Nutrition 29 (2013) 930–938

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Crosstalk among dietary polyunsaturated fatty acids, urolithiasis, chronic inflammation, and urinary tract tumor risk

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ARTICLE INFO

Article history:
Received 11 October 2012
Accepted 13 December 2012

Keywords:
PUFAs
Urinary Tract Tumors
Bladder cancer
Urinary calculi
Cystitis
Dietary lipids

ABSTRACT

Based on a consistent bulk of experimental and epidemiologic works, we proposed that abnormal metabolism and/or dietary deprivation of essential polyunsaturated fatty acids by inducing a chronic and subclinical essential fatty acid deficiency (EFAD) in urothelial cell membranes may enhance the risk for urinary tract tumor (UTT) development. This threat may be enhanced by the unusual fact that the fatty-acid profile of the normal urothelium is similar to that reported in EFAD. The risk for UTT may be worsened when coexisting with a low-grade chronic inflammation (LGCI) state induced by urolithiasis or disbalance management of peroxides, free radical molecules, and their quenchers. There is cumulative evidence linking the LGCI of the urinary tract mucosa, calculi, and UTT, due to the long-standing release of promitotic, promutagen, and pro-inflammatory antiapoptotic cytokines in these conditions. The dual role played by pro- and anti-inflammatory eicosanoids and bioactive lipids, cytokines, and the disbalance of lipid peroxidation is discussed, concluding that the moderate, long-standing consumption or dietary supplementation of ω-3 PUFAs may improve the chances of avoiding UTT development.

Introduction

Urinary tract tumor (UTT) in humans continues to be a major concern as death rates due to bladder neoplasms have not diminished appreciably over recent decades (revised in Andreatta [1,2]). It is possible that the tumorigenic effect of urothelial mutagens, whether ingested in the diet and/or flushed by urine, may be avoided by the normal integrity of the "passive barrier" to water-soluble molecules located at the luminal surface of the mammalian urothelium in normal conditions [3,4]. UTT are the 10th cause of cancer worldwide, with annual age standardized incidence rates being 100 per 100,000 for men and 36 per 100,000 for women, respectively, according to worldwide data from 2002 [1,5,6]. Even if this mortality is not remarkably high, the morbidity and recurrence of these tumors provides a serious challenge for oncologic treatment and follow-up. Our earlier studies on geo-location showed that UTT are the fourth in incidence among men in Argentina (South America), with intriguingly different patterns occurring in several countries of this region [6].

The causes of UTT are still scarcely understood. Because genetic background seems to play a minor role in their proneness, environmental factors become the main factors of suspicion [1,2]. The major environmental causes of UTT appear to be tobacco smoking [7], occupational risks occurring in the dye industries [8], chronic inflammation of the bladder by certain microorganisms [9–11], alcoholism [1,2,5,12,13], chronic arsenicism from drinking water in South America (mainly Argentina, Chile) [14–16] and China [17], accidental intoxication with melamine (as happened recently in China, as this compound has procarcinogenic capabilities in rodent urinary mucosa [18–20]), and possibly several artificial sweetners [5]. These risk conditions are probably worsened by the urinary tract infections and urolithiasis that often coexist with some of these conditions [9,21–23].

Although research into the possible associations between UTT and dietary factors has been limited, several food-protein derivatives exhibiting mutagenicity capabilities have been identified in the urine of humans and animals. These include nitrosamines as well as tryptophan metabolites, but evidence of their tumorigenic effects on the urinary tract (UT) mucosa is still vague [24]. Moreover, the role played by nutritional fats, mainly polyunsaturated fatty acids (PUFAs) in UTT etiology, is comparatively even less understood [25–27].

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http://dx.doi.org/10.1016/j.nut.2012.12.014

The main experimental, epidemiologic, and clinical aspects of the relationship between UTT and PUFAs were covered in our previous articles [1,2,4,5,18,19,28,29], in which we discussed considerable data indicating that dietary PUFAs play a crucial role in UTT. Hence, we proposed that the UT in mammals, including humans, might have a proneness to develop tumors if a deficiency or perturbations of the PUFA metabolism is present. In rodents, chronic essential fatty acid deficiency (EFAD) induces both urolithiasis, transitional hyperplasias and displasias, followed by the development of UTT [30,31], with Zhang et al. reporting similar results [31]. A high intake of saturated fats or non-essential fatty acids (EFAs), conditions that may induce a subtle chronic EFAD, increased the risk for bladder cancer in case–control studies. In other cell populations, EFAs, mainly those of the ω-3 family, are beneficial as preventive and therapeutic nutrients for avoidance and treatment of cancer. Therefore, we suggested that an abnormal metabolism and/or nutritional deprivation of EFA, by inducing a chronic deficiency or a subclinical EFAD together with chronic inflammation (urolithiasis), might enhance the risk for UTT [4,28,29]. Further studies provide support to this proposal [32–36]. The aim of this article was to give a fresh, updated review based on our basic and epidemiologic investigations and from other authors about the relationship among dietary fatty acids (mainly PUFAs), urolithiasis, chronic inflammation, and risk for UTT (Fig. 1).

Brief reminder of the metabolism and physiology of essential PUFAs

Dietary fatty acids (FAs) are oxidized to provide energy, stored in adipose tissue, and selectively incorporated into the phospholipids (PLs) of all cellular membranes. Once ingested in food, FAs are desaturated and elongated to yield several PUFAs, which are long carbon-chain molecules having two or more double bonds of the *cis* configuration. ω-3 and ω-6 PUFAs cannot be synthesized by metazoan, but must be ingested through the diet and hence are EFAs. The PUFA ω-6 family derive from linolenic acid (LA; 18:2 ω-6) and those belonging to ω-3 arise from α-linolenic acid (ALA; 18:3 ω-3). In contrast, monounsaturated palmitoleic acid (POA; 16:1 ω-7) and oleic acid (OA, 18:1 ω-9) are synthesized by the body. Although all EFAs are PUFAs, not all PUFAs are EFAs (revised by Das [37,38]). However, in this work PUFAs and EFAs are used synonymously. Non-EFAs refer to monounsaturated POAs and OAs and their non-EFA long-chain PUFA derivatives. Nevertheless, often saturated fat, *trans*-FA, and cholesterol are included under this name.

ALA and LA, and eventually non-EFA from the ω-7 and ω-9 families, compete for a common delta-5 and delta-6 desaturase. In this "race," 18:3 ω-3 ALA is desaturated preferentially, followed by 18:2 ω-6 LA, thus avoiding the conversion of OA to the more highly unsaturated ω-9 metabolites, of which one of them is considered a reliable "marker" of EFAD, namely 20:3 ω-9 (Mead's acid) [39]. Thus, under the normal dietary habits prevailing in Western countries [24,40,41], tissue lipids will contain considerable amounts of OA, a modest quantity of POA but not their long-chain non-EFA/PUFA derivatives. Although a dietary lack of EFA is rarely seen in developed countries, this abnormality may be subtly induced by the long-standing ingestion of foods enriched in non-EFAs (OA, *trans*-FA, hydrogenated and/or saturated fats, and cholesterol-rich foods). Indeed, one useful experimental approach to induce a fast EFAD is the supplementation of dietary formula with OA, cholesterol, or saturated fats [18,19,42]. When the dietary amounts of OA and/or other non-EFAs are abnormally high, the activity of delta-6 desaturase is progressively stimulated. Thus, OA ω-9 becomes preferred for further elongation and desaturation. This process is considered an ineffective attempt to replace with the long-chain highly unsaturated metabolites (mainly 20:3 ω-9), the missing EFAs both in the "structural" membrane PLs and as substrates for eicosanoids and other bioactive lipid metabolites (BALs). Despite 20:3 ω-9 not being an adequate precursor for eicosanoids and other BALs, this PUFA still may be converted to abnormal, prostanoids, several eicosanoids, hydroperoxy FAs, and active leukotrienes (LTs), with this being perhaps one of the causes for a disbalanced functioning of the eicosanoids in EFAD [25,28,43,44].

PUFAs are essential molecules for PLs, which are major components of all cell membranes including urothelium. Hence, PUFAs per se will give to membranes particular properties such as fluidity/viscosity, and in turn modulate the dynamics and biophysical properties of biomembranes [45,46], ligand-receptor interactions, and also many activities of membrane-bound enzymes, ions channels, glycoproteins, and proteoglycan receptors of immune cells [46–48]. Long-chain highly unsaturated PUFAs (as arachidonic acid [AA], docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) are highly flexible molecules compared with those more rigid areas of the bilayer caused by large amounts of monoenes and saturated FAs. The relative enrichment of cholesterol promotes lateral segregation of protein and the gathering of certain lipids in the bilayer, thereby forming more permanent clustered microdomains known as "rafts."These can prevent the movement of big protein complexes in the membrane, as happens with a peculiar variety of rafts, the uroplaquins of the mammal urothelium, whose structure is heavily modified by dietary PUFAs [49–53].

When PUFAs are released from PLs by the activities of several phospholipases [54,55], they are further processed through the activities of two main enzymatic pathways: the cycloxygenases (COX) and lipooxygenases, which lead to wide varieties of prostaglandins, eicosanoids, endocannabinoids, lipoxins, nitrolipids, neuroprotectins, maresins, resolvins, hydroxyeicosatetraenoic acids (HETEs), nitrolipids, and hepoxilins, among other BALs [37,38,56,57]. However, most of these BALs are very short-lived molecules, a fact that warrants accurate tissue homeostatic balance. BALs are produced locally when needed and are then almost instantaneously destroyed. Due to their intense activity at very low concentrations (even at values of nM or μM), it is easy to understand why there are no a pools of eicosanoids or BALs already formed in the body. Moreover, most eicosanoids arising from the same substrate (i.e., AA) exhibit an agonistic/antagonistic behavior, with their equilibrated balance being a key function as homeostatic cell controllers [37,38,58,59].

As mentioned previously, the relative availability of the ω-6 PUFA substrates in foods [24,40,41] tilts the synthesis to ω-6 BALs derivatives. However, if the ω-3 are progressively eaten, the BALs belonging to this family will be increased. The well-known beneficial activities of ω-3 PUFAs and its derivatives with regard to ω-6, but mainly in contrast to non-EFAs ω-9-BALs, have been consistently shown [58,60,61]. Simplistically speaking, taken as a whole, the PUFA derivatives from ω-3 exhibit anti-inflammatory and antineoplastic properties [62], with these comparatively beneficial properties having been demonstrated in several chronic diseases that have in common a long-standing "bed" of low-grade chronic inflammatory processes (LGIC), such as metabolic syndrome, obesity, type 2 diabetes, dislipidemias, stroke, coronary heart disease, lithiasis, endothelial dysfunction, atherosclerosis, and hypertension [38,61,63]. These complex and interlinked diseases have led UN Das to propose that endogenous anti-inflammatory PUFA derivatives (mainly from the ω-3