

The Nutritional Supplementation during 80 Consecutive Days with Glutathione (GSH), Alpha Lipoic Acid among other Bioactive Phytomolecules Significantly Rise Systemic (GSH) Levels and Reduces Hair's Aluminium (Al) in Patients

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Abstract: **Background:** Several studies have demonstrated that elevated Aluminium (Al) levels contribute to Alzheimer or ALS Multiple sclerosis pathophysiology. **Aim:** we have described three cases of patients who had extremely elevated Aluminium levels (Al) (before any treatment) by unknown causes. **Results:** These patients reduces 48 % their Aluminium levels and rise (67 %) GSH (Glutathione: reduced form) levels after 80 days of nutritional supplementation with Glutathione, Selenium (Se), alpha lipoic acid among other bioactive phytomolecules (Glutathione Complex formulation (GC), Celsus Lab, Spain) as compare their respective basal levels (controls : BEFORE any treatment). **Conclusions:** The GSH rise suggest that Glutathione (GSH) is recycled to remove excessive Aluminium (Al) level by conjugation. Since elevated Aluminium (Al) levels contribute to the progression of Alzheimer (AD)/ALS (Multiple sclerosis) disease, these bioactive phytomolecules as Glutathione, Selenium (Se), alpha lipoic acid from GC formulation may recycle Glutathione and reduce Al levels in patients.

Keywords: Glutathione (GSH), Aluminium, neurotoxicity

1. Introduction

The chronic Al administration (2 g/L/6 months) to aged rats rise ion metal release and affects Mossy fibers organization in the brain (1). It is necessary to investigate how bioactive phytomolecules with antioxidant properties may chelate or reduce Aluminium (Al) levels in patients. The role of Aluminium (Al) in the progression of Alzheimer disease (AD) is controversial. Al contribute to amyloid beta or tau deposition in AD (2) although Al addition in the drinking water did not influence CNS Alzheimer-like pathology (3). In fact, systemic Al levels did not differed between AD patients and participants with minor cognitive impairment (MCI) (4).

The biotrace element Selenium (Se) is necessary for Glutathione synthesis (GSH) and contribute to the excretion of heavy metals by conjugation with its reduced form (5,6). The dietary supplementation with Se can reactivate endogenous detoxification systems to remove excessive free radicals (6). Recently, a study indicates that grape seed extract supplementation significantly rise Glutathione (GSH) levels and decreases lipoperoxide as compare with their placebo groups (7). Other bioactive phytomolecule from Glutathione Complex formulation (GC, Celsuslab, Spain) is *Cephalosporium mycella*, which contribute to the bioremediation of organic pollutants in metal-organic mixed environment areas (8). The therapeutic role of Asianticosides from *Centella asiatica*, (present in Glutathione complex, GC formulation), is associated to CYP (CYP450, CYP3A4, CYP2D6, CYP2C9) without harmful effect (9). **Aim:** We

have studied whether 80 days of nutritional supplementation with Glutathione and alpha lipoic acid in GC formulation (GC) could rise GSH levels and reduce Al levels in patients as compare their respective basal levels.

The Glutathione Complex (GC) formulation contains these bioactive phytomolecules.

Glutathione Complex formulation (Celsus Lab, Spain) composition/day

Dry Extract of Cordiceps (*Cephalosporium mycella*, 70 %): 400 mg
Cephalosporium mycella, 7 % of manitol
N acetyl cysteine (NAC): 350 mg
Alpha Lipoic acid: 200 mg
L-glutamine: 200 mg
Calcium ascorbate: 200 mg
Dry extract of *Silybum marianum*, 80 % of silimarine: 150 mg
Dry extract of Asian Centella, 3 % of Asianticosides: 150 mg
Acetil L-carnitine: 150 mg
Dimetil-glicine: 120 mg
L-Glutathione (reduced form, GSH): 100 mg
SAMs (s Adenosyl L Methionine): 100 mg
Dry extract of Brecol (*Brassica oleracea*, 0,3 % of sulphoraphane): 50 mg
Vitamine E (mixture of different tocopherols): 60 mg
Vitamine C: 163 mg
Zinc Citrate: 15 mg

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Riboflavine: 15 mg
B6 Vitamine (P-5-P): 9,5 mg
Tiamine: 1,5 mg
Folic acid: 400 microg
Selenium (Sodium selenium): 105 microg
Moligdene (Amonium moligdate): 97,2 microg
B12 Vitamine (Cianocobalamine): 33 microg

These participants receive nutritional supplementation (Glutathione Complex, GC, Celsuslab, oral intake) during 80 consecutive days (AFTER). Their Al hair levels as well as systemic GSH percentages were compared after 80 days of treatment (AFTER) with their basal levels (controls: BEFORE: supplementation), respectively.

2. Material and Methods

All enrolled patients have been properly instructed and they consent to participate by signing the appropriate informed consent paperwork according to Helsinki Declaration (1974 and 2000). All efforts have been made to protect patient privacy and anonymity. CIROM Clinic (Centro de Implantologia Oral Multidisciplinaria, Murcia, Spain) has been approved and certificated by AENOR Agency (Spain: CIROM CERTIFICATE for dentist and research services: CD-2014-001 number; ER-0569/2014 following UNE-EN ISO 9001: 2008 as well as UNE 179001-2001 Directive from Spain).

Inclusion criteria: we have recruited patients with high Aluminium (Al) levels (>7 microg/hair). The normal range for Al is between 0-7 microg/g of hair in healthy population according to ICP-MS data in healthy population (Dr DATA Lab, USA). We have included three cases of patients visiting a dental clinical (CIROM) and they have high Al levels. Hair's basal Al levels were measured by ICP-MS before

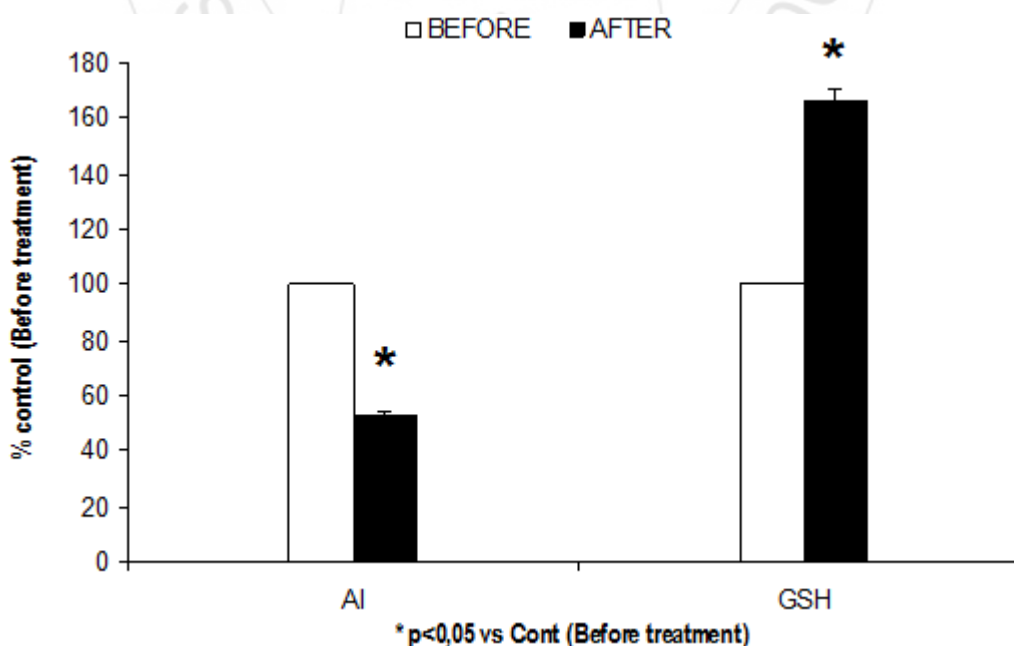
(BEFORE: controls) as well as after 80 days of nutritional supplementation with Glutathione Complex formulation (GC) (AFTER). They are 47 and 35 years old and their hair Al levels are higher than 7 microg/g. The odontogram shows four dental amalgams, two crowns and two titanium implants and they do not show behavioural alterations.

Exclusion criteria: we have excluded patients with psychiatric disease or those prescribed with DMSA/chelators or under current treatment for iron deficiency (anemia). They have no history of liver/kidney disease/autoimmune disease/renal diseases/Cushing Syndrome/metabolic diseases/tiroid pathology.

3. Results

The nutritional supplementation with Glutathione (GSH), Selenium (Se) and alpha lipoic acid significantly rise Glutathion levels (Reduced form) and decreases hair's Aluminium (Al) levels.

Their basal hair's Aluminium (Al) levels were measured by ICP-MS and systemic GSH levels (reduced form) were detected by colorimetric assay (BEFORE/AFTER 80 days of GC supplementation) following Cabaña-Muñoz et al., 2015 procedure (11). We found significant systemic GSH rise and lower hair Al levels after 80 days of supplementation (AFTER) with GC formulation (GC, Celsus Lab). This product contains Glutathione (GSH), alpha lipoic acid, Selenium (Se) and mushrooms among other bioactive phytomolecules (GC, see composition). Their basal Al control (BEFORE) are 100 % (Controls). The systemic GSH rise was compared after 80 days of GC supplementation (AFTER) and their basal levels (100 %: BEFORE any supplementation)



There nutritional supplementation with GC formulation significantly rise GSH levels (67 %, GSH: reduced form) and also reduces hair Al levels (48 %) after 80 days of Glutathione Complex (AFTER, GC) treatment as compare with their respective controls (BEFORE treatment). Results are expressed as control percentage.

4. Discussion

The nutritional supplementation with GC formulation during consecutive 80 days reduces hair's Al levels and rise systemic GSH levels. GC formulation contains several bioactive phytochemicals as Glutathione (GSH), alpha lipoic acid, Selenium (Se) and Mushrooms. These findings suggest GSH can be recycled in order to remove excessive Al levels in patients. Since high Al levels contribute to Alzheimer disease pathology (2), this chronic supplementation (with Glutathione, its precursors, Se and alpha lipoic acid among other synergic phytochemicals) may reduce Aluminium levels through conjugation with Glutathione. In addition, alpha lipoic acid from GC formulation may rise GSH levels since alpha-lipoic acid protects against oxidative stress-induced cadmium (Cd, other heavy metal) by increasing glutathione synthesis *in vitro* (10). Previously, we have demonstrated systemic GSH rises together elevated mercury hair's in women who have long-term dental amalgams levels (11). In addition, Silimarine from Glutathione Complex (GC) formulation may reduce Al levels because the chronic similarine (*Silybum marianum*, 200 mg/Kg/day) treatment significantly reduces Al-induced cognitive impairments and induces GSH synthesis. Al-neurotoxicity was induced during 42 days of treatment in this study (12). This concentration is the same in patients (200 mg/day). These elevated Al levels in the aged brain increases the susceptibility to oxidative stress. One could expect that chronic supplementation with bioactive phytochemicals from GC formulation as Glutathione, Selenium (Se), alpha lipoic acid may enhance endogenous antioxidant capacities in order to remove excessive Al levels in patients. As a consequence of GSH rise, these bioactive phytochemicals may reduce the susceptibility to oxidative stress. Since oxidative stress aggravate the progression of neurodegenerative disease (also AD), these bioactive phytochemicals could reduce Al-induced toxicity. In agreement with this hypothesis, selenium (a trace element necessary for Glutathione peroxidase activity: GPx) promotes glutathione synthesis (5). Se could enhance the chelation of Aluminium together sSAM (s-Adenosyl-Metionine) and cysteine. Thus, Glutathione and Se could chelate or enhance Al excretion by rising GSH levels in these patients. The abnormal Al metabolism were reported in two siblings with progressive CNS calcification (13). Other case of ALS (Amyotrophic Lateral Sclerosis) that did not remit with conventional ALS treatment reported lower Al levels after 30 days of EDTA treatment (chelator, twice/day). The clinical improvement on ALS symptomatology correlated with Al reduction in the urine to normal range, suggesting that Al may contribute to ALS pathology (14). These reduced Al levels after nutritional supplementation with bioactive phytochemicals from Glutathione Complex (GC) agrees with decreased Al-induced gliosis described in the prefrontal cortex of rabbits after treatment with two Aluminium quelators (desferrioxamine (DFO) and six-hydroxypyridin-4-ones,

CP) (15). The induction of detoxification capacities from mushrooms as *Cephalosporium mycella* (Cordiceps) can be used as therapeutic agent (16). Collectively, the nutritional supplementation with GC formulation during 80 consecutive days rise systemic GSH levels and reduces hair's Al levels. Vitamins B12, B6, E and C together N acetyl cysteine can synergically promote beneficial effects in the present study (11). Further studies will confirm whether Glutathione treatment may reduce Al levels in a cohort of patients.

5. Conclusion

Since high Aluminium (Al) levels contribute to Alzheimer or ALS Multiple sclerosis pathology, the chronic supplementation with bioactive phytochemicals from GC formulation (Glutathione, GSH), Selenium (Se), alpha lipoic acid) may recycle Glutathione levels (GSH) and reduce hair's Aluminium levels as preventive agents in patients.

6. Conflict of interest

None to declare by all authors

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