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Antioxidants; decrease or increase mortality?!

Free radical production occurs continuously in all cells as part of normal cellular function. However, excess free radical production originating from endogenous or exogenous sources might have role in many diseases.

In recent years, a substantial evidence has developed, supporting a key role for free radicals in many fundamental cellular reactions and suggesting that oxidative stress might be important in the pathophysiology of common diseases including; *atherosclerosis, chronic renal failure, and diabetes mellitus*. Therefore, antioxidants by preventing the formation of radicals, scavenging them, or by promoting their decomposition will consequently play an important role in preventing free radical-induced tissue damage[1]. Some evidence of the clinical beneficial effect of antioxidants has also been proved in clinical trials, such as;

¤ The combination of zinc and antioxidants had a statistically significant treatment effect on the progression of age-related macular degeneration compared with placebo[2].

¤ Another antioxidant, Coenzyme Q10 has shown promising results in the management of Parkinson's disease and some other chronic diseases. It is also reducing the cardiotoxicity of anthracyclines, and appears to be safe[3, 4].

These beneficial effects encouraged many patients to ask their physicians whether they should take antioxidants and vitamins.

On the other hand, results from recent studies and meta-analysis had shown that the use of vitamins and antioxidants may not be of value in the prevention of chronic diseases that are supposedly driven by oxidative stress, such as these in the following;

¤ A randomized controlled trial in more than 9000 patients with vascular disease or diabetes found that longer term supplementation with 400 IU of vitamin E per day did not prevent cancer or major cardiovascular events[5]

¤ A meta-analysis of 7 cohort studies found no association between, the carotenoid (another antioxidant that is related to vitamin A) intakes and the incidence of lung cancer during 7-16 years of follow-up[6].

¤ Finally, a meta-analysis of 3 small, relatively short trials in elderly people, found no benefit of vitamin C on mortality[7].

¤In addition, short-term randomized controlled trials have shown that taking vitamin C does not prevent upper respiratory infections. *You can find more data on vitamin C and upper respiratory tract infections in April issue of our newsletter.*

Furthermore, and this is the main concern of this article, antioxidants were associated with increased risk of mortality. Most of these data were reported with vitamin E, A and betacarotene. In a meta-analysis that was recently published at the Journal of American Medical Association JAMA, **Bjelakovic et al** (2007)[8] analyzed the effects of antioxidant supplements (beta carotene, vitamins A, C, and E, and selenium) on all-cause mortality.

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Article summary

- Free radicals play an important role in the pathophysiology of many chronic diseases.
- Co Q10 has promising effect in PD.
- Vitamin E 400 IU did not reduce cardiovascular events or cancer in a big-numbered Randomized Controlled Trial.
- Unnecessary antioxidants administration may pose the patients to adverse effects without gaining beneficial effect.

They performed a thorough search of multiple databases and relevant references for randomized controlled trials RCT, evaluating these supplements, either singly or in combination. When all the trials were combined, there was no significant effect of antioxidant supplements on mortality. However, an analysis of outcomes from only high-quality trials showed a significantly increased risk of mortality with beta carotene, vitamin A, and vitamin E, either singularly or combined. While the analysis showed that both selenium and vitamin C had no significant effect on overall mortality[8].

This metaanalysis was criticized by Mathew Brolyn [9], whereas he mentioned that the studies that have been analyzed had no discrimination concerning the dosage ranges and dosage duration, furthermore many clinical studies that have been excluded from the analysis specially those which did not have mortality incidence had involved about 40000 individuals. This of course would have affected the results if they were included in the analysis. Furthermore when the Complementary Healthcare Council of Australia (HCH) reviewed the same meta-analysis but included only those studies with the antioxidant doses that are approved in Australia and excluded studies which have less than 500 individuals, they found that only few studies are left to be applicable and some of these draw positive conclusions about the effectiveness of the products under investigation[9].

Conclusion:

Multivitamins in general and antioxidants in particular are being consumed nowadays by even normal population without medical advice, as people assume that these ingredients are safe, hence they are naturally available in food. The main issue here is the increased risk of exceeding the upper limit for these ingredients and consequently increased potential for adverse effects.

On the other hand persons who have a chronic illness or who want to prevent recurrence of a disease such as cancer or heart attack are those who will ask their physician or pharmacist for the benefits of antioxidants. Our mission is to give these people only information that is supported with evidence. Unfortunately the present evidence is insufficient to go along with or against the use of antioxidants in the prevention of theses chronic diseases, therefore it is not advisable to recommend antioxidants only for the patient's convenience unless there is compelling indication such as deficiency situations. We should endorse the use of many but not all antioxidants for many but not all chronic diseases (only those with conclusive evidences).

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DID YOU KNOW?

Ammonia:

This term was coined 1782 by Swedish chemist Torbern Bergman for gas obtained from sal ammoniac, salt deposits containing ammonium chloride found near temple of Jupiter Ammon (from Egyptian God Amun) in Libya, from Gk. ammoniakon "belonging to Ammon." The shrine was already ancient in Augustus' day, and the salts were prepared "from the sands where the camels waited while their masters prayed for good omens" [Shipley]. There also was a gum form of sal ammoniac, from a wild plant that grew near the shrine, and across North Africa and Asia.

A less likely theory traces the name to Gk. Armeniakon "Armenian," since the substance also was found in Armenia. Also known as Spirit of Hartshorn and Volatile or Animal Alkali.

http://dictionary.reference.com/browse/ammonia

Efficacy and safety of inhaled insulin

Exubera ® is a dry powder formulation of rapid - acting human insulin that is produced by **Pfizer**, and it has been approved by the FDA on January 2006. It is available in blisters of two doses (1 & 3 mg) which are equivalent to 3 units and 8 units respectively of subcutaneously injected regular insulin. A single blister is inserted into a handheld inhaler device with a clear chamber reservoir. Multiple blisters are needed for doses other than 1 or 3 mg, however only one blister can be administered per inhalation. Compressing the handle of the device punctures the blister and releases a visible cloud of insulin into the inhalation chamber. The aerosolized powder can then be inhaled and is absorbed through vesicular transport into the alveolar capillary circulation.

For more information about other characteristics you can visit the FDA site by using the following link.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

The bioavailability of inhaled insulin is about 10%. In a pharmacokinetic study by **Rave et al 2005**[1] that was performed on 17 healthy male volunteers, inhaled insulin had a more rapid onset of action =(32 minutes) than either insulin lispro which had an onset of action =(41 minutes) or regular insulin = (48 minutes). Inhaled insulin had a duration of action = (387 minutes) that was longer than lispro = (313 minutes) and slightly shorter than regular insulin = (415 minutes)[1]

Efficacy of the inhaled insulin had been studied in both type I and type II DM compared with other subcutaneous types of insulin and oral hypoglycemic agents respectively.[2-4]

In an open labeled study; three hundred thirty-five subjects with type I diabetes were randomly assigned to either receive pre-meal inhaled insulin plus bedtime Ultralente or two to three injections of regular and NPH insulin for 24 weeks. At the end of the study, there was no significant difference between the 2 regimens in the primary endpoint of decrease in glycosylated hemoglobin (HbA1c), or in the percentage of patients achieving HbA1c <7%[2].

In another study for the same period; 24 weeks (6month) **Skyler et al,** 2005[3] had investigated whether a basal/bolus insulin regimen involving rapid-acting dry- powder, inhaled insulin could provide glycemic control comparable with a basal/bolus subcutaneous regimen. Whereas, 328 DM type I patients who were on twice-daily subcutaneous NPH insulin were randomized to either receive pre-meal inhaled insulin or subcutaneous regular insulin.

There was no significant difference between the groups in the primary endpoint of a decrease in HbA1c or in the percentage of patients achieving HbA1c <7%[3].

From the above two studies one can conclude that inhaled insulin may provide an alternative for the management of type 1 diabetes as part of a basal/bolus strategy in patients who are unwilling or unable to use pre-prandial insulin injections.

In addition, the inhaled insulin was compared with subcutaneous insulin in diabetic patients type II, by Hollander et al, 2004[5] whereas glycemic control using inhaled, dry-powder insulin plus a single injection of long-acting insulin (Ultralente) was compared with a conventional regimen in patients with type 2 diabetes, which was previously managed with at least twice daily (mixed regular/NPH insulin)injections. The study included 299 patients and also lasted for 6 months. HbA1c which was the primary endpoint has decreased similarly in the inhaled and subcutaneous insulin groups; however HbA1c < 7.0% was achieved in more patients receiving inhaled than subcutaneous insulin.

As to concern tolerability; with the exception of increased cough in the inhaled insulin group, adverse effects were similar in both subcutaneous and inhaled insulin. However an adverse effect on pulmonary function was consistently reported with the use of inhaled insulin in short term clinical studies.

Therefore to assess the safety and tolerability of inhaled insulin for long term use; one randomized open labeled trial that included 627 patients with type II DM who were being treated with Subcutaneous (SC) insulin at baseline were randomized to inhaled insulin (n=316) or continued SC insulin (n=311) for 2 years. All patients then returned to treatment with SC insulin for 6 months, after which time they returned to their randomized therapy for 6 months. The primary end point was lung function and the secondary end points were the long-term efficacy of inhaled insulin versus SC insulin on glycemic control and the immunologic response following dis-

continuation and re-administration of inhaled insulin. Patients who used inhaled insulin experienced a small decline in pulmonary function. According to interim data analysis of this trial, the decline is not progressive and is reversible upon discontinuation of inhaled insulin. Upon reinstitution of inhaled insulin, the reduction in forced expiratory volume FEV1 was of the same magnitude as the initial decline.

Therefore the authors concluded that "The pattern of change is consistent with a physiologic, not pathologic, effect of inhaled insulin on lung function"

Furthermore in a similar design but including DM type I patients another study has come to the same conclusion.

The interim analysis of these last two studies was presented at the 67th Annual Scientific Sessions of the American Diabetes Association.

Abstracts are available at the following link;

http://scientificsessions.diabetes.org/index.cfm?fuseaction=Locator.SearchAbstracts&CalledByID=1006

Eventually the manufacturer recommends pulmonary function testing before starting the inhaled insulin, also at 6 months from the start and then annually. The drug should be discontinued if FEV1 declines ≥ 20% from baseline. The drug of course is contraindicated for patients with asthma, chronic obstructive pulmonary disease or other lung diseases.

On the other hand smoking may increase the effect of inhaled insulin therefore Exubera® is contraindicated in smokers or those who discontinued smoking < 6 months before starting treatment.

Conclusion:

The inhaled insulin Exubera® appears to be as effective as injected regular insulin in patients with either DM type I or II. Mild cough can occur and long term pulmonary safeties showed by the above analysis have showed mild physiologic, not pathologic, reversible decline on lung function. Therefore a spirogram should be performed before treatment with inhaled insulin to ensure adequate pulmonary function and patients who stop smoking should wait for approximately 6 months before initiating therapy with inhaled insulin.

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