Abstract. Yoga has the potential for prevention, rehabilitation, and even accessory treatment of some disorders, particularly those with endothelial dysfunction, as one of the pathogenetic links. However, this review has revealed insufficient information about biochemical markers of endothelial function to confirm or refute the effectiveness of yoga. Further methodologically robust trials are required to establish the yoga effectiveness in endothelial function normalization.

Keywords: yoga therapy, endothelial function, training, biochemical markers.

Introduction

It is demonstrated that yoga additionally to baseline medicines is helpful for the management of patients with different disorders, particularly arterial hypertension [1], diabetes mellitus [2], obesity [3], coronary artery disease [4], COVID-19 [5], and many others. Moreover, it is recommended for the prevention of particular conditions occurrence, including major adverse cardiovascular events [6] as well as for rehabilitation of patients with coronary artery disease [7,8], stroke [9].

It should be emphasized that the vast majority of studies are dedicated to revealing the final result of yoga therapy influence [1,2,3,5]. This plethora of trials has raised a question in our brain about what possible mechanism or complex of action provide such improvements if it is connected with psychological effects, influence onto a nervous system (autonomous or central) or yoga training enables
the metabolism conversion, changing the course of pathogenetic links of some diseases. While analyzing the list of therapeutic disorders yoga is helpful for we have noticed that most of them include endothelial dysfunction (ED) as one of the key factors for manifestation and progression. The endothelium is a multifunctional metabolic and endocrine organ with vascular hemostasis, vessels tone regulating, and barrier function between blood and tissues. Undoubtedly, it plays a crucial role in homeostasis maintaining [10].

Therefore, our research question was if yoga training can influence endothelial function (EF), particularly its biochemical indicators.

We performed a systematic search for relevant research studies from December 2011 to December 2021. The search was constructed around yoga-based techniques and EF/ dysfunction in databases like PubMed and Google Scholar. All the yoga-based interventional surveys on EF, its above-mentioned defined biochemical markers or disorders which are connected with ED were included in this review.

Main part

EF can be assessed by a study of the levels of endothelial origin molecules in circulating blood [11]. Thus, in this review, we have analyzed such biochemical markers indicating the endothelium condition [12] as an endothelial-derived hyperpolarizing factor (EDHF), nitric oxide, cyclooxygenases, lipoxygenases, endothelin-1, reactive oxygen species, endoglin, factor von Willebrand, the heparin-antithrombin III system, tissue factor, thrombomodulin/protein C system, and fibrinolytic qualities. In addition, the second group of indicators includes the indirect markers, normalization of which under yoga intervention appoints to the improvement in course of baseline disease and consequently EF.

Nitric oxide is one of the most investigated substances that endothelial condition is defined on. Endothelial nitric oxide -synthase (eNOS)-derived nitric oxide regulates not only blood flow and vascular tone, the suppression of proliferation and migration of smooth muscle cells, the interaction of leukocytes with endothelium [13] but even metabolic activity [14]. Decrease in nitric oxide production may further cause problems with vasoconstriction in coronary arteries resulting in ischemia, even myocardial infarction, adding more towards vascular
inflammation [15].

Udhan et al. registered a significant increase in total plasma nitric oxide in healthy individuals after 6 months of yoga training (6 days per week) [15]. This data corresponds with the previous trial of Lakshmanagowda et al. The latter group of scientists highlighted that in Seniors Batch (those who practice yoga regularly for more than 1 year) the total plasma nitric oxide concentration was higher in comparison with Junior Batch (yoga practice less than 1 year) [16]. Even in 12-week yoga-based program, a significant increase in eNOS and total nitric oxide concentrations were noticed (p<0.05) [17]. Regarding nitric oxide syntheses enhancement, Taneja MK has proposed modified Bhramari Pranayama use along with other modes in the treatment of COVID-19 as it is suggested that humming promotes nitric oxide production [18].

It is well established preventive role of EDHF in vascular dysfunction [19]. In a low statistical force trial (n=17 (yoga) vs n=18 (control)) a significant increase in EDHF concentration was registered in yoga-training patients with diabetes mellitus and arterial hypertension (a mean difference at 342.72±22.23 in the yoga group). Simultaneously, normalization of blood pressure (BP) was detected in the yoga group with a higher magnitude of changes (yoga vs. control systolic BP: 153.53±12.18 mm Hg vs. 156.47±11.6 0 mm Hg; p<0.001; diastolic BP 81.76±8.09 mm Hg vs. 90.00±6.12 mm Hg; p=0.002) [20].

Endothelin-1 as the most investigated member of the endothelin peptide family with multifunctional cytokine-like activity plays a tremendous role in arterial hypertension, coronary atherosclerosis, myocardial infarction, including myocardial infarction in the absence of obstructive coronary artery disease [21]. Although multiple trials with yoga intervention demonstrate a significant decrease in BP, no changes in endothelin-1 concentration were registered after short-term (10 days) yoga training in 30 overweight and obese men [20]. In contrast, a 12-week Yoga-based Cardiac Rehabilitation program (Yoga-CaRe) is suggested in patients after acute myocardial infarction due to improvement in ED. A statistically significant reduction in endothelin-1 (p<0.001) was found [17].

Endothelial microparticles are considered a brand new biomarker of
endothelial activation and damage. They are excreted from endotheliocytes in response to inflammation [22]. Hatha yoga training is proposed as prophylaxis of metabolic syndrome. In 8 weeks trial with 30 healthy females, a significant reduction in CD31+/CD42b- endothelial microparticles as well as other metabolic syndrome hallmarks (plasma cholesterol, low-density lipoproteins, insulin) were detected [23].

Endoglin, a type-III accessory receptor for the Transforming Growth Factor-β pathway, is characterized by a crucial role in endothelial cell proliferation and migration [24]. As it is a relatively new biomarker no trials with an assessment of endoglin concentration changes under the yoga intervention are noticed during the last 10 years. However, the concentration of endoglin is tightly connected with eNOS, particularly dynamic of both mentioned substances correlates under the action of some medicines (atorvastatin) [25]. So, we can suspect its increase under yoga intervention as in the case of nitric oxide, though it should be proved by relevant clinical trials.

Adipokines represent another group of EF markers providing tight cross-talk between inflammation, carbohydrate and lipid metabolism, immunity, hemostasis, neuroendocrine function, BP, and many more, often with opposite directed functions [26]. Yoga training provides a trend to normalization in both anti- (adiponectin) and pro-inflammatory adipokines (leptin, chemerin, visfatin, plasminogen activator inhibitor-1). Such effect was registered in 52 patients with metabolic syndrome after 1-year 3-times a week yoga training [27]. It should be noticed that short-term yoga intervention also causes a significant increase in the plasma adiponectin (median 4.95 μg/mL vs 6.26 μg/mL, respectively, p=0.014) [20].

Changes in the concentration of some EF markers under yoga training are rather well investigated. But not enough attention is paid for enormous others with not lower importance in pathogenetic links, that are produced by the endothelium, like markers of hemostasis (tissue factor, von Willebrand factor, tissue plasminogen activator and its inhibitors and many others).

The second part of the current research is dedicated to the surveys with yoga influence on hallmark indicators of different disorders associated with ED.
Arterial hypertension is defined to be connected with ED. Consequently, accurate BP control can improve endothelium state. Under yoga training decrease in systolic and diastolic BP in patients with concomitant diabetes mellitus was registered after 2-months exercising [28], 95 days of training (systolic BP -7.66 mmHg (95% CI: -10.4, -4.93), diastolic BP -3.86 mmHg (95% CI: -6.65, -1.06)) [28]. However, in terms of BP control at rehabilitation of patients after acute coronary syndrome, it didn’t show any significant improvements [17]. At the same time, LIMBS (Lifestyle Modification in Blood Pressure Study II) revealed the same effect of yoga as lifestyle modification/diet in healthy patients or with arterial hypertension (stage I) after 24 weeks of intervention [27].

As it was shown in 12-weeks research yoga leads to normalization of lifestyle and body mass index in obese patients (B=-0.26; CI [-0.56; -0.07]) [14]. After 2 months of yoga training a significant reduction in body mass index (-0.2±0.8 kg/m² vs 0.6±1.6 kg/m², p=0.05), waist circumference (-4.2±4.8 cm vs 0.7±4.2 cm, p<0.01) and weight (-0.8±2.1 kg vs 1.4±3.6 kg, p=0.02) was demonstrated in patients with diabetes mellitus [28]. But even on Day 10 a significant decrease in weight (74.60±7.98 kg vs 72.69±8.37 kg, p<0.001, respectively), body mass index (26.26±2.42 kg/m² vs 25.69±2.47 kg/m², p<0.001, respectively), and systolic BP (121.73±11.58 mm Hg vs 116.73±9.00 mm Hg, p=0.042, respectively) was registered. Moreover, there was a significant reduction in plasma interleukin-6 (median 2.24 pg/ml vs 1.26 pg/mL, respectively, p=0.012) [20].

It is well defined that long-term inflammatory response is associated with an impairment in endothelial barrier function. On the one hand, deviation of endothelial barrier function leads to the development of inflammatory diseases. On the other hand, proinflammatory cytokines (tumor necrosis factor) modulate further changes of endothelial barrier function via Rho GTPases, Rac-mediated generation of reactive oxygen species, modulation of cell-cell interaction via adhesion receptors (ICAM-1, VCAM-1, PECAM-1). Besides, inflammation leads to modification of leukocyte transendothelial migration and endothelial permeability [29]. Kiecolt-Glaser JK et al. demonstrate that 3-months of 90-minute twice per week hatha yoga classes provide a decrease in the production of proinflammatory cytokines
interleukin-6 (p=0.027), tumor necrosis factor alpha (p=0.027), interleukin-1β (p=0.037) in comparison with the control group. Furthermore, even 3 months post-treatment decrease in interleukin-6 (p=0.01) and interleukin-1β (p=0.03) (but not tumor necrosis factor alpha production, p>0.05) was registered [30].

Pina AA et al. fixed rather impressive results concerning lipid metabolism after yoga training. It was highlighted that even a single bout of yoga (1-hour yoga session) can significantly decline the non-high-density lipoproteins cholesterol (p<0.05) [31].

However, in contrast to the abovementioned studies at a 3-month UK study with 25 yoga training group vs 35 participants without yoga intervention, no efficacy at any of the investigated indicators (BP, heart rate, effects on the hypothalamus-pituitary-adrenal axis, autonomic function, body fat, blood lipids, glucose) was demonstrated [7]. And this survey corresponds with Sweden study. No improvements in BP, body mass index, weight circumference, inflammatory biomarkers (high sensitive C-reactive protein, interleukin-6), lipid metabolism (cholesterol, triglycerides, low-density lipoproteins, high-density lipoproteins), carbohydrates metabolism (FP-glucose, HbA1c) were demonstrated even with more participants (n=83) with the time of intervention – 3 months [32].

Summarizing our search based on included researches, we would like to emphasize a few issues. Most trials with yoga intervention are with low power that possibly may lead to statistical bias, even more – cause irrelevant results. In addition, rather often the design of researches is unstandardized. These points may be the explanation for contradictive results. Furthermore, the longevity, intensity, regularity of yoga training are the obvious factors that we should take into account. Moreover, mechanisms due to which yoga can cause changes are still under question.

Conclusion

Yoga influence on EF is underinvestigated. Trials with low statistical power prevail among the yoga therapy surveys. There is a lack of studies with analysis of EF biochemical markers. Consequently, additional surveys as well as further meta-analysis for evidence-based assessment of yoga training influence on the EF should be provided.
References:
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