

7.0 DISCUSSION

In this randomized clinical trial involving 10 weeks of yoga intervention for T2D patients compared to a control group with routine exercises, the study results showed significant improvements in various outcome measures for the Yoga group. Yoga group showed a significant reduction in DNA damage, as indicated by changes in Tail Moment and Olive Tail Moment compared to the Control group. This may have been due to consistent improvement observed in causative parameters like blood sugar, lipid levels, and oxidative DNA damage (8-OHdG) observed in the Yoga group, though the improvement observed in the antioxidant status (TAC) was not significant (**Table3**). Previous studies also have reported that yoga practices reduce blood sugar (Nagarathna et al., 2012), oxidative stress, and improve antioxidant status and thus may have therapeutic effects on metabolic disorders (Gordon et al., 2008; Hegde et al., 2019; Yadav et al., 2019). Tolahunase et al. reported a significant reduction in cellular aging rates, represented by lower levels of 8-OHdG, ROS, cortisol, IL-6, increased TAC, and telomerase activity in healthy populations practicing yoga (Tolahunase et al., 2017).

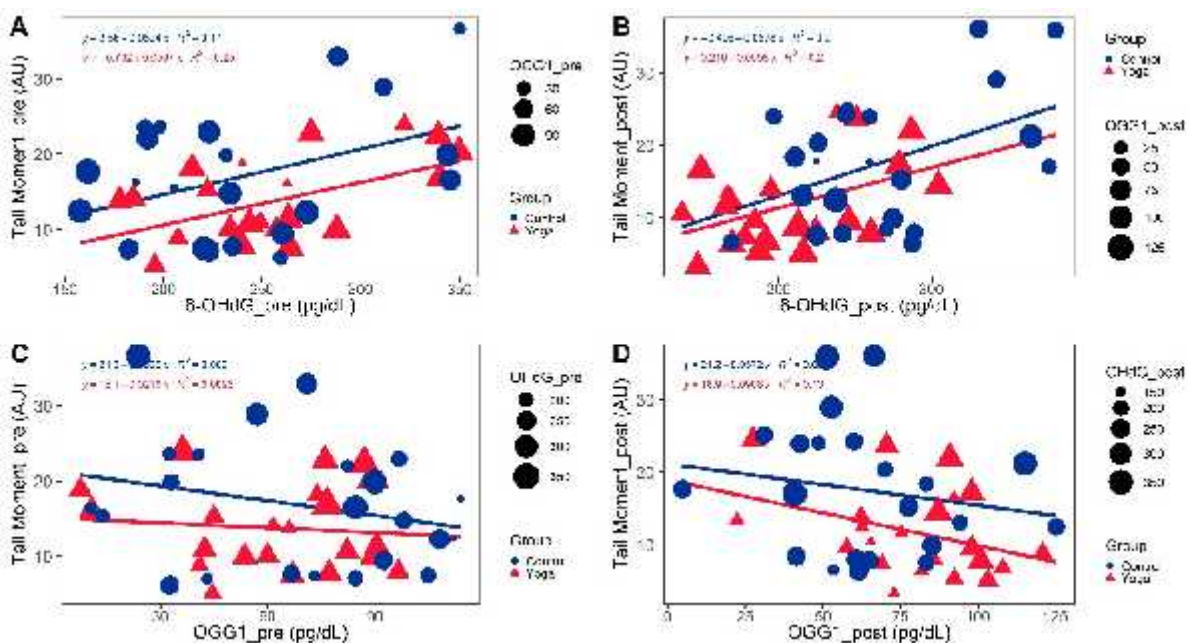


Fig 7. Causative relationship between mediators and DNA damage

Figure 7. (A-D): Causative relationship between the mediatory variables' Oxidative DNA damage (8-OHdG) and DNA repair (OGG1) with DNA damage (Tail Moment) in the light of a 3rd variable (indicated by dot / triangle size) for both pre-and post-intervention

On the DNA repair front, results from the present study showed significant improvement in OGG1 protein expression. It is evident from the results that DNA damage is diminishing in the Yoga group post-intervention as indicated by the slopes of the regression equation compared to baseline (**Fig 7**), with lower 8-OHdG and higher OGG1 levels. This shows, that oxidative DNA damage was reduced and the efficiency of DNA repair was enhanced in the Yoga group. None of these improvements were observed in the Control group (**Fig 8**). Similar observations were made by studies employing exercise and yoga training in people with T2D and a healthy population. While exercise training increased genomic stability with better regulation of DNA damage response in T2D patients (Dimauro et al., 2017; Pittaluga et al., 2015), others reported regular exercises increased OGG1 activity and promote DNA repair (Radak et al., 2019) and yogic practices were found to upregulate DNA repair genes like *PARP* and OGG1 in sperm cells leading to reduced DNA damage (Dhawan et al., 2018).

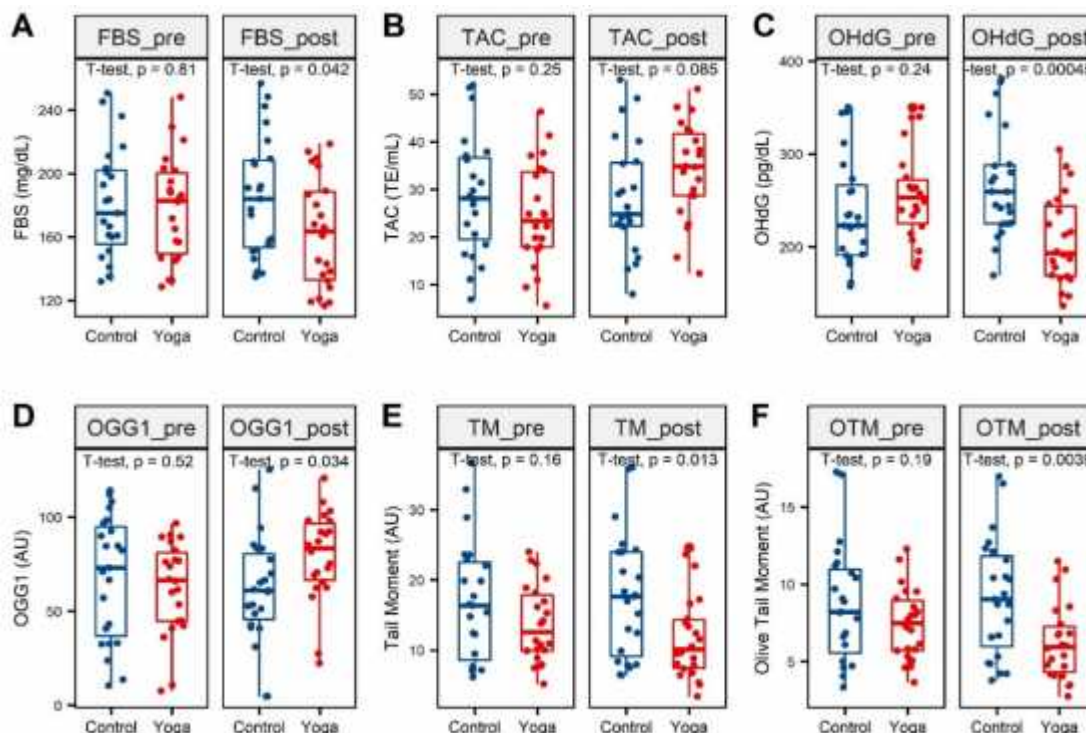


Fig 8. Group comparison of primary outcome measures with its distribution profile

Figure 8. (A-F): Distribution profile of primary outcome measures with group comparison for both pre and post-scenario. *P*-values were obtained using independent t-test. (A) Fasting Blood Sugar; (B) Total Antioxidant Capacity; (C) OHdG (8-hydroxy-2'-deoxyguanosine); (D) OGG1 (8-Oxoguanine glycosylase); (E) Tail Moment; (F) Olive Tail Moment

Interestingly, oxidative stress was also found to diminish OGG1 protein stability by downregulating p300 mediated acetylation (Shah et al., 2018) apart from its down-regulation in hyperglycemic conditions (Simone et al., 2008). Increased DNA damage found in the Control group with lower OGG1 levels in the present study is in tune with the above observation. Hence, lower DNA damage observed in the Yoga group in the post scenario could be due to the combined effect of lower systemic oxidative stress, better scavenging of oxidative radical by the antioxidant mechanism, and enhanced DNA repair among the practitioners. A scientific review observed that yoga and meditative practices conserve DNA integrity by reducing OS-induced DNA damage and better regulation of genes involved in the DNA repair process, cell-cycle control, and anti-inflammatory effects (Bisht et al., 2017).

Among secondary parameters, study results showed significant improvements in biochemical and anthropometric measures in the Yoga group compared to the Control. Along with significant improvements observed in lipid profile which is reported to decrease free fatty acids and thereby improve insulin sensitivity (Raveendran et al., 2018), improvements observed in body composition indicators like WHR and BMI might have contributed to better glucose uptake and reduced hyperglycemia-induced oxidative stress. Previous studies involving yoga intervention for T2D also reported similar benefits (Gordon et al., 2008; Nagarathna et al., 2012), while others reported improvements in weight, waist circumference, and BMI except for blood sugar (McDermott et al., 2014). Systematic reviews and meta-analyses on the effect of yoga on T2D reported significant improvements in glycemic control, lipid profile, blood pressure, BMI, WHR, and cortisol levels for yoga practitioners compared to exercise (Thind et al., 2017; Vizcaino et al., 2016). Our study findings are consistent with the conclusions of various studies involving yoga intervention for T2D (Innes & Selfe, 2016; Mccall et al., 2013; Thind et al., 2017; Vizcaino et al., 2016).

Mechanism of action of yoga as obtained from the mediation analysis

Apart from assessing the effect of yoga on DNA damage in T2D patients, we also elucidated its mechanism of action by employing a statistical mediation analysis.

The SEM-based analysis showed that (**Fig 6**) there exists a causative relationship between Group (binary variable; presence/absence of yoga) and DNA damage reduction in T2D patients, and that effect was carried forward by its influence on oxidative DNA damage and DNA repair, acting as mediators. Further, the analysis showed, the bulk of that effect (70.9%) was mediated through a reduction in 8-OHdG and less (26.5%) through OGG1 enhancement. Differential results from the analysis showed that the path *Group* → *8-OHdG* → *TM* (a1, b1) was more significant than the *Group* → *OGG1* → *TM* (a2, b2) path. This significance should be understood in the light of their proportional contribution while considering the total effect. Individually considering, all regression coefficients (a1, b1, a2, and b2) of both paths were significant. While the combined contribution of mediators or total indirect effect (a1b1 + a2b2) was found to be highly significant at 97.5%, that of the direct path () was insignificant at 2.5%, which means that majority of the yoga-effect was carried by the mediators. Though studies with similar settings and analysis were not observed, few showed that yoga practices reduce OS and enhance DNA repair gene activities (Bisht et al., 2017; Dhawan et al., 2018). Mediation results indicate that yoga's effect is mainly mediated through reduced oxidative DNA damage and enhanced DNA repair in T2D related DNA damage, though the former was more prominent than the latter.

Studies also observed that medication-based intensive glucose control may lower the risk of cardiovascular events but may not yield long-term mortality benefits (Reaven et al., 2019). But when medication is combined with behavioral changes, long term benefits like reduction of vascular complications (Gæde et al., 2008) and all-cause mortality (Gong et al., 2019) were observed, though the 'LOOK AHEAD' study (Wing et al., 2013) observed non-significance, nevertheless reported benefits like better glycemic control, physical fitness, quality of life and reduced health expenditure as other studies. These evidences make a case for integrating holistic and mind-body practice like yoga, with its empowering nature that promotes positive health, which is also cost-effective and relatively safe, in the management of a lifestyle- disease like T2D.