Could cyanogenic glycoside rich diet cause increased risk for carbamylation-induced protein damage in individuals with chronic inflammatory diseases?

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\section*{ABSTRACT}

Cyanogenic glycosides are found in a diverse group of plants and are metabolized into thiocyanate by the intestines and liver. Conversion of plant derived thiocyanates into cyanide and isocyanic acid occurs by the activity of neutrophil-derived enzyme myeloperoxidase. Therefore, increased intake of cyanogenic glycoside rich plant based diet may lead to increased isocyanic acid induced protein carbamylation in chronic inflammatory states (increased myeloperoxidase activity). As there is a close relationship between non-enzymatic post-translational modification and protein function, carbamylation induced structural changes also affect the functions of proteins. Carbamylation induced structural alterations of proteins have recently drawn a great attention in the current literature, especially regarding the alterations of proteins with long half-life such as type I collagen, elastin, α-crystallin. We hypothesize that a plant-based natural diet, rich in cyanogenic glycosides, may have unintended consequences on native protein structure/function in individuals with chronic inflammatory diseases such as chronic kidney and rheumatological diseases because of the higher rate of transformation of plant derived thiocyanates into isocyanic acid by the increased activity of neutrophil-derived enzyme myeloperoxidase. Regulation of myeloperoxidase activity or moderation of cyanogenic glycoside rich diet might be important in the prevention/modulation of dangerous protein carbamylation process, especially in this patient group.

Cyanogenic glycosides are synthesized from amino acids by numerous plant families. The long list of plant families that synthesize cyanogenic glycosides includes Euphorbiaceae, Rosaceae, Asteraceae, Passifloraceae, Fabaceae, and Poaceae [1]. Some commonly consumed foods which have cyanogenic glycosides include corn, sweet potatoes, beans and bitter almonds. Overall, cyanogenic glycosides can be described as O-β-glycoside of α-hydroxynitriles (cyanohydrins) [1]. Enzymatic hydrolysis of the cyanogenic glycosides (such as amygdalin and prunasin) in the digestive tract and their processing by the liver leads to the formation of hydrocyanic acid (prussic acid, cyanide), which is detoxified to thiocyanates by the liver, which could then be converted by myeloperoxidase to isocyanic acid, implicated in protein carbamylation (Fig. 1).

Myeloperoxidase is a pro-inflammatory enzyme which produces reactive hypochlorous acid in the presence of hydrogen peroxide and chloride ion. This pro-inflammatory reaction is commonly employed by the immune system to fight against invaders. However, as previously mentioned, myeloperoxidase could also use thiocyanate as a substrate, half-life of which is calculated to be around 3 days in healthy subjects [2], and generate isocyanic acid and hypothiocyanous acid (Fig. 2) [3]. The amplified importance of this pathway lies in the fact that previous studies indicated that in patients undergoing hemodialysis, thiocyanate levels are six to seven times higher compared to healthy patients, and that compared to chloride and bromide, thiocyanate is the favored (1:60:730 respectively) co-substrate for myeloperoxidase [4,5]. In addition, salivary thiocyanate levels have been found to be four times higher in smokers compared to non-smokers, and thiocyanate levels have been found to cumulatively increase as smoking pack-year increases [6]. Even though isocyanic acid and hypothiocyanous acid are thought to play an important role in host defense against the invaders [7], increasing experimental evidence also supports an alternative result for myeloperoxidase-derived oxidants in the pathogenesis of dis-

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eases. That is, excessive production of hypohalous acids particularly during chronic inflammation could lead to accumulation of macro-molecular damage implicated in various pathologies such as atherosclerosis, rheumatological diseases, neurodegenerative diseases, and kidney diseases [8]. Therefore, we hypothesize that consumption of cyanogenic glycoside rich foods under chronic pro-inflammatory states may also lead to the excessive formation of highly reactive isocyanic acid via myeloperoxidase activity on thiocyanate derivatives [9–11] (Fig. 2). Subsequently, isocyanic acid non-enzymatically reacts with nucleophilic functional groups of proteins, such as α-amino groups of N-terminal amino acids and ε-amino groups of lysine residues in various proteins, and contributes to their molecular aging (Fig. 2) [4,6], a reaction recently termed as protein carbamylation (or carbamoylation). As there is a close relationship between non-enzymatic post-translational modification and protein function, carbamylation induced structural changes would also be expected to alter the function of proteins. In fact, recent studies indicate a strong relationship between protein carbamylation and unfavorable structural-functional remodeling [12]. In addition, protein carbamylation is accepted as a marker of aging [13], and we recently proposed anti-carbamylation strategies to slow down the progression of carbamylation induced structural damage [14].

Increased myeloperoxidase activity has been proposed as a potential biomarker for atherosclerosis, acute coronary syndrome, and chronic obstructive pulmonary disease. In addition, several reactions could be targeted to slow down myeloperoxidase activity [15]. Myeloperoxidase inhibitors are currently tested in clinical trials against multiple system atrophy (BHV-3241) and heart failure.

**Fig. 1.** Metabolic pathway leading to thiocyanate formation from cyanogenic glycoside-rich plant-based diet.

**Fig. 2.** Metabolic pathway leading to isocyanic acid formation from thiocyanate and the reaction of isocyanic acid with nucleophilic functional groups such as α-amino groups of N-terminal amino acids and ε-amino groups of lysine residues to form carbamylated proteins. Obtained from Jaisson et al., cited in (3).
(NCT03611153). Myeloid cell activity, inflammation and cardiovascular complications are recently reviewed in [16], and Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial recently indicated that modulation of immunity with interleukin 1β improves cardiovascular health [17].

Therefore, we hypothesize that a plant-based diet that is rich in cyanogenic glycosides may lead to harmful alterations on native protein structure/function in individuals with up-regulated myeloperoxidase activity, due to higher rate of transformation of thiocyanates into cyanide and isocyanic acid (Fig. 2). Because of their considerably long half-life, extracellular matrix proteins, such as type I collagen and elastin may be particularly at risk for carbamylation induced damage in patients with chronic inflammatory disease. Hence, the degree to which, if any, the contribution of cyanogenic glycosides on protein carbamylation in patients with up-regulated myeloperoxidase activity needs to be elucidated with experimental studies. In this subgroup of patients, inhibition of myeloperoxidase activity and/or decreased consumption cyanogenic glycosides-rich food products might play a role in the prevention/modulation of excess, uncontrolled protein carbamylation.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109275.