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Commentary (point of view)

No evidence supports vitamin E indiscriminate supplementation

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Running title: Vitamin E supplementation

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Historic Perspective

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6 Ever since Adam (the Hebrew word for human) ate the forbidden fruit of the tree of
7 knowledge of good and evil (and was therefore expelled from the Garden of Eden), we
8 humans realize that we are mortal. Generally speaking, we are quite unhappy about this fact
9 of life (i.e. death). Hence, we developed several mechanisms to cope with it. First, we do not
10 think about it in our daily life. Second, many people believe in "life after death", hoping that
11 it will be more pleasant than life on earth. Yet, in spite of these mechanisms, almost
12 everyone would do almost everything to prolong his (or her) life on earth, preferably in good
13 health. When it comes to health, either ours or that of our loved ones, we are ready to
14 sacrifice almost everything. People sell houses to pay doctors' fees or to pay healers (or
15 pretenders) who promise them some hope for a few more years on earth, just sufficient to
16 be able to attend a meaningful event, very often associated with their children or
17 grandchildren (birth, Bar-Mitzvah, graduations, marriage, or any other "milestone event").

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19 Irrespective of our belief in an after life, people have always fantasized about ways to
20 slow down the aging process and prolong life, such as drinking some magic water or eating
21 some illusive wonder vegetable or fruit or smelling a rare flower. Literature is full of stories
22 on the devotion of parents to children (or vice versa) that led people to heroic activities
23 associated with getting a magical tool that can help their loved ones "to live happily ever
24 after". In several respects, some measures of "Alternative Medicine" may be regarded as
25 being the modern versions of this search for magic ways to prolong healthy lifetime.

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28 This is not to say that all ethno-botanic medications are worthless. In fact, the
29 development of many of the evidence-based medications is based on the experience of
30 laymen. Understanding of the mode of action of drugs is not a prerequisite for using them.
31 The term evidence-based medicine requires empirical evidence for the effectiveness and
32 safety of potential drugs, as evaluated in controlled prospective trials. For a chemical (or
33 mixtures of chemicals extracted from a natural source) to be approved for medical use, it
34 has to be demonstrated that its effects are beyond the placebo effect. This, in turn, leads to
35 a very strict definition of demands that a potential drug has to fulfill to be approved by the
36 appropriate public authority as a drug.

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39 Food supplements are different. Long shelves in natural products stores, drugstores
40 and even supermarkets are devoted to products that, according to their labels, are "health
41 food" and/or "functional food" and/or "organic" and/or "natural" products that will hopefully
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prolong our lives and/or promote our health. In many cases, the producers are even less modest than that, making claims that relate to established risk factors such as “the product lowers bad cholesterol and elevates good cholesterol”, or “the product is a most potent antioxidant”, assuming that the public already knows that antioxidants are good for our health. In this respect, the way we relate to antioxidants is similar to the way that previous generations related to “wonder flowers.”

Given the evidence for the involvement of (the ill-defined term) “oxidative stress” in more than 200 diseases [11], the use of natural antioxidants, including synthetic vitamins, makes perfect sense. The lipid-soluble “natural” antioxidant vitamin E is one of the most widely used and systematically studied [1,23,27]. Based on data available at the end of the second millennium, the conclusions of Pryor’s review [24] sounded reasonable: “The scientific community must recognize”, he wrote, “that there never will be a time when the science is complete.” Hence, Pryor concludes, “in view of the very low risk of reasonable supplementation with vitamin E” and the difficulty in obtaining sufficient vitamin E from the diet, “some supplementation appears prudent now” [24].

The outcome of supplementation of vitamin E as a trade-off between benefits and harm, a review of meta-analyses.

In the present millennium, several alarming studies undermined Pryor’s comment (shared by many other leading scientists) in favor of high dose, indiscriminate supplementation of vitamin E. Specifically, Pryor’s comment regarding the “very low risk” of high dose vitamin E supplementation is inconsistent (at least apparently) with the results of two independent meta-analyses that reported that the average mortality of those individuals that were supplemented with high dose vitamin E was higher than that of a control placebo group [3,20]. Furthermore, recent studies revealed that under certain conditions antioxidants may interfere with the normal function of various organs. As an example, in a recent publication, Ristow et al show that “antioxidants prevent health-promoting effect of physical exercise” [25]. Notably, such negative effects are not necessarily due to the antioxidative activity of Vitamin E. Similarly, other effects, both negative and beneficial, may result from mechanism(s) other than free radical scavenging [30].

The conclusion that vitamin E supplementation is associated with increased mortality invoked many responses from supporters of vitamin E supplementation [4,21]. Thus, many leading scientists criticized the latter two meta-analyses. Furthermore, in a series of 11

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3 letters to the editor of the "American College of Physicians", the authors raised serious
4 arguments regarding the validity of the conclusions of Miller, et al [20]. Briefly, the major
5 critique raised by these and other authors related to four issues:
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10 (i) The choice of clinical trials included in these meta-analyses and particularly the
11 exclusion criteria [10,13,16], mostly the exclusion of trials that did not contain at
12 least one case of death.
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15 (ii) The heterogeneity of the participants with respect to both their health state and their
16 treatment details, with respect to the source of vitamin E (synthetic vs. natural), the
17 dose, the common combinations with other antioxidants, minerals and other drugs,
18 including statins and aspirin [6,14,19].
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21 (iii) The model used to analyze the data (hierarchical logistic regression model vs. the
22 traditional meta regression) [21]
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25 (iv) The endpoint used (mortality vs. cardiovascular morbidity) [6,10,13].
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31 In their response to the critique, Miller et al. were sufficiently careful to note that
32 although their meta-analysis was based on 19 clinical trials that included 135,000
33 participants, all it showed is that their study "provided evidence that high dosage vitamin E
34 supplementation **may** increase total mortality" [21] (i.e., it may not). Yet, they "stand by
35 their conclusion that the use of high dosage vitamin E supplementation should be avoided",
36 at least until "future trials will refine the estimate of the effect of vitamin E supplementation
37 and the dose at which the relative risk for death exceeds 1." This conclusion is actually not
38 inconsistent with Pryor's rationale [24]. Specifically, Pryor's recommendation to the public, to
39 supplement the diet with vitamin E, was based on the assumption that even if the benefit is
40 not high, the risk of supplementation is very low. If the latter assumption is not valid, Pryor's
41 conclusion might have been to avoid indiscriminate high dosage supplementation.
42 Accordingly, the debate on whether "to E or not to E" is presently focused on whether or not
43 the risk is "very low".
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54 **Decision analysis based on a Markov Model**

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56 The issue of interest to public health is whether or not to supplement our food with a high
57 dose of antioxidants. This of course is a question of a trade-off between the risks and the
58 expected benefits with respect to both mortality and morbidity. In turn, evaluation of this
59 trade-off requires a unifying approach that will enable considerations of both morbidity and
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3 mortality. Such an approach is quite commonly used by HMOs in their evaluation of the
4 expected utility of drugs considered for sponsoring. One of the most commonly used
5 "endpoints" is the composite of morbidity and mortality denoted quality-adjusted life years
6 (QALY) [22]. Using this end-point, the results of clinical trials are analyzed after adjusting the
7 total longevity for morbidity by weighting each year of life according to the individual's state
8 of health [2]. Specifically, each year of healthy, illness-free life equals 1 QALY, whereas each
9 year of life of a CVD patient, following MI or stroke or revascularization, equals less than 1
10 QALY. In other words, the QALY is a sum of products $QALY = \sum n_i p_i$, where i denotes given
11 health state, n_i is the number of years of life at any given health state and p_i is a "preference
12 score" of a value between one (for a healthy participant) and zero (for a dead participant).
13 As an example, if the preference score for CVD post MI is set at 0.7 and during a period of
14 20 years, a person was healthy for 10 years prior to having an MI and the next 10 years he
15 (or she) lived with prevalent CVD (his or hers) QALY would be 17 ($10 \times 1 + 10 \times 0.7$).
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27 In our view, the debate between respected epidemiologists regarding the question of
28 whether or not to recommend supplementation of high dose vitamin E to the general public
29 turned into the question of whether or not it is harmful, as proposed by the meta-analyses
30 mentioned above. In turn, the basis of this debate is whether or not the meta-analyses were
31 conducted appropriately. "Non-epidemiologists" cannot judge which of the approaches is
32 correct. Nonetheless, we think that even if the analysis of the available data indicates that
33 vitamin E is not harmful, chronic supplementation is justified only when there is evidence for
34 significant benefits of supplementation. We are unaware of any such evidence for vitamin E.
35 We think that under the present conditions, the results of the meta-analyses conducted thus
36 far are sufficiently alarming to avoid high-dose indiscriminate supplementation of vitamin E.
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45 Nevertheless, being aware of the limitations of meta-analyses, it is not surprising that
46 supporters of indiscriminate supplementation of vitamin E are not convinced by the meta-
47 analyses conducted thus far. We have therefore adopted a completely different
48 methodological approach, based on decision analyses and designed to answer equivocal
49 questions. The Markov model approach used in our recent analysis [9] is based on
50 evaluation of the probabilities of transitions between predefined health states, using Monte-
51 Carlo simulations on the basis of published data of all the prospective controlled clinical trials
52 and on data available from registries. Our analysis was based on commonly accepted
53 assumptions and axioms used by more than 40 different models that were designed to
54 assess longevity of CVD patients [28]. Unlike meta-analyses, the Markov model approach
55 enables adjustment of the results with respect to most of the heterogeneities [26].
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3 Unfortunately, the results could not have been normalized for heterogeneities in the form of
4 the supplemented vitamin E. Yet, adjusting for most other factors in the Markov model is
5 likely to result in more reliable estimates of the effects of vitamin E than meta-analyses.
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10 Inclusion of all the available data from controlled trials, including trails in which
11 nobody died, normalization of the results with respect to heterogeneities and using QALY as
12 a composite end-point, answers most of the concerns raised against the conclusions of Miller
13 et al [20] and Bjelakovic et al [3]. The main result of our simulations (an average loss of
14 about 0.3 QALY [9]) is also consistent with the conclusions of the latter two studies, namely
15 that indiscriminate supplementation of high-dose vitamin E to the general public may be
16 harmful not only with respect to cardiovascular and all-cause mortality. By using QALY, we
17 have adjusted for the beneficial effects (i.e. reduction of the incidence of non-fatal MI), while
18 considering the overwhelming effect of increased cardiovascular (and all cause) mortality.
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26 Notably, the gain (or loss) of QALY depends very much on the "preference score".
27 We used the commonly-accepted values given in registries that assign these scores on the
28 basis of many clinical trials [2]. Our recent sensitivity analysis show that reasonable changes
29 in preference scores as well as in other important parameters of the Markov model, within
30 accepted ranges, affect the results only quantitatively, without undermining the main
31 conclusion: indiscriminate high dose supplementation of vitamin E to the general public does,
32 on the average, more harm than good. Our more recent preliminary analysis indicates that
33 selective supplementation to people with low vitamin E levels may be beneficial. However,
34 this prediction has to be verified experimentally, as described below.
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42 **Economic aspects of antioxidant supplementation**

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45 Essentially all the studies regarding the effects of antioxidants disregarded the financial
46 aspect of supplementation. Since the HMOs do not pay for antioxidant supplementation, the
47 approach of "money is not an object" reflects our readiness to pay much, even if the
48 expected benefit is questionable. In our search for a long and healthy life, hope substitutes
49 for evidence in bridging between us (especially when we are sick) and our food supplements.
50 Although most of us have limited resources, we often disregard the question of whether the
51 cost of supplements could have been used more reasonably.
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58 Under these circumstances, aggressive promotion by the producers of antioxidants
59 helps increase sales, resulting in an impressive income for the producers. In turn, the
60 producers rightfully spend some of their profits to support research of the effects of their

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3 products and to develop new "improved" products. This raises another issue that is the
4 dependence of the results of scientific research on its funding.
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8 In a recent communication, Lesser et al [15] described the results of their systematic
9 examination of the association between the outcome of scientific publications devoted to the
10 effect of soft drinks, juices, and milk products, on one hand, and the financial support for
11 these studies by relevant industries, on the other. As intuitively expected, the authors found
12 that "industry funding of nutrition-related scientific articles may bias the conclusions in favor
13 of the sponsors' products with potentially significant implications for public health". In their
14 summary of the latter report, the editors note that "it is not clear from this research study
15 why or how this bias comes about." Yet the results did not surprise anybody.
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22 **Selective supplementation**

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25 As stated above, we think that there is no sufficient evidence to justify high dose vitamin E
26 supplementation to the general public. Intuitively, we tend to accept the possibility of
27 selective supplementation proposed by Witztum in his 1998 editorial entitled "To E or not to
28 E, how can we tell?" [29]. In the latter (and other) publication, the authors advocated
29 vitamin E supplementation to people under oxidative stress (OS). Unfortunately, the latter
30 term is ill-defined [8]. Furthermore, in our analyses of the correlations between the most
31 commonly used criteria of OS, we found that no universal criterion can be defined [8].
32 Another approach to the question of who is likely to benefit from vitamin E, can be based on
33 data that connect OS with specific diseases. Specifically, if we discover that a given disease
34 is associated with OS, it implies that these patients are likely to gain from antioxidants. Up to
35 date, we are unaware of any large clinical study that tested the correlations between any
36 criterion and the outcome of selective supplementation of vitamin E. Such a criterion should
37 not necessarily be a criterion of oxidative stress, as discussed below.
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49 In fact, selective treatment of individuals under "oxidative stress" appears to be
50 inconsistent with the results of the population-based Cache County Study [17]. Based on the
51 results of the latter study, Hayden et al [12] proposed that although the use of vitamin E
52 "was unrelated to mortality", the apparent null finding may "represent a combination of
53 increased mortality in those with severe cardiovascular disease and a possible protective
54 effect in those without". Furthermore, the authors advocate "further caution regarding the
55 use of vitamin E by those with existing cardiovascular disease". Under the assumption that
56 CVD patient are under high oxidative stress, the assumption that people under oxidative
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3 stress can be expected to benefit from vitamin E is inconsistent with the experimental results
4 of the Cache County Study [12]. This apparent contradiction may be either due to an
5 unrealistic estimation of the role of oxidative stress in CVD or/and with the hypothesis that
6 vitamin E treatment is helpful for people under oxidative stress.
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11 The latter study [17] may not be general because it involved a rather homogeneous,
12 relatively limited population (old, primarily Caucasian residents of one county). Yet, these
13 results must be considered (and further investigated) before implementing the strategy of
14 antioxidant supplementation to people under oxidative stress. In light of the latter results,
15 we think that none of the methods that were recently developed to evaluate the "oxidative
16 status" can be used to determine who is likely to benefit from vitamin E supplementation.
17 For a method to be capable of predicting whether "to E or not to ", it must be shown in a
18 controlled (preferably double blind) study that people diagnosed as being under "oxidative
19 stress", as detected by the given method, benefit from vitamin E supplementation.
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27 **Conclusions**

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29 In view of the above considerations, we conclude that **indiscriminate supplementation**
30 of high dose vitamin E can not be recommended to the general public. In our subjective
31 view, the reduced rate of non-fatal MI is insufficient to compensate for the increased
32 mortality. Even if we do not accept the conclusion of the meta-analyses of Miller et al [20]
33 and Bjelakovic et al [3], which warn against vitamin E supplementation, we do not share
34 Pryor's view that vitamin E supplementation "is prudent now" just because it is safe [24]. We
35 do not know the mechanisms responsible for harmful effects of vitamin E, but several recent
36 studies show that the outcome of vitamin E supplementation may be negative. As an
37 example, antioxidants prevent health-promoting effects of physical exercise [25]. Another
38 example is the work of Koshkarev, Barshtein and Yedgar, recently presented in the 24th
39 annual meeting of the Israel Society of oxygen and free radical research. In their report, the
40 authors show that vitamin E promotes the adhesion of red blood cells to endothelial cells and
41 conclude that vitamin E is a "double-edge sword".
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54 **Selective treatment** with vitamin E, as proposed by Witztum [29], requires an
55 established selection criterion. The recent results of the Cache County Study [12], as
56 described above, indicate that CVD can not be an indication for vitamin E treatment and may
57 in fact be a contraindication for vitamin E supplementation. Assuming that CVD patients are
58 under oxidative stress implies that the ill-defined term "oxidative stress" (as evaluated by
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3 any method, including commercial testers such as FORM), is not likely to become a
4 diagnostic tool for "telling" whether "to E or not to E".
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8 The only conclusion that may be accepted by both the supporters and those opposing
9 vitamin E supplementation is that of Krishnan et al [14], who advocated conducting a
10 "carefully-conducted randomized clinical trails with long follow-up and well-defined end
11 points". We suggest that such studies should be designed with special effort to identify a
12 criterion capable of predicting who is likely to benefit from supplementation of vitamin E.
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18 Based on the preliminary results of our ongoing study (Dotan, Pinchuk and Lichtenberg,
19 in preparation), we propose that until such a study is conducted, the only criterion to decide
20 whether to initiate supplementation is the low level of vitamin E in the circulation, as
21 recommended by Meagher et al [18]. In a recent study Costantini and Verhulst [7] have
22 shown that a low level of the total antioxidant capacity by itself is "not indicative of oxidative
23 stress". Hence, the decision of whether or not to expect benefit from chronic
24 supplementation of vitamin E should be based on whether or not one month of vitamin E
25 supplementation to patient with low vitamin E level results in a significant decrease of the
26 blood level of lipid peroxidation markers (e.g. MDA).
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34 As a last comment, we wish to raise a general issue regarding the oxidative stress theory
35 of atherosclerosis. The rationale of this theory is that "oxidative stress" plays a role in the
36 pathogenesis of atherosclerosis [5,27]. The most trivial prediction based on this theory is
37 that antioxidants should reduce CVD. In view of the failure of the latter prediction, we should
38 consider **the possibility that the theory is wrong**. Alternatively, we may explain the
39 inconsistency by refining both the theory and predictions as follows:
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45 (i) The ill-defined term "oxidative stress" does not differentiate between different
46 types of oxidative stress [8].
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49 (ii) Different antioxidants may have different antioxidative activity against different
50 types of oxidative stress.
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53 (iii) The failure of antioxidant-supplementation may be a consequence of the latter
54 two facts. Specifically, correlation between the oxidative stress and antioxidative
55 potency of various antioxidants can not be expected because different
56 antioxidants are more effective towards different types of oxidative stress.
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3 The latter speculation implies that different types of oxidative stress are likely to be
4 affected differently by different antioxidants. This hypothesis is not yet verified
5 experimentally and should be tested by studying the relative potency of antioxidants to
6 inhibit differently the production of different markers of oxidation of the various types of
7 oxidative stress. If this possibility is confirmed experimentally, it would mean that the
8 different effects of an antioxidant on the various types of oxidative stress results in
9 heterogeneity of the system with respect to the overall effect of the antioxidant on the
10 concentration-dependence and/or on the various mechanisms responsible for each of the
11 types of oxidative stress. In practical terms, we are quite certain that, on the average,
12 indiscriminate supplementation of high dose vitamin E is not beneficial. Yet, many people
13 may gain from vitamin E because they are under a type of "oxidative stress" that is sensitive
14 to vitamin E. Hence, a study of the effects of antioxidants on the production of different
15 markers that relate to the different types of oxidative stress may yield criteria on "who is
16 about to gain from antioxidant supplementation".
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