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LINKAGE OF YOGA TO OXIDATIVE STRESS IN PATIENTS WITH DIABETES MELLITUS, TYPE 2

Abstract. *Although yoga has been practiced for around thousands of years with developing up-to-date therapeutic approaches it is being explored more and more with each passing day. Numerous questions are still not enlightened. This brief research aimed to reveal the influence of yoga on oxidative stress in patients with diabetes mellitus type 2 and highlight underinvestigated queries.*
Keywords*: yoga therapy, diabetes mellitus type 2, oxidative stress, free radicals, glycaemia.*

Introduction

Oxidative stress (OS) is one of the pathogenetic links in a plethora of disorders including diabetes mellitus, type 2 (T2DM) [1] – a disease which is among the most important public health problems [2] with intensively increasing prevalence worldwide.[3]

Dysregulation between production and counterbalance of free radical species leads to OS.[4] The latter plays a pivotal role in the development of T2DM complications as it has been implicated as the root cause underlying manifestation and progression of insulin resistance, β-cell dysfunction, macro- and microangiopathy, and neuropathy. OS appears when cells do not destroy adequately the excess of free radicals formed.[5]

Now the question arises: what are free radical species? These are nothing but free radicals that cause cell death by damaging DNA, RNA and proteins in cells and

tissues by reacting with other molecules in the cell.[4] Reactive oxygen species (ROS) include superoxide anion ($O2^{\cdot -}$), hydroxyl ($\cdot OH$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl) while reactive nitrogen species (RNS) comprise nitric oxide ($\cdot NO$), nitrogen dioxide ($NO_2^{\cdot -}$) and peroxynitrite ($OONO^-$).[6] Free radicals (RONS) are produced either from normal cell metabolisms in situ or under the influence of external sources like pollution, cigarette smoke, radiation, and medication.[7]

Oxidants play a duplex role as both are toxic and beneficial compounds depending on the concentration within the body. At low or moderate levels, RONS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate OS - a deleterious process that can damage all cell structures, resulting in inflammation and the development of other pathological conditions.[8]

Different methods are used to decrease the OS level including both pharmacological as well as non-pharmacological ways. One group of these antioxidants is enzymatic (intracellular),[4] which includes superoxide dismutase (SOD),[9] glutathione (GSH) peroxidase, and catalase (CAT).[10] Also, we have some natural antioxidants (vitamins A, C, E, selenium, carotenoids, etc.) and low-molecular-weight synthetic ones (acetylcarnitine, acetylcysteine, ascorbic acid, β-carotene, etc.).[11]

Physical training, including yoga, is another activity leading to alleviating OS.[12]

Our main focus of this review is to analyze data regarding yoga training’s influence on OS in patients with T2DM. For this purpose, we provided a systemic literature search of evidence-based data in databases PubMed and Google Scholar for the period from 2002 to April 2022.

Main body

Although yoga has been practised since ancient times, yoga as therapy is still a relatively new and emerging trend in the healthcare field. Extensive research has explored changes in biochemical, electrophysiological, cellular, genetic, neuromuscular, and radiological parameters related to yoga practice. This has

facilitated the practical application of yoga in various diseases, and it is now being recognized worldwide as a clinically viable treatment. Traditionally a mind-body practice with the ultimate goal of spiritual enlightenment, yoga is a science of health management, rather than a therapy for treating specific diseases. Yoga being a slow, static muscular exercise is considered to be one of the favourable, cost-effective options in the treatment and prevention of T2DM, as it can reduce stress-related hyperglycaemia and have a positive effect on blood glucose control. It is speculated that the above-mentioned yoga effects are associated with increased insulin sensitivity in target tissues, leading to decreased insulin resistance, and improvement of peripheral utilization of glucose. Furthermore, it has also been postulated that yoga can accelerate the regeneration of β-cells of the pancreas [13].

Hyperglycaemic-induced OS increases the levels of pro-inflammatory proteins leading to local and systemic inflammation.[14] Besides, considerable variation in OS biomarkers in T2DM patients were registered.[15] It has been shown that the release of inflammatory mediators is prompted by hyperglycaemia and mediated by OS confirming the link between T2DM, OS, and inflammation.[6]

Yoga can be a powerful complex method of influence on OS level. Thus, Manna I. et al registered a reduction in the OS parameters, particularly malondialdehyde (MDA) level ($P < 0.001$), among the yoga group after 12 weeks when compared to baseline data (0 weeks). At the same time, there was an increase in SOD ($P < 0.001$), CAT ($P < 0.001$), as well as decrease in GSH ($P < 0.001$) and ascorbic acid levels ($P < 0.001$).[4]

Predominantly OS state is assessed by MDA, and SOD levels, but adiponectin also reduces inflammation and OS. Moreover, even adequate control of blood glucose level is considered to normalise OS markers (increase in SOD, total antioxidant capacity, decrease in MDA, $P < 0.005$).[16] A hyperglycaemic state can lead to an increase in the levels of OS-induced DNA damage markers such as 8-hydroxy-2’-deoxyguanosine (8-OHdG) and 8-oxo-7, 8-dihydro-2’-deoxyguanosine; lipid-peroxidation products measured as thiobarbituric acid-reactive substances (TBARS); protein oxidation products such as nitrotyrosine and carbonyl levels and also lower the activity of antioxidant enzymes.[6] Viswanathan et al noticed a

significant reduction not only in blood glucose levels, HbA1C, and lipid levels but also IL6, TNFα, and TBARS as well as a marked improvement in adiponectin levels in 150 patients practicing yoga for 3 months 50 minutes 5 days a week.[17]

It is registered that even glycaemic variations over a daily period have been positively linked to OS. Controlling acute glucose fluctuations over a daily period in T2DM patients reduces the activation of OS.[18] It has been shown that changes in the mitochondrial membrane could lead to activation of complexes in the electron transport chain thereby contributing to the production of oxygen radicals. In addition, NADPH oxidase is documented to produce ROS and is viewed as the principal source of glucose-induced ROS formation in the tissues and cells of T2DM models. Additionally, xanthine oxidase plays a role in the generation of ROS that causes the manifestation of T2DM and the progression of its complication. Besides, glucose and its metabolites have been reported to react with hydrogen peroxide in the presence of iron and copper ions to form hydroxyl radical during auto-oxidation thereby promoting the generation of ROS and the development of diabetic complications. RONS are produced through various routes such as intensified polyol pathway, formation of advanced glycation end-products, and protein kinase C activation. The OS initiated by hyperglycaemic is due to the increased intracellular and extracellular free radical concentrations. Decreased levels or activities of antioxidant protein (GSH), enzymes (CAT, GSH peroxidase, SOD), micronutrients (selenium and zinc), and vitamins (C, E and A), as a result of hyperglycaemia, stimulates the generation of RONS. Consequently, OS in turn triggers the production of inflammatory cytokines and chemokines.[5]

Chronic hyperglycaemia is seen as a principal factor in promoting the development of micro- and macrovascular complications in T2DM, as hyperglycaemia is known to be responsible for the damage of DNA, lipids, and proteins. The degree of damage has been linked to the intensity of hyperglycaemic-induced production of RONS. At the same time, OS is also strongly suspected to be involved in chronic hyperglycaemia-induced insulin resistance.[6] The metabolic T2DM abnormalities cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels.[19]

Yoga therapy as a complex intervention with various components improves glycaemic control, reduces the risk of T2DM complications, and impacts remarkably on the course of the disease.[20] Patients with T2DM who completed the yoga program were characterised by significantly lower HbA1c, fasting blood glucose, and stress level compared to the group with low adherence to yoga training.[21]

Consequently, yoga is vastly used in the management of T2DM. Moreover, it is considered that yoga can prevent the disease from developing by rejuvenating pancreatic cells and exercising the muscles.[20]

Meta-analysis of 4 trials (440 adult patients diagnosed with T2DM) indicated that yoga significantly reduced MDA (SMD: -1.4; 95% CI -2.66 to -0.13; P = 0.03; I2 = 97%), fasting plasma glucose levels (SMD: -1.87: 95% CI -3.83 to -0.09; P = 0.06; I2= 99%), and HbA1c (SMD: -1.92; 95% CI - 3.03 to -0.81; P = 0.0007; I2 = 92%) in patients with T2DM. No such effect was found for SOD (SMD: -1.01; 95% CI -4.41 to 2.38; P = 0.56; I2= 99%). Definitely, yoga would be beneficial in the management of T2DM as a complementary therapy. Furthermore, even dispute regarding usage of yoga as a main but not add-on therapy has been arisen. However, considering the limited number of studies further stronger investigations are recommended.[22]

One of the studies was conducted at the diabetes clinic of Kasturba Medical College hospital and four community diabetes clinics offering primary care to diabetic patients in Mangalore, India. A total of 123 T2DM patients aged between 40 and 75 years were training a complex of yoga exercises, particularly tadasana, padahastasana, vrikshasana, trikonasana, parsvottanasana, vajrasana, vakrasana, gomukhasana, paschimottanasana, uttanapadasana, pawanamuktasana, bhujangasana, shalabasana, dhanurasana, viparita karani, sitkari and bhramari pranayama, anuloma viloma, and savasana for three months. A significant improvement in MDA (reduction by 20% (-10.8 ± 1.4 μmol/L)), GTH, and vitamin C were registered, unlike the control group.[23] These results correspond to Gordon et al study with 6 months of yoga training and a 19.9% reduction in OS in T2DM patients.[24]

Yoga exercises have the physiologic substantiation of their mechanisms. For

instance, a study showed that vaman dhauti practice (emetic therapy) helps in the reduction of fasting and postprandial blood sugar levels, increases glucose uptake, minimises insulin resistance, and promotes the function of insulin by reducing levels of circulating free fatty acids in the body. The abdominal pressure created during exhalation in kapalbhati improves the efficiency of β-cells of the pancreas. Shankhaprakshalana is the process of cleansing the intestinal tract by practicing a set of yoga postures and drinking lukewarm water with salt in between. This sequence is repeated till only water is evacuated. The level of blood glucose falls significantly with this intestinal cleansing process. It has been claimed that this practice increases insulin production and helps in the control of diabetes. Surya namaskar (sun salutation) is performed in an energetic way that increases cellular requirements for oxygen and glucose and to meet these requirements, insulin production is stimulated through brain signaling. Seated postures such as ardha matsyendrasana, yoga mudra, and mandukasana improve pancreatic function whereas asanas with forwarding bends massage and pressurize the pancreas and stimulate the secretion of insulin. In patients with diabetes, pancreatic cells may be regenerated and pancreatic β-cell sensitivity may be increased by the alternating abdominal contractions and relaxations involved in yoga practice. Improved blood supply to muscles may enhance insulin receptor expression in the muscles, causing increased glucose uptake. In a study, it was observed that optimum control of diabetes was achieved by practicing dhanurasana and matsyendrasana. Even more, yoga practice is thought to have “beyond the drug action,” which refers to the potential to induce stem cell trafficking from the bone marrow to the peripheral blood, leading to tissue regeneration by replacement and recruitment of cells differentiated from the stem cells. However, yoga mudra and shalabhasana worsened participants’ diabetic status, for reasons that are not clearly understood.[14]

Controlling mental stress (stress management) is one of the keys to the treatment of T2DM. Stress increases the risk and severity of T2DM by stimulating the hypothalamic-pituitary-adrenal and sympathetic axes and parasympathetic withdrawal, resulting in increases in the levels of cortisol, epinephrine, norepinephrine, growth hormone, glucagon, catecholamines, prolactin, leptin, and

neuropeptide Y. Psycho-neuro-endocrine and immune mechanisms are involved in the beneficial effects of yoga on T2DM patients. Stress management can be done by using controlled breathing techniques, meditation and body postures, yoga, and other mindfulness-based programs to invoke a relaxation response. This response helps in regulating cortisol and other stress hormones, which increases blood pressure and blood glucose levels [19]. Yoga effectively reduces stress, depression, and anxiety resulting in increased wellness, improvements in the physical, psychological, social domains and total quality of life.[25]

Conclusion

Yoga is considered to be helpful in T2DM, particularly due to reducing OS. However, not enough high-quality trials were conducted yet, high heterogeneity in non-standardised low power researches was observed. Moreover, there are certain questions that still remain unanswered. Further research is needed to objectively proof the positive influence of yoga on OS in T2DM and precisely elucidate disputable points.

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[3]Exposure of β-cell line and isolated pancreatic islet cells to oxidative stress has been shown to inhibit the promoter activity and mRNA expression of the insulin gene therefore, decreasing insulin gene expression . So Oxidative stress has been found to be involved in chronic hyperglycemia-induced insulin resistance . To verify whether Oxidative stress linked to glycaemic variations, a randomised trial was conducted in which evaluation of the effects of daily glucose excursions on plasma oxidative stress parameters were done . All the participants had 48 hour continuous subcutaneous glucose monitoring at first and third visits. Conclusion came out to be that activation of oxidative stress can be reduced by controlling acute glucose fluctuations over a daily period in type 2 diabetic patients. In diabetes, oxygen radicals are produced due to changes in the mitochondrial membrane due to activation of complexes in the electron transport chain. NADPH oxidase produces reactive oxygen species (ROS) and is principal source of glucose-induced reactive oxygen species formation in the tissues and cells of diabetic models.The oxidative stress which is initiated by hyperglycemia is due to the increased intracellular and extracellular free radical concentrations. Decreased levels or activities of antioxidant protein (glutathione), enzymes (catalase, glutathione peroxidase, superoxide dismutase) and micronutrients (selenium and zinc) and vitamins such as vitamin C, E and A, as a result of hyperglycemia stimulate increase production of reactive oxygen species, further contributing to oxidative stress.

Yoga with several subtypes and physical postures (asanas), controlled breathing (pranayama), deep relaxation, and meditation proved to be of great help in lots of diseases .

[3]A hyperglycaemic state can lead to an increase in the levels of oxidative stress-induced DNA damage markers such as 8-hydroxy-2’-deoxyguanosine (8-OHdG) and 8-oxo-7, 8-dihydro-2’-deoxyguanosine that further lower the activity of antioxidant enzymes.