Chapter 5

DISCUSSION

Blood glucose control is a primary goal of diabetes management and in the present study It is found that *Yoga* intervention as an effective intervention to non- *Yoga* in controlling the blood glucose level among T2DM patients. Present study assessed the impact of *Yoga* in blood glucose non- *Yoga* and genetic markers through multi-centric trial, residential short-term *Yoga* intervention and long-term *Yoga* practitioner.

Three studies were conducted to assess the efficacy of *Yoga* in improving glycemic non-*Yoga*, metabolic homeostasis, and also the specific molecular changes in T2DM patients.

5.1. *Yoga* and glycemic non-*Yoga*

Study 1- Multicenter Trial

The study 1 which was a multicenter trial on 598 participants from 6 districts in south India was intended to assess the impact of *Yoga* after 3 months on fasting and postprandial blood glucose levels among T2DM patients. After three months of IY intervention significant decrease in fasting and postprandial blood glucose was observed. The non- *Yoga* group did not show any significant change. Between groups comparison of post FBG and PPBG showed significant difference suggestive of superiority of add-on *Yoga* intervention over conventional management. To the best of our knowledge this is the first study to assess the impact of *Yoga* on glycemic non- *Yoga* in T2DM in a multi-centric trial.

Study two which was a retrospective study on 590 patients with T2DM who underwent two weeks of residential *Yoga* -based lifestyle intervention also showed significant decrease in FBG and PPBG after two weeks of intervention. The study2 also showed significant improvement in blood glucose levels, physiological variables and anti-Diabetes medication requirement following 15 days of residential IYP in patients with T2DM. This suggests a potential role of RIYP in T2DM management.

Study 3 was a cross-sectional study to assess the impact of long-term *Yoga* intervention on systemic homeostasis and genetic change among 40 T2DM patients. Of these 20 were long term *Yoga* practitioners and 20 were non- *Yoga*. In this study patients who were practicing *Yoga* for long term had better glycemic control, lipid profile, insulin: proinsulin Ratio and cortisol levels as compared to non- *Yoga*.

5.2. Comparisons

Yoga based lifestyle intervention, is a comprehensive intervention that consists of several physical and mental practices. *Yoga* is also cost effective and easy to maintain, requiring little in the way of equipment or professional personnel, and there is evidence indicating excellent long-term adherence and benefits (Manchanda et al., 2000; Agte & Tarwadi, 2004).

A randomized controlled trial by Nagarathna R, showed a significant reduction in oral hypoglycemic medication requirement and reduction in blood glucose, HbAlc, LDL, Triglyceride, total cholesterol and VLDL with increase in HDL following *Yoga* -based lifestyle modification program (Nagarathna *et al*., 2012)**.**

As part of the study, T2DM patients stayed for 15 days, RIYP for diabetes was imparted to them. *Yoga* based lifestyle takes into consideration the five important factors of lifestyle: 1) Diet, 2) physical activity, 3) Sleep, 4) Habits and 5) Psychological stress. The designed RIYP was developed to address each of these lifestyle factors and bring balance at all the levels. Medication compliance and adherence to *Yoga* was controlled by the medical doctor and *Yoga* therapist in-charge in the section; the diet was controlled as standard saatvik food was provided; the location of health, home being away from city life and amidst nature could be considered as a calming factor to combat stress. Many previous studies have shown beneficial effects of *Yoga* in improving overweight, blood pressure (Büssing, Michalsen, Khalsa, Telles, & Sherman, 2012) (Esteves *et al*., 2008), insulin levels, triglycerides, FBG and PPBG levels, (A. Singh, Tekur, Metri, *et al*., 2018; Amita S *et al*, 2011; Singh, 2001) and pulse rate. Most of the above-mentioned studies where *Yoga* therapy was beneficial in reducing blood glucose levels involved *Yoga* intervention of discrete *Yoga* sessions (asanas, pranayama or both) as usual routine (mostly for 60 minutes per day 1-5 days/week) and the duration of intervention ranged from 6 weeks to 6 months (A. Singh, Tekur, Nagaratna, *et al*., 2018).

During the study, similar effects were observed with much lesser duration of 2 weeks. This suggests that if different component of *Yoga* viz., *āsana*, *prāṇāyāma*, meditations, relaxations, devotional sessions, study of scriptures and *yogic* counseling are integrated together on the basis of the philosophy of *Yoga* -based lifestyle then they may act synergistically thereby providing better results than those produced by any of the component of *Yoga* alone. Though it may be argued that such intense program throughout the day may not be feasible and may have less translational value, such programs may be utilized for gaining quicker results and

for beginners who would like to explore *Yoga* therapy as the potential solution for T2DM. After initial intensive therapy, patients may feel more confident and may choose the practices that suited them the best and were most effective to be a part of their lifestyle, as per the feasibility.

Though present retrospective study was performed on a large number of T2DM participants, lack of non- *Yoga* group is a major limitation of the current study. Future studies should use a non- *Yoga* group where participants follow conventional lifestyle change program in a residential set up and then compare residential conventional lifestyle change program with residential *Yoga* -based lifestyle program (RIYP).

5.3. Comparisons of glycemic control

The findings of the present study are supported by previous studies. A study by Lorenzo et al 2008 reported significant decrease in blood glucose concentration following three months of Hath *Yoga* intervention. (Stettler *et al*., 2006;Kendall *et al*., 2005). A similar study by Robi found a significant decrease in fasting blood glucose level following three months of the *Yoga* intervention in T2DM patients (Review, 2008;Gary, McGuire, McCauley, & Brancati, 2004).

Similarly, it is also reported a significant decrease in FBG and PPBG values after three months of IY intervention compared to baseline. This study reconfirms the usefulness of the *Yoga* intervention in management of T2DM, thus indicating its efficacy in reducing FBG and PPBG. However, the present study differs from the previous study in term of sample size, frequency of *Yoga* session in a week and type of *Yoga* module used.

A study by James found significant improvement in FBG and IGTT following 10 weeks of aerobic training among patients with T2DM. This study concluded that aerobic exercise improves glucose homeostasis in T2DM.

Another study by Monro reported significant improvement in glucose homeostasis (significant decrease in FBG and HbA1C) following 12 week of *Yoga* intervention compared to the non- *Yoga*. Another study by Savita Singh, observed a significant reduction in FBG, PPBS, heart, systolic and diastolic blood pressure following 40 days of *Yoga* intervention among patients with T2DM, Nidhi reported a significant decrease in insulin resistance, low density lipoprotein and following 12 week of *Yoga* intervention among adolescents with

PCOD. These studies indicate that practice of *Yoga* helps to improve the homeostasis (glucose homeostasis, blood pressure, blood cholesterol etc.) in different health conditions including T2DM.

5.4. Mechanism

Changes in FBG and PPBG found in this study may be attributed to increased physical activity during asanas, suryanamaskaras, and loosening practices, which is associated with increased insulin sensitivity and glucose uptake (Saltiel & Kahn, 2001) (Shepherd & Kahn, 1999) slow breathing practice during pranayama is associated with reduced HPA axis activation which is related to decreased cortisol and decrease cortisol is associated with decreased hepatic glycolysis (Pariante & Lightman, 2008; Stranahan, Lee, & Mattson, 2008).

Excess production of large sized adipocytes is thought to be one of the important causes of insulin resistance in T2DM (Kahn, Hull, & Utzschneider, 2006; Pratley, 2016). Large sized of adipocytes are involved in insulin resistance in T2DMadiposity is associated with impaired proliferation and differentiation capacity of adipocytes (Nishizumi *et al*., 1995). Physical activity is involved in decreased production of large sized adipocytes, which may be via correcting the impairment in proliferation of differential capacity of mesenchymal cells (Parizkova & Stankova, 1964) (Nikkilä, Taskinen, Rehunen, & Härkönen, 1978) in the present study IY module included many practices which increase the physical activity; this might have enhanced the mesenchymal cell proliferation and thus contribute to decrease in insulin resistance (van Praag, Kempermann, & Gage, 1999; Van der Borght *et al*., 2009).

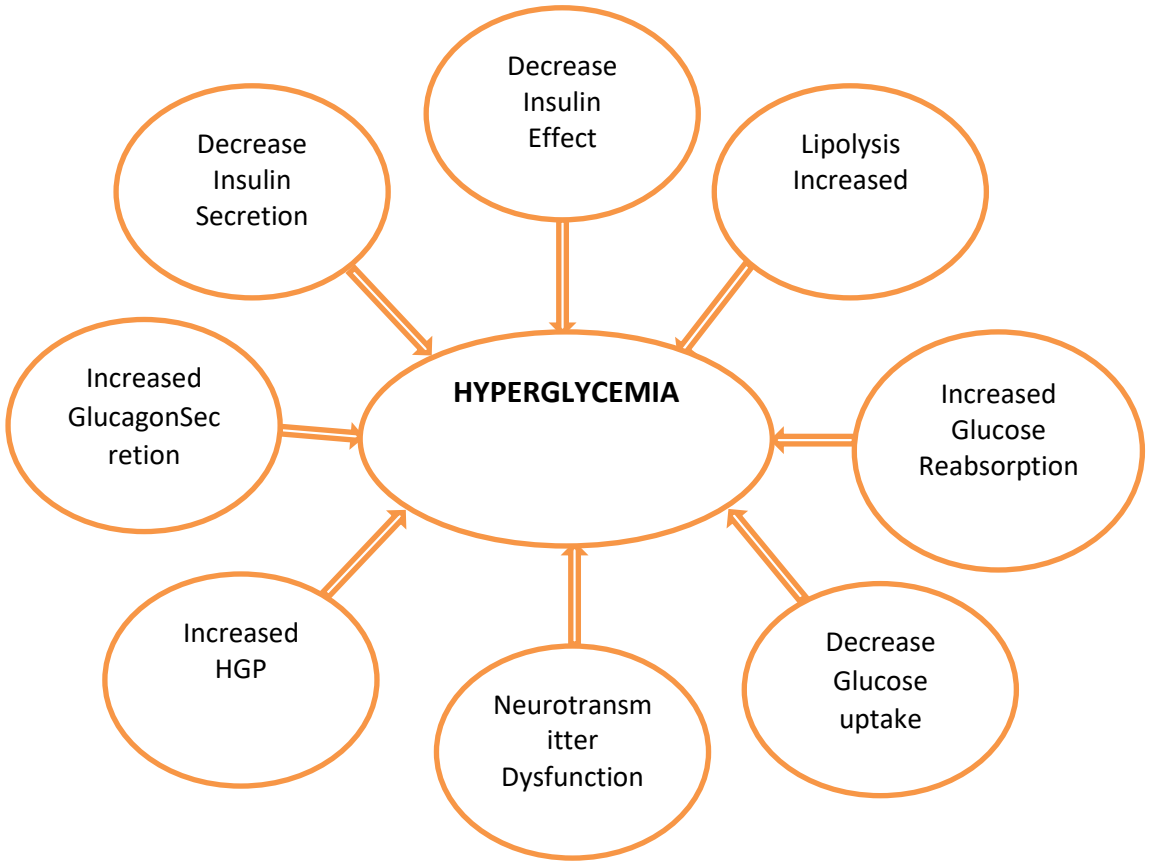
5.6. Beta cell dysfunction

Oxidative stress has been an important contributing factor in the beta cell dysfunction. Studies have reported that patients with T2DM had high oxidative stress. High oxidative stress is involved in decrease of transcription of insulin gene. *Yoga* has been found to decrease oxidative stress by enhancing anti-oxidant activity, glutathione, superoxide dismutase, glutathione, malondialdehyde, Vitamin C and Vitamin E profile.

Yoga studies showed a reduction in oxidative stress and increased anti-oxidant defense, by improving superoxide dismutase, glutathione, malondialdehyde, Vitamin C and Vitamin E profile.

A study comparing the effects of *Yoga* with walking, found *Yoga* to improve GABA levels better than walking. *Yoga* reduces sympathetic activation and enhances parasympathetic activity through direct stimulation of the vagus nerve.

Fig 43: **Ominous octet is an indicator of dysregulated homeostasis**



Yoga – Āsana and *prāṇāyāma* have shown to improve insulin sensitivity in T2DM. Insulin sensitivity is found to be significantly higher in regular practitioners of *Yoga* (Nagarathna *et al*., 2012). The observed increase in glucose sensitivity could be attributed to the possible activation of AMPK through muscle contractions involved during *Yoga* postures (Malhotra *et al*., 2002;Zhang, Zhou, & Li, 2009). Reduction in the pro-inflammatory markers such as tumor necrosis factor α, interleukin-6, C-reactive protein (CRP) and high sensitivity CRP, and increase in the anti-inflammatory markers such as adiponectin are consistently reported through various studies on *Yoga* (Kiecolt-Glaser *et al*., 2012; Sarvottam & Yadav, 2014; Vijayaraghava, Doreswamy, Narasipur, Kunnavil, & Srinivasamurthy, 2015). Adiponectin

activates AMP kinase of liver and thereby help reduce hepatic glucose production (HGP) (Combs, Berg, Obici, Scherer, & Rossetti, 2001). Role of adiponectin on improving endothelial nitric oxide synthesize (eNOS) and resultant increase in endothelial nitric oxide production is well established (Hattori, Suzuki, Hattori, & Kasai, 2003; H. Chen, Montagnani, Funahashi, Shimomura, & Quon, 2003) which is beneficial in the prevention of neuropathy, cardiovascular complications and improve delayed wound healing in diabetes. Systematic review on the effect of exercise on adiponectin states that moderate intensity exercise programs have significant impact on the adiponectin levels. This was ably supported by a study which found regular *Yoga* practice to increase adiponectin levels.

5.7. Increased Hepatic glucose production

Hepatic glucose production is primary cause fasting hyperglycemia. It contributes to 80% of diurnal hyperglycemia in T2DM. In T2DM there is dysfunction in insulin secretion in response to fasting hyperglycemia.

5.8. Glucose re-absorption

Kidney is involved in blood glucose regulation. It is found that patients with T2DM have increased glucose re-absorption in proximal convoluted tubule compared to controls. This further contributes to hyperglycemia in T2DM. Increased sympathetic activity is also associated with increase renal glucose absorption. *Yoga* is known to reduce sympathetic activity via down-regulation of HPA-axis activity.

Despite several RCTs available suggesting the significant impact of *Yoga* in T2DM, the present study is unique in its type by being a multicenter trial with large sample size. The present study suggests the *Yoga* as an adjunct intervention in management of T2DM.

More than two-fold differentially regulated genes (DRG) were obtained by comparing averaged signal intensities of the *Yoga* and non- *Yoga* groups. We tabulated 368 genes, which were more than two-fold differentially regulated. Functional grouping of DRG was performed using gene ontology analysis. Over representation analysis of the DRG was visualized using Clue-Go App in Cystoscopy. Significantly regulated pathways were obtained following correction using Fischer's exact test from Consensus Pathway Database. Also, the genes associated with T2DM from the list of DRGs were tabulated.

The preliminary result suggests that *Yoga* might be beneficial in T2DM patients by regulating the genes and processes associated with inflammation, cytokine signaling, immune signaling and platelet functioning. It also appears that genes associated with pro-inflammatory cytokine signaling and platelet aggregation are down-regulated. This might be responsible for reduced insulin resistance and decreased cardio-vascular morbidity.

5.9. Glucose uptake

T2DM is characterized by decreased glucose uptake, *Yoga* practice promotes glucose uptake in the peripheral tissue and muscles as shown in many studies. A study by Nagaratna found significant decrease in plasma fasting blood glues and HbA1C following 9 months of *Yoga* based lifestyle modification. Another study by Satrupa showed significant decrease in FBG and PPBS following 40 days of *Yoga* intervention among patients with T2DM. These studies suggest that *Yoga* improves glucose uptake among patients with T2DM.

5.10. *Yoga* promotes Homeostasis

Yoga is found to be effective in improving various physiological variables such as heart rate, blood pressure, heart rate variability, etc., thus it improves homeostasis. Similarly, in the present studies it is observed that a greater number of patients with T2DM who received *Yoga* intervention achieved normal fasting and post-prandial blood glucose level compared to the controls.

Evidence -1 in the retrospective study out of 598 patients who received 15 days of residential *Yoga* intervention exhibited significant decrease in FBG (14%) and PPBG (5%). Similarly, in the multicentric study, 137 of patients who underwent three months of *Yoga* intervention showed significant decrease in FBG (32.4%) and PPBG (34.7%).

Further, in the cross-sectional study in the participants who were long term practitioners of *Yoga* showed blood glucose and other parameters such as serum creatinine, serum cortisol, lipid profile parameters within the normal limits for more number of patients in the *Yoga* group compared to the non- *Yoga* group. Also, not only in the number of patients with normal values of different variables were higher but the standard deviation for FBG, PPBG, serum creatinine, lipid profile parameters were also small suggestive of many patients had achieved normalcy for FBG, PPBG, serum creatinine, lipid profile parameters. Decreased SD after *Yoga* (not seen in the non- *Yoga* group) observed in all three studies on glucose values

indicates that *Yoga* may help all cases to move near the group mean values supporting the hypothesis that *Yoga* helps in systemic homeostasis.

Similar, findings were observed in many of the previous studies. A study by Janice, 25 women long term *Yoga* practitioners were compared with 25 novices. In this study all long-term *Yoga* practicing women had less SD for heart rate, systolic BP, diastolic BP compared to non- *Yoga*. Further, number women, who had 41% high level for Il-6, were significantly more in the non- *Yoga* groups compared to long term *Yoga* practitioners.

In another study by Shantakumari, among adolescent boys who performed 8 weeks of *Yoga* intervention showed significant decreased in SD for total cholesterol and LDL and HDL level compared to baseline and the non- *Yoga* group (Shantakumari *et al*., 2013).

Evidence 3- genetics

5.11. Inflammation and T2DM

Chronic low-grade inflammation is observed in obesity which is associated with obesity related T2DM. Several inflammatory markers such as C-reactive protein, interleukin 1, IL-6, and tumor necrosing factor are known to be elevated in T2DM. These pro-inflammatory marks are associated with increased insulin resistance. Chronic low grade inflammation is considered to be risk factor for T2DM. White blood cells, pro-inflammatory cytokines, chemokines are the predictors of T2DM. Elevated level of CRP has been associated with increased risk of T2DM. These elevated inflammatory markers also predict the cardiovascular risk in T2DM patients. Adipose tissue, liver, muscle and pancreas are most common sites of inflammation in the presence of obesity and T2DM (Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014).

5.12. T2DM and platelet aggregation

T2DM is characterized by platelet dysfunction cascade. Studies have found that patients with T2DM have increased platelet aggregation compared to non-T2DM patients. Increased levels of fibrinogen and plasminogen activator inhibitor 1 favor both thrombosis and defective dissolution of clots once formed. Platelets in type 2 Diabetes individuals adhere to vascular endothelium and aggregate more readily than those in healthy people. Loss of sensitivity to the normal restraints exercised by prostacyclin (PGI2) and nitric oxide (NO) generated by the

vascular endothelium presents as the major defect in platelet function (Angiolillo *et al*., 2006).

Thus, the defects in insulin action in diabetes create a milieu of disordered platelet activity conducive to macro vascular and microvascular events. IR segregates with abnormalities in factors involved in coagulation, including platelet agreeability, platelet adhesion, and levels of thromboxane, von Will brand factor, factor VIII, tissue plasminogen activator (TPA), and fibrinogen. It decreases fibrinolytic activity due to increased levels of PAI-1. Levels of plasma insulin, proinsulin, cytokines, and glucose and the concentration of modified lipoproteins all affect PAI-1 release. T2DM is associated with increased platelet aggregation and fibrin deposition leading to thrombosis and atherosclerosis (Ferroni, Basili, Falco, and Davi, 2004).

5.13. Relationship between inflammation, immune system, cytokines, and platelet aggregation and pathology of T2DM

Insulin resistance has been a hallmark of T2DM. Obesity, aging, tissue lipid accumulation, oxidative stress, endoplasmic reticulum stress (ER-stress) in b-cells, tissue inflammation, and physical inactivity are associated with insulin resistance. Research has suggested that a chronic type of inflammation that affects the whole body is linked to diseases like type 2 diabetes and disease. Inflammation is one of the main reasons why people with diabetes experience heart attacks, strokes, kidney problems and other, related complications.

Stress is the main cause for provoking inflammation in pancreatic tissues (Bhansali *et al*., 2009) (Ozcan *et al*., 2006).

5.14. T2DM and systemic inflammation

Glucolipotoxicity: it can be stated as one of critical determinants of T2DM.

In general, glucolipotoxicity is a term used for the combination of

1. Gluco-toxicity
2. Lipo-toxicity (Poitout & Robertson, 2002).

Glucotoxicity is term for constantly elevated levels of blood glucose (hyperglycemia) that causes damaging effects on normal functioning of b-cells and finally decreases insulin

secretion. Similarly, elevated levels of lipids (lip toxicity) specifically; FFAs have been also known to regulate insulin secretion (Correa *et al*., 2010).

The Glucolipotoxicity in turn creates the ER-stress within pancreatic islets (Cnop, Igoillo-Esteve, Cunha, Ladrière, & Eizirik, 2008). ER stress causes the synthesis of majority of proteins including pro-insulin in pancreatic b-cells. The hyperglycemic state promotes the generation of reactive oxygen species (ROS) inducing oxidative stress in b-cells (Saad *et al*., 2014) (Akash, Rehman, & Chen, 2013). The oxidative stress promotes the production and release of pro-inflammatory mediators (cytokines and chemokines), which have been known for their involvement in causing b-cell dysfunction leading to insulin resistance and inflammation attributing to T2DM (Akash *et al*., 2013).

Due to frequent overconsumption of nutrition, the high levels of numerous cytokines and CRPs may induce the activation of the innate immune system in T2DM patients; however, these inflammatory mediators do not clearly reveal the magnitude of inflammation in different peripheral tissues. The circulating levels of these mediators are considered to vary from individual to individual and tissues to tissues (Bhansali *et al*., 2009).

In patients with Type II diabetes, augmented circulating levels of various pro inflammatory cytokines and chemokines along with the tissue inflammation have been detected (Bhansali *et al*., 2009) (Donath, Størling, Maedler, & Mandrup-Poulsen, 2003). From the above-mentioned facts, it is evident that inflammation plays a crucial role in the dissemination of T2DM. Thereby, T2DM may be stated as a chronic form of auto inflammatory disease producing IL-1b from b-cells of pancreatic islets; which eradicates b-cells themselves (Donath *et al*., 2003) leading to b-cell dysfunction (Fig. 2).

5.15. Insulin Resistance and stress induced kinesis

Many metabolic processes cause insulin resistance in peripheral tissues. They provoke inflammation and stress-induced kinases such as IkB kinase-b (IKKb) and JUN N-terminal kinase (JNK). These kinases are known to efficiently contribute in pathogenesis of diabetes (Fig. 1) (Donath et al., 2003; Shoelson, Lee, and Goldfine, 2006). IKKb may potentiate the stimulation of nuclear factor-kB (NF-kB), which in turn induces pro-inflammatory cytokines (TNF-an & IL-1b) in liver and adipose tissues. These cytokines cause insulin resistance in peripheral tissues (Shoelson *et al*., 2006). However, JNK potentiates activates the transcription factor-2 (ATF2) and ELK1. Though, the role of JNK stimulated transcription

factors is not known (Solinas & Karin, 2010), some experimental studies have provided ample evidences that JNK plays its crucial role in inflammatory responses for pathogenesis of T2DM.TNF-a and IL-1b, which are produced by the activation of NF-kB are also known to stimulate both NF-kB and JNK in response to feed-forward mechanism through the involvement of their particular receptors (Donath & Shoelson, 2011).

Along with NF-kB and JNK pathways, FFAs and advanced glycation end-products may promote insulin resistance and overt T2DM by the activation of toll like receptors (TLRs) and receptors for advanced glycation end-products (RAGE) (M. P. Chen *et al*., 2006). The most promising part among multi-factorial patho-physiology for spreading of T2DM is activated by numerous pro-inflammatory cytokines such as IL-1b, TNF-a, and IL-6. These cytokines released from adipose tissues induce inflammation not only in the corresponding tissue but also in the b-cells of pancreatic islets and ultimately leads to insulin resistance (Donath & Shoelson, 2011;Nakamoto *et al*., 2003).

Apart from, IL-1b, TNF-a also plays an essential role by creating a linkage among insulin resistance, obesity, and inflammation. TNF-a has been recognized as a key factor linking inflammation and insulin resistance. It modulates the activities of IKKb/NF-kB and JNK pathways regulating insulin resistance (Nakamoto *et al*., 2003). Excessive production of TNF-a in adipose tissues causes insulin resistance in peripheral tissues by the induction of inflammation and b-cell death in pancreatic islets (Donath & Shoelson, 2011).

The role of IL-6 in T2DM is considered to be complex and controversial, however, there are various experimental studies which have confirmed that IL-6 induces insulin resistance in peripheral tissues, apoptosis in pancreatic islets together with other inflammatory cytokines (Akash *et al*., 2013) and stimulates the inhibition of cytokine's signaling proteins (Donath & Shoelson, 2011). Due to these deleterious effects, IL-6 is considered as an independent risk factor and acts as a predictor and pathogenic marker for insulin resistance and progression of T2DM (Nakamoto *et al*., 2003).

Pro-inflammatory cytokines may induce the inflammatory mechanisms in peripheral tissues as well as in pancreatic islets, IL-1Ra is the only naturally occurring anti-inflammatory cytokine that exterminate these mechanisms by neutralizing the actions of pro-inflammatory cytokines (Akash *et al*., 2013). IL-1Ra is highly expressed in endocrine pancreas of normal individuals. The expression level of IL-1Ra is decreased in type-II Diabetes patients that

increase the ability of IL-1b to exert its deleterious effects on pancreatic islets (Donath *et al*., 2003).

Figure 44: Pathogenesis of 2DM

Glucolipotoxicity

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ER-stress, oxidative stress

↓

Release of pro-inflammatory markers, cytokines

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β-cell dys-function

↓

Insulin Resistance and inflammation

↓

Diabetes

Altered Platelet function in Diabetes

Diabetes thrombocytopathy is the term which refers to altered platelet function in T2DM which is seen as differences between Diabetes and non-Diabetes individuals. (Kubisz, Stančiaková, Staško, Galajda, & Mokáň, 2015). Among Diabetes individuals, increased platelet agreeability and adhesiveness are due to the following:

Table 39: Factors that lead to Diabetes thrombocytopathy

1. Reduced membrane fluidity
2. Altered Ca^{2+} and Mg^{2+} homeostasis (increased intracellular Ca^{2+} mobilization and decreased intracellular Mg^{2+})
3. Increased arachidonic acid metabolism
4. Increased TXA_2 synthesis
5. Decreased prostacyclin production
6. Decreased NO production
7. Decreased antioxidant levels
8. Increased expression of activation-dependent adhesion molecules (e.g., GpIIb-IIIa, P-selectin)

Platelets from patients with type 1 and T2DM exhibit enhanced platelet aggregation activity early in the disease course that may precede the development of CVD. Numerous biochemical abnormalities have been found that correlate with platelet hyper-reactivity. Platelets from Diabetes patients exhibit reduced membrane fluidity, which may reflect changes in the lipid composition of the membrane or glycation of membrane proteins. Arachidonic acid metabolism is increased in platelets from Diabetes patients; this leads to enhanced TXA_2 production and may contribute to increased platelet sensitivity (Sebag, Buckingham, Charles, & Reiser, 1992).

In diabetes, an increase in calcium mobilization from intracellular storage pools, resulting in increased intracellular calcium levels, has been correlated with reduction in membrane fluidity. In addition to alterations in platelet calcium homeostasis, intracellular magnesium concentrations are reduced, consistent with an increase in platelet hyper-agreeability and adhesiveness Magnesium supplementation can reduce these abnormal platelet functions in people with diabetes (Paolisso & Barbagallo, 1997;Nakamoto et al., 2003).

Platelets from Diabetes participants produce less no and prostacyclin, which normally inhibit platelet-endothelium interactions and promote endothelium-mediated vasodilation. The concentration of no synthase in platelets from patients with type 1 and T2DM is less than half that measured in platelets from non-diabetes individuals. However, insulin will stimulate no synthesis in platelets. Moreover, platelets from Diabetes participants contain reduced antioxidant levels, which tend to be associated with increased agreeability and low platelet vitamin C levels (Mutus *et al*., 2001; Trovati *et al*., 1997).

Patients with type 1 and T2DM have increased platelets that express activation-dependent adhesion molecules, such as activated GpIIb-IIIa, lysosomal Gp53, thrombospondin, and P-selectin. The increased expression of GpIIb-IIIa is consistent with the enhanced fibrinogen binding and agreeability seen in platelets from Diabetes participants. Further, serum fibrinogen levels are also elevated in many patients with type 1 or T2DM. In addition to reflecting increased agreeability, the enhanced surface expression of these adhesion molecules suggests that platelets can also communicate with leukocytes and possibly play a role in inflammation-mediated tissue damage in the vasculature. Finally, platelets may interact with plasma constituents, such as glycosylated LDLs, immune complexes, or WF, to increase platelet agreeability or adhesion (Ferroni *et al*., 2004; Papanas *et al*., 2004).

5.16. Mechanisms

5.16.1. Autonomic regulation

The autonomous nervous system is primarily involved in the homeostasis mechanism. Homeostatic regulation is primarily maintained by the parasympathetic activity (Manzella and Paolisso, 2005). *Yoga* is known to enhance parasympathetic activity and reduce sympathetic tone. Further, the decrease in the sympathetic activity is associated with decreased blood glucose, serum cortisol and HPA axis activity. *Yoga* helps in reducing sympathetic activity by down-regulating HPA axis activity (V. P. Singh, Khandelwal, & Sherpa, 2015).

5.16.2. Reduction in HPA axis activity

Several endocrine hormones apart from insulin and glucagon are involved in blood glucose maintenance such as cortisol, ACTH, *Yoga* through non-regulation of HPA axis activation reduces ACTH and cortisone thus contributing to a decrease in plasma glucose (Ross *et al*., 2010).

5.16.3. Anti-inflammatory activity of *Yoga*

Yoga has anti-inflammatory activity. *Yoga* reduces systemic inflammation, which has been identified as an important cause for several metabolic disorders including diabetes. Systemic inflammation is involved in insulin resistance and beta cell dysfunction contributing to hyperglycemia. *Yoga* reduces systemic inflammation and its effects (Rajbhoj, Shete, Verma, & Bhogal, 2015) (Bower *et al*., 2014).

Enrichment analysis on gene expression in our study 3 has shown specific genes suggest that [27202] Complement component 5a receptor 2 (C5AR2); [51266] C-type-lectin domain family 1 member B (CLEC1B); [9332] CD163 molecule (CD163); [3554] interleukin 1 receptor type 1(IL1R1) were statistically significantly enriched from amongst the differentially regulated genes (Bosmann, Haggadone, Zetoune, Sarma, & Ward, 2013).

5.16.4. Molecular Genetic mechanism

Gene Ontology results suggest that *Yoga* might regulate the effects in T2DM patients by regulating inflammatory process, platelet degranulation, immune system activity and cell signalling to decrease insulin resistance. Over representation analysis using ClueGo suggest

that platelet regulation as one of the key processes regulated in the *Yoga* practitioners (Chohan, Nayar, Thomas, & Geetha, 1984) (Jayashree *et al*., 2013).

5.16.5. Conclusion:

Present study is a comprehensive observational study suggesting *Yoga* as an effective intervention in improving glycemic non- *Yoga* in T2DM in both short and long term *Yoga* practice. This study also showed improved homeostasis by improving renal function, dyslipidemia and liver function. Also, *Yoga* helped in improving the quality of life and reducing the perceived stress. *Yoga* also down-regulate the expression of genes responsible for platelet aggregation and inflammation in T2DM.