Evidence to Review Your Vitamin C Dosage

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ABSTRACT

In 1999, the American Aging Association sponsored a consensus conference on the optimum dosage of vitamins C (AA) and E. They concluded that between 200 and 400 IU of vitamin E and 200 to 1,000 mg of AA in divided doses daily was best. The debate over the optimal dosage of AA remains unresolved, but new information is worth considering. First, a paper in Nature highlights that the [AA] differentials throughout the body are based on gene expression. Second, it was recently reported that AA interferes with benefits obtained from exercise. This study has been widely refuted in professional circles, though many remain unaware of this. Third, a recent study published in the Am. J. of Clinical Nutrition reported that AA supplements above 250 mg/d may cause lower urinary tract symptoms (LUTS) similar to prostate hyperplasia. Fourth, a study from Sweden published in 2010 reported that AA supplements accelerate the development of cataracts, although previous research has indicated that it reduces that risk. In an effort to resolve the latter controversy, I have recently begun an investigation of the concentration of AA in the human eye, for which preliminary data will be available at the meeting. Fifth, AA has been shown to be inversely associated with stroke damage in humans, just as in nature it is found to protect animals from reperfusion injury. Physicians especially should be aware of the inverse relationship between AA and stroke damage, and the safety of AA consumption below the Upper Limit of 2,000 mg daily, which was established under the guidance of Dr. Maret Traber of the Linus Pauling Institute.

INTRODUCTION

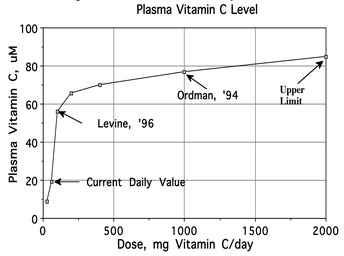
In 1956, Denham Harman proposed the free radical (ROS) theory of aging (Beckman and Ames 1998). Linus Pauling proposed megadoses of the water-soluble antioxidant vitamin C (ascorbic acid, AA) to trap free radicals, recommending dosages up to 16 g per day (Pauling 1970). In 1994, King *et al* discovered that 500 mg of AA taken orally every 12 hr were sufficient to provide continuous excretion of excess AA into the urine. In 1996, a similar study by Levine *et al* confirmed those results, showing that 500 mg of AA bid provides the highest statistically significant concentration in plasma for protection from free radical damage. But they recommended that the RDA be only 200 mg AA, as that can be provided by dietary sources. This intake provides the plasma AA level necessary to saturate certain white blood cells (figure 1).

A panel of The Food and Nutrition Board of the Institute of Medicine (directed by Maret Traber of the Linus Pauling Institute (LPI)) raised the RDA for AA for men and women to 90 and 75 mg resp., with an Upper Limit (UL) for safety established at 2 g daily. This poster updates my review of the latest evidence of the risks and benefits of AA bid (Ordman 2010). NHANES (2000) reported 11% of people in the US took AA supplements. Table 3 shows that most people attending the LPI conference in 2007 took AA supplements or multivitamins (Lai 2009), as did people who receive the Nutrition Investigator Newsletter (Ordman 2011).

Table 3. People getting Nutrition Investigator emails or Attending LPI meeting are more likely to take AA

Vitamin C	LPI	NutInv	ClinTrial
None	45%	41%	63%
60 to 500	26%	23%	39%
500 to 999 mg	19%	24%	8%
1000 to 1999	6%	8%	
2000+	10%	5%	
Twice daily	10%	8%	8%

Figure 1: Effect of Twice Daily Oral Dose on Plasma Vitamin C Level



EVIDENCE

Choice of AA Intake Has Tremendous Effects

[AA] varies a thousand fold in different tissues (Table 2). Hediger (2002) reviews how expression of AA transporter genes causes variability in human tissues. In a process called nutrient signaling, nutrients can transform metabolic processes as hormones do (Bhalla and Iyengar 1999; Ordman 2008). For instance, AA signals cell differentiation of brain (Prozorovski *et al* 2008) and heart (Takahashi *et al* 2003) stem cells . Figure 1 shows how daily intake affects serum concentration. Table 1 summarizes risks and benefits of particular intakes verified in peer-reviewed literature.

TABLE 2: CONCENTRATION OF AA IN VARIOUS HUMAN TISSUES

TISSUE	[AA]	Ref
Blood	10 to 90 μM	Levine *et al* (1996)
Neutrophils	1.3 mM	Levine *et al* (1996)
Eye lens (67 yr human)	0.4-1.1 mM	Fan *et al* (2006)
Eye lens mild cataract	88 μmoles per 100g lens	Tessier *et al* (1998)
Neurons	10 mM	Hediger (2002)
Astrocyte	1 mM	Hediger (2002)
Hippocampus, Adrenal glands	Up to 10 mM	Fan *et al* (2006)
Adrenal gland, lung, pancreas, spleen, testis, ovary, eye	"high"	Hediger (2002)
Fetal brain	"high"	Castro *et al* (2001)

TABLE 1: SUMMARY OF **RISKS** AND BENEFITS OF AA INTAKES OF 500 MG TWICE A DAY

BRAIN	AA reduces the risk of stroke (Yokoyama *et al* 2000)
	AA reduces cognitive decline (Araujo *et al* 2005)
	AA inactivates ROS that contribute to Alzheimer's (Su *et al* 2008)
	AA reduces reperfusion injury (Rozell 1998)
	AA reduces damage from head trauma (Polidori *et al* 2001)
	AA generates new neurons (Prozorovski *et al* 2008)
HEART	AA reverses endothelial dysfunction (Levine *et al* 1996).
	AA generates new cardiac myocytes (Takahashi *et al* 2003)
	AA (500 mg twice daily) protects plasma (Moser *et al* 2006)
EYES	**AA acceletates cataracts** (**Rautiainen *et al* 2010**, Linetsky *et al* 2008, Fan *et al* 2006)
	AA reduced cataract odds 64% (Valero *et al* 2002)
	250-700 mg AA daily reduces risk (Robertson *et al* 1991, Hankinson *et al* 1992)
	AA supplements have no effect (Mares *et al* 2010)
COLDS	AA (500 mg) reduced frequency of colds by 66% (Sasazuki *et al* 2006)
KIDNEY	AA reduces the risk of kidney stones (Lawson 1999)
CANCER	AA reduced mutations causing metastases (Ishikawa *et al* 2008)
SAFETY	Upper Limit established at 2,000 mg AA daily (Food and Nutrition Board 2000)
	Up to 2,000 mg AA daily is safe (Hathcock *et al* 2005)
	Supplements over 250 mg daily may cause lower urinary tract symptoms (Maserelian *et al* 2011)

Abbreviations: AA- ascorbic acid (Vitamin C)
ROS-Reactive oxygen species (free radicals)

BRAIN: AA is a water-soluble antioxidant that crosses the blood-brain barrier. Taking 500 mg of vitamin C bid may lessen Alzheimer's, stroke, and head trauma damage. Stroke is the leading cause of disability worldwide (Zweifler 2003), and head trauma is common in war veterans. Many studies reveal the value of elevated levels of AA for protecting brain function. Yokoyama *et al* (2000) found that stroke risk in people in Japan was inversely related to AA intake. "Strong inverse associations were observed between serum vitamin C concentration and all stroke (sex- and age-adjusted hazard ratios were 0.93, 0.72, and 0.59, respectively, for the second, third, and fourth quartiles compared with the first quartile), cerebral infarction (0.71, 0.59, and 0.51), and hemorrhagic stroke (0.89, 0.75, and 0.45)." In humans with Alzheimer's and mild cognitive impairment, tissues and biofluids show evidence of oxidative stress (Su *et al* 2008). Cognitive decline in aging dogs is lessened simply by adding antioxidants to the diet, and then the deposition of amyloid-beta is decreased (Araujo *et al* 2005).

AA is produced in the liver of most mammals. Hibernating animals naturally store high concentrations of AA in the brain for protection from the metabolic stress that accompanies arousal (Toein *et al* 2001). In humans, brain stroke damage continues when blood flow resumes. AA substantially prevented this reperfusion injury (Rozell 1998). Polidori *et al* (2001) show that AA is much lower in plasma for those with head trauma or intracranial hemorrhage when compared to healthy subjects, while other antioxidants such as vitamin E are unaffected. Even at a dose of 200 mg AA/day, ischemic stroke-related lipid peroxidation decreased significantly in humans (Polidori *et al* 2005).

Via nutrient signaling, AA may exert effects on brain maintenance and recovery. How neural progenitor cells (NPCs) differentiate is determined by the redox state of the brain (Adler 2008). In the reducing environment produced by AA, NPCs become neurons. Under oxidizing conditions, astrocytes are formed. Prozorovski *et al* (2008) conclude that nontoxic manipulation of redox conditions in the brain influences NPC fate to produce neurons. People are able to generate new neurons throughout their entire lives (Song *et al* 2005). High AA concentrations in the brain maintain the potential to generate new neurons.

CATARACTS: Tessier *et al* (1998) measured AA in the human and states that [AA] decreases with cataract severity, but Linetsky *et al* (2008) in calf lens demonstrated that glycation by ascorbic acid oxidation products leads to the aggregation of lens proteins. Fan *et al* (2006) report lens data that strongly implicate AA in lens crystallin aging and may serve as a model for protein aging in other tissues particularly rich in AA, such as the hippocampal neurons and the adrenal gland. A study in Sweden in 2010 reported that AA accelerates the development of cataracts (Rautiainen *et al* 2010). However, in Sweden the typical AA supplement is 1,000 mg, that may increase intake above the US UL. A major study in Europe shows that blood levels of AA above 49 μmol/L were associated with a 64% reduction in odds for cataract (Valero *et al* 2002). US daily value for AA provides only about 20 μmol/L, while 500 mg twice daily provides about 75 μmol/L. The aqueous humor of the eye cycles directly from serum, so the [AA] is likely to match.

LOWER URINARY TRACT SYMPTOMS (LUTS): LUTS can be caused by high-dose supplemental and total AA ≥ 250 mg/d, (Maserejian *et al* 2011). LUTS include difficulties with voiding (intermittency, weak urinary stream) and storage (urgency, frequency), which might be mistaken as symptoms of benign prostatic hyperplasia, particularly among older men.

KIDNEY STONES: Many urologists and nutritionists advise patients that AA causes kidney stones, which are often made from oxalic acid, which is a metabolite of AA. However, numerous studies, reviewed by Lawson (1999) of the Linus Pauling Institute, have shown that those who take AA supplements have a reduced risk of kidney stones.

DISCUSSION

ANTIOXIDANT CONUNDRUM: At the 2009 LPI meeting, Dr. Stampfer (2009) spoke on the Antioxidant Conundrum, and how the media often "vilify" antioxidants, misinterpreting studies on topics like AA and exercise, then concluding erroneously that AA may be hazardous.

HOW MUCH AA DO YOU GET? Table 3 indicates that 55% of participants in the Linus Pauling Conference in 2007 consumed supplements that include AA. Yet many choices are inconsistent with figure 1, which shows useful intakes of AA. The daily value for AA has risen steadily to 90 mg. King *et al* (1994), using the kidney as a biomarker, found 500 mg bid as the level of supplementation that causes continuous excretion of AA. Levine *et al (1996)* advocate 200 mg daily, a level that can be obtained from diet alone, which saturates particular white blood cells

MOST RECENT CONS: In 2010 it was discovered that AA supplements cause LUTS in some men, with symptoms similar to prostate hyperplasia. Also that year it was reported that AA may accelerate, rather than delay, the development of cataracts, though this may only occur at doses above the UL.

MOST RECENT PROS: Many studies indicate that AA may reduce the risk of various causes of cognitive decline, especially stroke and damage from stroke. AA also may lower the risk of cancer, and have potential administered intravenously as a treatment of cancer (Hoffer *et al* 2008*)*.

CONCLUSION

With lifespan increasing 3 months per year (Couzin-Frankel 2011), our aging population is likely to require less medical care if we consume sufficient AA. Evaluation of results in Table 1 may lead to recognizing the benefit of 500 mg bid, which provides a serum level not statistically different from the UL.

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