and abstracts were carefully examined. Based on the criteria, ineligible full-text articles were excluded. Removed records were excluded by humans, not by automation tools. Five reviewers independently conducted full-text screening and data extraction. This initial search yielded 567 distinct entries. Further sources were found by examining these articles for additional potential references. In the end, 170 articles were included in the review, and the final sources are listed in the references section.

Puberty – a Turning Point

Physiology

Puberty is a natural phase of development where a child's body undergoes significant physical changes, transforming into an adult body capable of reproduction. These changes include the maturation of genital organs, the development of sexual characteristics, a growth spurt, shifts in emotional state, and, in females, the onset of menstruation (known as menarche). It occurs due to the activation and enhanced release of gonadotropin-releasing hormone (GnRH) in the hypothalamus, which stimulates the gonads to produce hormones [7]. Most GnRH cell bodies in humans and other primates are found in the medial basal hypothalamus (MBH) and periventricular regions of the infundibulum [8]. GnRH is released into the pituitary portal veins, which triggers the periodic release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the adenohypophysis [9]. These two hormones work together to regulate the gonads, allowing them to generate sex steroids and gametes. GnRH secretion is not solely triggered at the onset of puberty. GnRH is also released during fetal development and the phase known as 'mini-puberty' postnatally [10][11]. This phenomenon is due to a decrease in the levels of placental sex hormones and the resulting loss in negative feedback on gonadotropin-releasing hormone (GnRH). Despite increased estradiol levels, mini-puberty is not associated with growth acceleration, contrary to puberty occurring during childhood. The hypothalamic-pituitary-gonadal axis (HPG) activity during “mini-puberty” ranges from birth to 4-6 months and two years in males and females, respectively [12]. After this period, the GnRH pulse generator halts until puberty, which slows reproductive function. The mechanisms that trigger the reinitiating of the GnRH pulse generator and the inception of puberty are not yet precise, although several factors regulate pubertal timing [13][14].

The KNDy system, consisting of kisspeptin/neurokinin B/dynorphine A, is the key regulator of GnRH secretion. Kisspeptin, produced by Kiss1 neurons in the arcuate nucleus and anteroventral/periventricular nucleus, plays a crucial role in the GnRH pulse generator. Neurokinin B and dynorphin A provide stimulatory and inhibitory signals that modulate kisspeptin oscillation. These neurons are influenced by sex gonadal steroids, with AVPV/PeN Kiss1 neurons driving preovulatory LH increase in females and ARC Kiss1 neurons regulating the tonic release of GnRH/LH in response to negative feedback.[15]. Neurons expressing this Kisspeptin in the hypothalamus seem to directly act on individual GnRH neurons, which is characterised by potent depolarisation [16]. Kiss1 neurons have also been recognised in mice's posterodorsal part of the medial amygdala. These neurons regulate the GnRH pulse generator, influencing emotional and sexual behaviour, pubertal timing, and ovulation[17][18]. Although the KNDy system plays an essential role in the GnRH pulse generator activity, several observations showed that this is not the only system that regulates pubertal timing[19]. Recently, the kisspeptin-nNOS-GnRH or “KiNG” network that is responsible for generating the “GnRH pulse” and “GnRH surge” has emerged among the regulators of pubertal

development [20]. NNOS and kisspeptin act in tandem, akin to their ability to integrate and coordinate distinct signals to inhibit or promote GnRH secretion, respectively.

Phoenixin, a neuropeptide recently discovered through data obtained from the Human Genome Project, has been found to stimulate the activation of GnRH and kisspeptin neurons. This neuropeptide plays a role in regulating fertility by influencing anterior pituitary function [21]. The research has also shown that phoenixin and its receptor, GPR173, directly stimulate human ovarian follicles [22], and phoenixin induces dose-dependent oestradiol production. Phoenixin induces gonadotropin secretion through GnRH stimulation mediated by kisspeptin [23][24]. Notably, the essential role of kisspeptin in puberty has been confirmed, as demonstrated by the inability of patients with inactivating mutations of the kisspeptin receptor to undergo pubertal progression [25][26].

The physiological significance of leptin in puberty is widely recognised. Leptin, a cytokine primarily generated by fat cells, functions as an appetite suppressant and crucially regulates body weight, food consumption, and energy equilibrium by inhibiting the hypothalamic neuropeptide Y (NPY) to curb the appetite. [27][28]. To avoid pubertal dysfunction, average body weight and composition must be attained during childhood [29]. In addition to the leptin-NPY interaction, some studies showed that leptin acts on puberty and reproductive function by directly interacting with the Kiss1gene. GnRH neurons lack leptin receptors, but Kiss1 neurons express them. Leptin directly stimulates kisspeptin release and mediates the pulsatile release of GnRH [30]. After puberty, gonadotropin-releasing hormone (GnRH) is usually released from the hypothalamus to stimulate the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland [31]. Neurons that express GnRH are found in different regions of the hypothalamus. This placement allows the GnRH network to be influenced by neuroendocrine and metabolic signals [32]. A diet high in fat can directly stimulate neuropeptide signalling in the hypothalamus, leading to an inflammatory condition. As a result of the processes initiated by the joint and multifaceted impact of these factors, a child experiences the transformation, attaining somatic growth and reproductive maturity.

Pubertal Timing in Girls

Adolescence timing is influenced by various risk factors and their intricate interaction. Definitions of expected pubertal timing in girls, including progression of secondary sexual characteristics and pubertal growth spurt, are based on hallmark studies performed by Marshall and Tanner in the late 1960s [33]. Pubertal onset in girls takes place between the ages of 8 and 13.5 years. The end of puberty in girls corresponds to menarche, followed by ovulatory cycles several months later [34]. A unique individual variability characterises pubertal timing in humans. The physiological range of age at the onset of puberty covers five years, representing about 6% of a life span [34]. Precocious puberty (PP) refers to the development of secondary sexual characteristics before the age of 8 in girls. It is classified as either Central PP (CPP), involving early maturation of the hypothalamic-pituitary-gonadal axis, or Peripheral PP (PPP), marked by excessive sex hormone secretion regardless of gonadotropin levels.[35]. Although the factors that explain individual differences in pubertal timing are not fully identified, evidence shows that the GnRH neuronal network acts under genetic control and environmental influence [36][37].

Factors affecting puberty.

Genetic background explains about 50-80% of the variability in pubertal onset and progression [38]. Some ethnic groups, mainly African American and Hispanic, show an earlier onset of puberty due to genetic and nutritional factors [39]. Through a balance between repression and activation of gene expression [40], epigenetic mechanisms regulate the

expression of critical factors in the HPG axis, along with its probable role in adapting pubertal timing according to the environment [41]. Most genetic and epigenetic changes involve the genes responsible for kisspeptin, GnRH, LH, FSH, and their receptors, which are significant factors in the hypothalamic-pituitary-gonadal (HPG) axis. Identification of epigenetically regulated genes, such as Makorin ring finger 3 (MKRN3) and Delta-like 1 homologue (DLK1), respectively responsible for the repression and the activation of pubertal development, provides additional evidence of how epigenetic variations affect pubertal timing [42][43]. Epigenome plasticity refers to adapting to the environment and regulating gene expression without altering DNA. This flexibility of the epigenome, often referred to as "epigenetic memory," plays a significant role in determining the timing of puberty, although the exact pathways involved are not fully understood. [44].

Maternal education, social level, age of menarche occurrence, pre-pregnancy body mass index (BMI), ethnicity, age upon delivery, smoking habits, and alcohol/coffee/ tea consumption during pregnancy are reported to correlate with pubertal timing variations in the offspring [45]. Girls from urban areas and high socio-income families attained menarche earlier than girls from poor socio-economic status [46], and girls from urban areas attained menarche earlier than girls in rural areas [47].

Prenatal conditions, such as intrauterine growth restriction (IUGR) and small for gestational age (SGA) birth, may affect pubertal development [48]. Optimal early nutrition during lactation and early childhood may be necessary in determining sexual maturity and successful reproduction later in life [49][50]. Maternal breastfeeding appears to inhibit the early onset of puberty, mainly due to the positive effect on childhood overweight [51]. Numerous studies have indicated that the length of breastfeeding was linked to the onset of menarche and breast growth [52][53]. Recently, age at puberty was shown to be lowered by in-utero exposure to phytoestrogens in a British cohort. At the same time, the consumption of soy products during infancy is linked to early menarche in girls in the same cohort [54] and to altered menstrual patterns in young adults in an American cohort [55][56].

Numerous studies have reported relations between early (prenatal or childhood) exposure to Endocrine-disrupting chemicals (EDCs) and clinical timing of puberty [57] or concentrations of circulating reproductive hormones [58], indicating alterations in the development of the hypothalamic-pituitary-gonadal axis. Several animal models of EDC exposure have confirmed the impact of EDCs on pubertal timing, as reviewed by Parent et al.[34]. Endocrine-disrupting chemicals (EDCs) can disrupt natural hormone levels by interfering with the production, release, transportation, function, and breakdown of hormones using mechanisms that affect hormone receptors and signalling pathways. They may function through traditional nuclear receptors, non-nuclear steroid hormone receptors, non-steroid receptors, orphan receptors, enzymatic pathways related to steroid production and breakdown, and other mechanisms that play a role in the functioning of the endocrine system [59]. Numerous external substances or combinations of substances have been classified as endocrine-disrupting chemicals (EDCs) because they can imitate or hinder the function of the endocrine system and metabolism, leading to adverse effects on health.[60]. Substances like phthalates, dioxins, polybrominated biphenyls, and polychlorinated biphenyls have a role in influencing pubertal timing [61][62][63]. Exposure to flame retardants such as PBDEs also appears to affect puberty timing in girls, with effects depending on the timing of exposure [64][65][66].

Finally, nutritional conditions such as excess energy intake, macro/micronutrient imbalance and dietary styles can determine the early activation of the HPG axis [51]. Early and precocious puberty may occur when children continuously ingest naturally occurring

sex hormones from commercial food [67][68]. As a factor that can be modified, the impact of diet and nutrients on the timing of puberty onset is receiving significant attention. However, the results revealed an inconsistent correlation. Dietary patterns can trigger mild inflammation in the hypothalamus. This, in turn, activates microglia, releasing prostaglandins and neurotrophic factors that affect GnRH cells, potentially accelerating the onset of puberty.

Additionally, research indicates that fatty acids can stimulate the secretion of phoenixin, a neuropeptide that directly influences GnRH neurons. Therefore, the diet may promote phoenixin secretion, impacting GnRH neurons and potentially contributing to early activation of the GnRH system. On the other hand, phoenixin may also have a role in modulating neuronal inflammation [69][70][71]. Diets with high sugar and high-fat content tend to cause obesity in children and animals [72][73][74]. Rogers et al. [50] found that high meat intake predisposed girls to earlier menarche in Britain, while Wu et al. did not observe this positive correlation [75]. Similarly, there has been an ongoing debate regarding the impact of carbohydrate consumption on early menarche [46] [76]. Meanwhile, insulin resistance, via its obesity-inducing impact, is vital to advancing menarche onset [77].

Obesity is also a significant factor [78]. Research by Ferrari et al.[79] suggested that girls with a higher BMI were more susceptible to early menarche and breast development. Furthermore, an unstable family environment may also contribute to early puberty. From reported studies, it was noted that girls with a higher BMI (overweight and obesity) attained menarche early compared to those without excess weight [46][81].

Our focus group centres around the topic of nutrition, dietary endocrine disruptors and weight fluctuations, given the concurrent increase in obesity and precocious puberty among girls.

Exposure Window

In humans, it is difficult to provide evidence of causal relationships between exposure and changes in pubertal timing. Additional issues include simultaneous exposure to small amounts of numerous chemicals, the time lapse between exposure to EDCs in early childhood, and the potential impact on the timing of puberty [82]. Research has demonstrated that early exposure to EDCs can immediately affect the formation of various cell types within the gonads or the development of the reproductive tract, depending on the specific EDC type, dose, and timing of exposure. Additionally, long-term effects may manifest in hormonal balance, somatic cell differentiation, gamete production, and gamete quality. [83][84].

Early exposure is a long-standing concern in the medical field. A fetus is highly susceptible to the environmental and maternal components surrounding a pregnancy [85]. Dr David Barker first popularised "the fetal basis of adult disease" [86]. Furthermore, it represents a complex and multifactorial idea of fetal origins of adult disease. It is hard to establish the developmental age at which exposure to advanced glycation end products (AGEs) is critical. Considering the latency from exposure is an essential factor, representing the time it takes for AGEs to show its effect. The remarkable impact of advanced glycated end products is due to the plentiful presence of AGE receptors on various tissue cell surfaces [87][88].

Our research team aims to investigate the exposure windows that have the most significant effects on the relationship between nutrition, weight fluctuations, and pubertal development in girls, focusing on understanding the potential consequences of these exposures.

The changing patterns: delving into the shifting onset of puberty

The study of pubertal timing changes over the past centuries provides a fascinating glimpse into the evolving factors that have influenced the onset and progression of puberty in girls. Insights into this historical trend not only shed light on the impact of various environmental, nutritional, and social factors on pubertal development but also offer valuable perspectives in understanding the implications of these changes on overall health and well-being. The mean age of puberty appearance has decreased significantly over the last 100 years in Europe and worldwide.

The mean age at menarche in the nineteenth century was approximately 17 years. A secular decrease in age at menarche between 1890 and 1960 was thought to be caused by improvement in nutritional and socio-economic status [89][90]

Several American and European studies have indicated an advancement in breast development in girls over the last 30 years [91][92][93]. Overweight/obesity rates have been dramatically increasing during the last 40 years in many European countries, exceeding 30% and 10% among children and adolescents [94]. The Pediatric Research in the US Office Setting (PROS) indicated that the timing of breast development in white American girls was advanced from 10.6 years in the 1930s-1940s to 9.96 years in 1992-1993 [95]. Some specific populations appear to show a high prevalence of precocious puberty (breast development before the age of 8 in girls). In Belgium and other developed countries, migrating children have a markedly increased risk of sexual precocity [90]. Such rapid evolution of developmental landmarks led to the hypothesis that puberty timing could be affected by exposure to environmental factors.

The age of B2 among girls in Denmark was 9.86 years in 2006-2008, nearly a year earlier than the 10.88 years reported in 1992-1993 [91]. During the last 15 years, a 12-month decline in the mean age at the onset of breast development in Danish girls [91] has been found, while similar findings are reported in both Greek and Turkish populations [96][97]

More recent data align with the trends as mentioned above, suggesting that the age distribution of pubertal signs is skewed towards earliness for initial pubertal stages and lateness for final pubertal stages [34] [57]

The prevalence of PP needs to be well-documented. The literature shows that girls' precocious puberty (PP) frequency ranges from 6.7% to 10.4% [98] [99]. Nevertheless, in the Danish population, a small percentage of girls (0.2%) and an even smaller percentage of boys (less than 0.05%) appeared to exhibit some PP [100]. Another study in Spain suggests that the annual occurrence of CPP ranges from 0.02 to 1.07 per 100,000 individuals. [101]. The most remarkable discovery is the decrease in the average age at which puberty begins.

Nutrition Dynamics - Unlocking Flavor Alchemy
The Maillard reaction and Advanced Glycation End Products (AGEs)

The Maillard reaction, commonly known as non-enzymatic browning, is an interaction between free amino groups of proteins and carbonyl groups of reducing sugars [102]. Maillard-like reactions also occur in living organisms, and the products generated in vivo are named advanced glycation end products (AGE) and advanced lipoxidation end products (ALE) [88]. The evolution of the Maillard reaction can be traced back to the top of culinary history. As our ancestors discovered the transformative effects of applying heat to food, they began to harness the Maillard reaction to enhance the sensory appeal of their meals. Over time, this process has

been honed and perfected by various cultures worldwide, developing diverse cooking techniques, flavour combinations, and culinary traditions.

The difference between the Maillard reaction during cooking at home and in mass production or ultra-processing lies primarily in the scale, control, and potential additives involved. When cooking at home, the Maillard reaction occurs on a smaller scale, allowing for more hands-on control over heat and ingredients. In contrast, mass production and ultra-food processing involve larger-scale operations with strict parameters and the potential for added preservatives, flavour enhancers, and other ingredients to achieve specific outcomes. This ultra-processing can result in differences in flavour, texture, and overall product quality between home-cooked and commercially processed items.

It is important to note that thermal processing time is directly correlated with the production of Maillard reaction products. According to studies by Ledl and Schleicher [103] and Poulsen et al. [88], increasing the process temperature by 10◦C can at least double the rate of the Maillard reaction. Furthermore, when using browning as an indicator for the progress of the reaction, it has been observed that approximately the same results in terms of browning are achieved within four weeks at 20◦C, 3 hours at 100◦C, and 5 minutes at 150◦C. These findings highlight the significance of temperature and time in influencing the Maillard reaction and its resulting products during thermal processing [103][88]. There is no clear consensus on how dietary Maillard reaction products may specifically affect human health. Diverse Maillard reaction products (MRPs) act as antioxidants, bactericidal, antiallergenics, antibrowning agents, prooxidants, and carcinogens. Most of these properties depend on food processing [104]. Still, high levels have been associated with potential health implications and lower nutritional quality due to the loss of essential and semi-essential amino acids [105][106][107][108].

The Western diet, abundant in heat-treated foods, offers a substantial daily intake of MRPs. The intricate nature of MRPs stems from the existence of various compounds at the initial, intermediate, and final stages. These compounds generate diverse flavours and aromas in processed foods [109] while diminishing their nutritional value, primarily by lowering protein digestibility [105]. This connection underscores the significance of MRPs in influencing the overall nutritional quality of food. The most important compounds are furosine, acrylamide, heterocyclic amines (HCAs), 5-Hydroxymethylfurfural (HMF), advanced glycation end products (AGEs) and melanoidins that are present in processed foods from animal and vegetal origins [105].

When proteins or fats interact with sugars, they form a collection of substances called advanced glycation end products (AGEs). The reaction mechanism of AGE formation by the Maillard reaction is mainly the formation of dicarbonyl compounds at Shiff's base and Amadori Rearrangement Product stage [110][111]. Amadori and reactive dicarbonyls are early Maillard reaction products (AGEs precursors) formed from lysine residues [112].

AGEs in humans come from two sources: external intake through the diet and internal formation within the body. The body's own production of AGEs is influenced by factors such as lower physiological temperatures and specific pathways like glycolysis. Unhealthy lifestyles, including sedentary behaviour and lack of exercise, also contribute to the formation of AGEs. [113], smoking, and long-term alcohol intake [114][115][116]. Researchers have suggested that younger people are vulnerable to the effects of AGEs. Putte et al. [117] found that AGEs begin to accumulate in people as young as 20 years old and then seemingly increase steadily.

Nutrition is an essential source of exogenous AGEs where thermally processed foods, especially lipid and protein-rich foods typical of Western-style diets, contain many toxicant AGEs. In standard diets, where proteins and lipids mixed with reactive sugars are routinely processed under elevated temperatures, such as broiling, roasting, or grilling, high oxidants such as AGEs are produced spontaneously [118]. Although the average total daily intake of AGEs in an adult's regular diet is ∼1600 AGEs kU/d, consuming a diet high in heat-processed foods, sugar, and fats can increase the daily intake of AGEs to >200,000 Ku/d [119]. It was observed that dietary AGEs show interference with insulin, testosterone, estradiol, and progesterone activities. Additionally, it was demonstrated that AGEs can interfere with anti-mullerian hormones and gonadotropins [120]. Moreover, AGEs affect adipose tissue and thyroid hormones and seem to play a crucial role in the development of type 2 diabetes (T2D) [121][122][123]. Regarding their mechanisms of action, direct or indirect interaction with hormonal receptors, disturbance of transport and delivery of hormones, and interference with specific signalling pathways have been discussed. However, the exact mechanisms behind the disruptive effects of AGEs appear to remain unclear [124]. Eating regimens low in dietary AGEs have been linked to noteworthy weight loss. They also led to reduced levels of leptin in the bloodstream and increased adiponectin, which further aid weight loss efforts and support long-term weight management [125]. Another study combining various research findings revealed that diets low in AGEs substantially reduced inflammatory markers like TNF-α and 8-isoprostanes among healthy individuals [126]. Although many studies have been conducted, the connection between AGE properties and biological functions has yet to be conclusively established.

AGEs are categorised into fluorescent cross-linking AGEs (pentosidine and crossline), non-fluorescent cross-linking AGEs (imidazolium lysine cross-links, alkyl formyl glycosyl pyrrole (AFGP) cross-links and arginine-lysine imidazole (ALI) cross-links), and non-cross-linking AGEs (pyrraline, carboxyethyl lysine (CEL) and carboxymethyl lysine (CML)) [127][128].

CML physiology and bioavailability

N^{ε}-(carboxymethyl) lysine (CML), with the chemical formulation of $C_8 H_{16} N_2 O_4$ and a molecular weight of 204.224 g/mol [129], was identified as the initial glycoxidation product in 1985 by Dr. Ahmed during attempts to determine the primary compounds formed when glucose reacts with lysine in physiological conditions. CML can be produced in food and biological systems. Of the various pathways for CML formation documented in scientific literature, the primary ones include the conversion of fructosyl-lysine (an Amadori product) to CML through the AGE pathway, as well as the direct interaction of glyoxal, generated through lipid peroxidation, with the ε-amino group of lysine, resulting in CML formation through the ALE pathway [130][131]. Due to multiple formation pathways, CML is considered one of the predominant MR compounds in extensively heated foods and living organisms. CML is a valuable indicator of AGE accumulation in food products and animal and clinical research [132]. It is stated that there are two separate forms of dietary CML: the free form and the protein-bound form (covalently bonded with proteins and peptides) [133][134].

Multiple factors will influence the rate at which CML is absorbed, including its solubility following gastrointestinal digestion, molecular weight, and whether it is free or protein-bound [135]. It is stated that free CML is quickly absorbed due to its low molecular weight [136]. In contrast, protein-bound CML is thought to be very difficult to absorb due to insufficient degradation by gastrointestinal enzymes [88].

CML and Diseases

Various mechanisms have been identified through which CML can lead to tissue damage. Following their ingestion, 10% remains in the circulation, and 2/3rds stay in the body and get incorporated covalently in tissues, ultimately leading to systemic and local insulin resistance (IR) as well as inducing mitochondrial dysfunction and reactive oxygen species (ROS) production [137]. AGEs stimulate proinflammatory cytokine synthesis and release, setting the stage for the sustained activation of innate immune responses by triggering transcriptional factors such as nuclear factor kappa B [138][139]. For instance, Cai et al. conducted a study where wild-type mice were given methylglyoxal-modified BSA (MG-BSA) as a precursor of AGEs for six months. Their research findings revealed a direct connection between MG-BSA consumption and the increased presence of oxidative stress markers [140]. Concurrently, insulin resistance was observed in four consecutive generations of mice on the same diet [121]. Dittrich and colleagues (58) examined how the delivery method affects CML levels in infants during the first three days after birth. They found that newborns delivered vaginally had urinary CML levels that were twice as high as those delivered by caesarean section (1306 vs. 601 ng mL−1), even though both groups were formula-fed. The authors concluded that during the first few days after birth, urinary CML excretion reflects endogenous oxidative stress rather than nutritional intake, suggesting that oxidative stress is likely higher during vaginal childbirth compared to caesarean delivery [141].

Our understanding of how dietary advanced glycation end products (AGEs) contribute to the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) is not yet comprehensive. It is still being determined whether these conditions are influenced only by internally produced AGEs or if AGEs from our diet also play a part in their progression. The vital link between diabetes and advanced glycation end products (AGEs) is that high blood sugar levels increase glycation, especially in tissues that do not rely on insulin for glucose uptake. Prolonged hyperglycemia, the main symptom in patients with diabetes mellitus, dramatically accelerates the formation of advanced glycation end products (AGEs) generated from non-enzymatic glycation (NEG) of proteins and lipids. [142] [143]. Moreover, within the diabetes context, removing old or impaired proteins is impeded by the potential glycation of the enzymes involved. This glycation diminishes the efficiency of protein breakdown mechanisms, causing a slowed or reduced protein turnover and, consequently, contributing to the buildup of CML (carboxymethyllysine) [144]. In a study by Hofmann et al. involving insulin-resistant db/db mice (a model of type 2 diabetes) fed either a high or low-AGE diet for 20 weeks, it was observed that the progression of diabetes worsened with higher dietary AGE levels. The AGE-rich diet resulted in a twofold increase in serum CML and methylglyoxal concentrations and elevated body weight gain [145]. People with diabetes mellitus and cardiovascular disease are estimated to have an average daily intake of CML at approximately 3.1 mg [146][107]. In a meta-analysis of 18 manuscripts, Jalil et al. observed significantly higher circulating AGEs (CML and MG-H1) only in subjects with obesity with at least one component of metabolic syndrome versus normal weight individuals, whereas no significant difference among AGE concentrations of individuals with obesity without any metabolic syndrome components versus normal weight individuals. The authors suggested that in individuals with obesity with one metabolic syndrome component, there were also higher

circulating amounts of inflammatory factors, including leptin, tumour necrosis factor (TNF)-a, and receptor for the advanced glycation end product (RAGE) that promote deteriorating effects of AGE in metabolic syndrome-prone patients with obesity. [147]. The results of a study by Semba et al. suggested a reverse relationship between fat mass and serum CML levels. The authors proposed two possible explanations for this association: first, fat tissue stores CML selectively; second, adipocytes (fat cells) could potentially impact the metabolism of AGE (advanced glycation end products), which leads to the production of CML [148].In this context, the presence of CML in the bloodstream does not accurately represent the overall amount of CML present in the entire body.

Diet plays a significant role in fertility, even if one is not obese, and specific nutrients seem to have a more pronounced impact on reproductive well-being [149]. The study by Tatone et al. revealed that consuming dietary AGEs is associated with a more extended non-ovulatory phase, known as the diestrus phase, and disruptions in the production and development of hormones and follicles in the ovaries, regardless of obesity. The accumulation of AGEs in the ovaries hinders follicle development and negatively affects eggs' maturity, growth, and chromosomal composition within the ovaries [150].

CML and Diet.

Several studies investigated the existence of CML in food, such as those carried out by Goldberg et al.[150] and Uribarri et al.[151]. A more recent study by Hull et al. [130] analysed 257 commonly consumed food items in the Western-style diet. The query pertains to the degree of impact that dietary CML may have on the potentially significant contribution to the progression and severity of the disease.

Numerous studies have underscored the significance of considering an individual's health status (whether healthy, with or without T2DM, or with CVD) when analysing the significance of dietary advanced glycation end products (AGEs) on disease risk markers [153][154][155]. These studies highlight that the effects of dietary AGEs can vary depending on a person's specific health condition, further emphasising the need for personalised assessments in understanding the relationship between dietary AGEs and disease risk markers.

In a research investigation focused on improving insulin resistance in individuals with type 2 diabetes through dietary restriction of glycation products, findings indicated that patients with type 2 diabetes exhibited notably elevated fasting blood glucose levels and increased serum concentrations of CML and the dicarbonyl methylglyoxal compared to nondiabetic, healthy control individuals before the intervention. Following a 50% reduction in dietary advanced glycation endproducts (AGEs), the diabetic subjects displayed reduced serum CML and methylglyoxal levels and diminished intracellular methylglyoxal levels compared to their pre-intervention levels [156]. Research demonstrates that adopting a diet restricted in advanced glycation end products can reduce serum advanced glycation end product levels among individuals and vice versa [157][158][159]. Similarly, dietary CML significantly increases circulating CML levels[130]. Ingestion of a Western-style diet is associated with ovarian dysfunction [160][161] that leads to diminished ovarian reserve [162], mitochondrial dysfunction [162], abnormal menstrual cycle length [163], anovulation, abnormal uterine bleeding, endometrial hyperplasia/cancer, and subfertility [164][165]. The Mediterranean diet is linked to increased chances of clinical pregnancy and live births in young women. In contrast, a Western-style diet negatively affects fertility and glucose tolerance in macaques, regardless of obesity and diabetes [149][166].

Recent research conducted by the International Agency for Cancer Research [167] has categorised red meats as Group 2, indicating they are probably or possibly carcinogenic. In contrast, processed meats fall under Group 1, signifying a higher level of carcinogenicity. The report underscores a key finding: the potential to mitigate the presence of compounds such as carboxymethyl lysine [168].

Additionally, these diets catalyse the transition from healthy obesity to unhealthy obesity. Therefore, ensuring proper regulation of advanced glycation end (AGE) levels in our food is significant.

Tools of detection CML

The nature of samples and the complexity of food matrices make analysing CML in blood and food challenging due to variability in content and analytical approaches. Factors such as cooking methods and processing techniques can significantly impact CML levels, leading to difficulty in obtaining consistent measurements. The complex food composition also makes separating CML from other components technically challenging and may affect result reliability.

Establishing reliable standards and reference materials for CML detection in blood and food is essential for ensuring accurate and comparable results across different studies and laboratories. However, the need for widely accepted standards can make comparing data obtained from diverse sources complex.

CML levels can be quantified using GC-MS or ELISA [169]. Additionally, commercially available AGE assay kits often come with their standard curves for quantitative analysis.
Uribarri et al. significantly advanced by creating a comprehensive database of food products and their concentrations of advanced glycation end products (AGEs), utilising CML levels measured through ELISA [152]. Our team investigated several studies evaluating AGEs and their precursors using either *in vitro,* animal or human-based models.

Addressing Gaps in Understanding the Impact of CML Intake on Pre-Pubertal Girls
Proposals for research

Our narrative review encompassed studies involving experiments and research on the impact of carboxymethyl-lysine. Our study team intends to calculate the approximate carboxymethyl-lysine intake by the pre-pubertal girls (aged 4-8) with a 24-hour dietary recall method to emulate this dietary intake pattern in a preclinical model to simulate a child's nutritional intake from birth to pre-maturation. This approach will enable us to assess the isolated impact of Carboxymethyl-Lysine on pubertal timing, eliminating the influence of other potential environmental or dietary endocrine disruptors. The selection of female children is predicated on the higher incidence of early sexual maturation in girls than in boys [170]. Based on the information provided, we propose that dietary modifications to reduce advanced glycation end products (AGEs) may have potential implications for addressing precocious puberty in girls. Although it is challenging to modify multiple endocrine disruptors and genetic predispositions, exploring subtle nuances in modifiable factors such as nutrition may significantly impact the prevention and management of sexual precocity.

Moreover, we investigate the potential significance of altering cooking methods and implementing targeted nutritional interventions as pivotal factors that could substantially impact pubertal timing shifts. Exploring the impact of Carboxymethyl-lysine on sexual

maturation may provide a targeted connection between cooking methods and food processing concerning sexual development, thereby serving as a catalyst for motivating parents and children to consider nutritional interventions on par with pharmaceutical and lifestyle interventions.

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