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NOT to be distributed inside Egypt
There is no doubt that physical exercise is an integral part of any diabetes management plan, diet and exercise alone could be satisfactory for some people with Type 2 diabetes and should be complementary to drug therapy for others. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals. ADA recommends a regular physical activity program, adapted to the presence of complications for all patients with diabetes who are capable of participating.1

However this exercise plans are not risk free especially in people with diabetes having some cardiovascular problems or at risk of getting those problems, also diabetics with microvascular complications like retinopathy or diabetics with uncontrolled blood sugar levels up and down are also at risk of developing problems with inappropriate exercise plans. So, it seems that the crucial question is, How much physical activity to recommend?

In an editorial just published in Diabetes Care by James O. Hill, PhD, he talked about walking and Type 2 Diabetes where he indicated that you can get impressive improvements in health and reductions in health care costs just by getting your patients with type 2 diabetes to make modest increases in physical activity. A second message is that you can produce these increases in physical activity in a large proportion of your patients with a simple counseling program that requires only a modest commitment of time and effort.2

In this editorial, James discussed a very interesting study done by Di Loreto et al.3

In this study all patients were given a counseling program designed to increase physical activity by at least 10 MET h/week. After 2 years, the results were analyzed based on how much physical activity was actually performed. The authors found significant health benefits with increases in physical activity of >10 MET h/week, and they suggest that this is the minimum increase in physical activity required to achieve health and financial benefits in sedentary patients with type 2 diabetes. Further, they found that the health benefits of physical activity continued to increase as physical activity increased up to a maximum of 21–30 MET h/week. Thus, they recommend 27 MET h/week as a good target for sedentary patients with type 2 diabetes.2

It is likely that your patients and may be yourself ( like mine before reading that article ) do not understand what METs are? how to measure them? or how to calculate MET h/week? METs are metabolic equivalents and measure physical activity in multiples of resting energy expenditure. For example, an activity that is 2 MET has an energy expenditure of two times resting metabolic rate. Calculating physical activity in MET hours per week is a conversion that attempts to account for both duration and intensity of the physical activity. to achieve 11 MET h/week you have to walk 30 minutes a day for a distance of 1.2 Mile ( 1.92 Km ) or a 2400 steps a day, to achieve 27 MET h/week you have to walk 77 minutes a day for a distance of 3.2 Mile ( 5.12 Km ) or a 6400 steps a day.

This article reminded me of a very nice slogan launched by the WHO last year. EAT LESS, WALK MORE!!

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Editor, Middle East Edition
Antioxidant therapy in diabetes - Where Are We Now?

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Diabetes mellitus is a complex disease in which hyperglycemia leads to overproduction of reactive oxygen species (ROS) by the mitochondrial electron transport chain. ROS are reactive chemical entities which in low concentrations serve as signaling molecules; Insulin-induced ROS serve a second messenger function and play an important role in facilitating the insulin action cascade. These positive responses to cellular ROS may seem "paradoxical" because chronic exposure to relatively high levels of ROS have also been associated with functional β-cell impairment and the chronic complications of diabetes. Overproduction of ROS is a first and common step in diverse pathways leading to an increase in polyols, hexosamines, advanced glycosylation products, NF-kappa B, and protein kinase C, which, in turn, contribute to the vascular complications. Oxidative stress could also directly damage cellular proteins, membrane lipids, nucleic acids and eventually lead to cell death. It was demonstrated that the first 2 h of hyperglycemia are sufficient to induce oxidative stress and programmed cell death in neurons exposed to hyperglycemia. Hyperglycemia induced increase in superoxide may induce mutations in mitochondrial DNA. Defective electron transport complex subunits encoded by mutated mitochondrial DNA could increase superoxide production even during subsequent periods of normoglycemia (hyperglycemic memory). Living organisms have evolved a network of antioxidant defense mechanisms to maintain their survival against oxidative stress. These mechanisms are different in the intracellular and extracellular compartments and are of enzymatic or non-enzymatic nature. Among the intracellular enzymatic mechanisms are superoxide dismutase (SOD), catalase and glutathione peroxidase.

Is antioxidant beneficial? Reports using cell cultures and diabetic animal models clearly demonstrated that maneuvers preventing ROS production attenuate or completely abrogate early micro- and macrovascular end-organ damage of diabetes. Therefore, antioxidants appear to be a logical therapy. But does the use of antioxidants have produced a clinical benefit?

Several experimental trials had demonstrated beneficial effect of antioxidant vitamins especially vitamin E and C. The antioxidant vitamins reduce cardiovascular events by improving endothelial function and by preventing oxidative modification of low-density lipoproteins. Unfortunately, despite extensive studies in both observational and randomized trials, the weight of evidence points to little or no benefit from antioxidant therapy. However, if vitamins are to be used as antioxidants several concepts must be considered. Vitamin and mineral Supplementation are not recommended unless patients are deficient. Use of vitamins in excess may have adverse effects. Giving too much of one vitamin in an altered redox environment may change its effect from an antioxidant to a pro-oxidant. After acting as an antioxidant (donating an electron), a vitamin may become an oxidant if the net redox state is not corrected. Treatment with proper amounts of antioxidant vitamins is best accomplished with adequate intake of vegetables and fruits. A high consumption of fruit and vegetables (700-1000 g/day) by diabetic patients seems to produce an improvement in some redox status parameters. The growing interest in the substitution of synthetic food antioxidants by natural antioxidants has fostered research on vegetable sources for identifying antioxidants. Several studies suggested that many of naturally occurring substances possess antioxidant properties e.g fenugreek seeds, walnut, grape seed extract, Zingiber officinale Roscoe and Coffee.

The weak effect of vitamins as antioxidants in clinical trials may be due to their effect on scavenging already-formed oxidants and their activity against only some components of oxidative stress. New antioxidant therapy e.g. SOD or catalase mimetics, L-carnitine and lipoic acid, which work as intracellular superoxide scavengers, improving mitochondrial function and reducing DNA damage, may be good candidates for such a strategy.

As hyperglycemia plays a key role in the generation of ROS, it is not strange that tight metabolic control is beneficial. Hyperglycemia-induced oxidative stress can be prevented if good metabolic control is initiated very early, but are not easily reversed if poor metabolic control is maintained for longer durations. Strict glycaemic control with intensive insulin therapy was found to prevent or reverse ultrastructural and functional
abnormalities of hepatocyte mitochondria.\textsuperscript{15}

Alpha lipoic acid may have a unique self-regenerating capacity as a mitochondrial antioxidant,\textsuperscript{16} and the possibility that it restores endothelial dysfunction in diabetic patients has been suggested.\textsuperscript{17,18} Alpha-lipoic acid improves albuminuria and patholgy in diabetic animals by reducing oxidative stress, while in healthy animals, alpha-lipoic acid may act as a pro-oxidant, contributing to renal dysfunction.\textsuperscript{19} Alpha-lipoic acid also prevents glucose-induced oxidative stress and cell death in neurons and it could have broad application to the treatment of diabetic patients.\textsuperscript{4}

L-carnitine act as an intracellular superoxide scavenger, improving mitochondrial function and reducing DNA damage. Treatment of diabetic rats with L-carnitine resulted in partial restoration of the endothelium-dependent relaxation response to acetylcholine and normalized the oxidant/antioxidant state.\textsuperscript{20}

Increasing L-carnitine levels may improve FFA-induced and obesity-associated endothelial dysfunction. This improved endothelial function may delay or prevent the development of excess cardiovascular disease.\textsuperscript{21} Acute intravenous administration of carnitine in patients with type 2 diabetes with PAD improved PAD-related symptoms as well as glycaemic control.\textsuperscript{22}

SOD mimetic compounds could normalize endothelial dysfunction in diabetic rats.\textsuperscript{23} However, the exact beneficial role of SOD or catalase mimetics need further studies to be clarified. LY 333531 which block the protein kinase [beta] isofrom may also be a promising tool.\textsuperscript{19}

It is now evident that some of the already available drugs possess antioxidant benifits e.g. thiazolidinediones, statins, calcium channel blockers, and ACE-I and it has been suggested that many of their beneficial ancillary effects are due to this property.\textsuperscript{24} Antioxidant benefits have also been reported in diabetic patients treated with gliclazide,\textsuperscript{25} metformin,\textsuperscript{26} amylin analog, pramlintide\textsuperscript{27} and aldose reductase inhibitor, fidarestat.\textsuperscript{28}

Summary: Oxidative stress is involved in the pathogenesis of diabetes and its complications, implicating that strategies to monitor and combat oxidative stress should have a role in the management of diabetic patients. Although, clinical trials with antioxidants vitamins have failed to demonstrate a beneficial effect, antioxidant drugs that could target subcellular compartment may prove promising. There is definitely a need for large clinical trials to evaluate the effectiveness of different antioxidants in diabetic patients. However, nowadays several strategies could reduce oxidative stress e.g. optimizing metabolic control, increasing intake of vegetables and fruits, alpha lipoic acid, L-Carnitine and selecting drugs that simultaneously had antioxidant benefits.

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