CHAPTER 3

REVIEW OF SCIENTIFIC LITERATURE: SCREENING FOR T2DM, AND YOGA FOR T2DM PREVENTION AND GLYCEMIC CONTROL

3.1 OVERVIEW

As mentioned in Chapter 1, the public health challenge of T2DM in India has four dimensions to it: prevalence determination, screening, prevention, and treatment. The scope of this report involves the last three dimensions, with the prevention aspect focusing on individuals who are high risk but still normoglycemic.

There exist many T2DM screening methods that are already deployed in the world. In India, the most commonly used method is the Indian Diabetes Risk Score (IDRS). IDRS has four components: family history, physical activity, age, and obesity(Mohan et al., 2005). Of these, the first three are easy to measure in the sense that there are no competing metrics to choose from; however, obesity is more complex and controversial. Depending on the country, one sees the use of general adiposity (e.g. Body Mass Index, BMI) or central fat distribution (e.g. Waist Circumference, WC). There are competing hypotheses, each supported by a plethora of research data, as to which of these is an effective anthropometric measure for obesity. Therefore, our report has focused on defining the best anthropometric obesity measure (we've used a composite measure which combines BMI and WC) and using that as the obesity component of IDRS in order to improve it. Our scientific literature review will focus primarily on existing studies on various obesity measures as it relates to diabetes risk.

Diabetes is a condition with a complex etiology; risk factors include obesity, age, stress, poor diet, sedentary lifestyle, insulin resistance, and so on. The risk factors themselves have interrelationships among them. For example, obesity and a sedentary lifestyle are well established risk factors for insulin resistance (Joslin & Kahn, 2005). Thus, when investigating the impact of yoga on a broad outcome such as diabetes prevention or glycemic control, we have to not only review existing scientific literature on the connection between the intervention and the outcome ("does yoga reduce risk of diabetes?"), but also include in the review the connection between the intervention and the underlying risk factors ("does yoga reduce obesity?"). Accordingly, we conduct a broad-scope review that encompasses studies involving Yoga and: obesity, stress, dietary outcomes, insulin resistance, and β-cell dysfunction (in addition the primary outcomes of Yoga and diabetes risk reduction, and glycemic control).

3.2 SCREENING FOR T2DM AND MEASURES OF OBESITY

Many screening models have been developed to assess diabetes risk (Buijsse, Simmons, Griffin, & Schulze, 2011). Each of these screening models have their advantages and disadvantages. Below we review five scores that have been developed across various locales and populations. These were chosen because each of them was developed with the data from of large studies and/or studies done over long periods of time.

German Diabetes Risk Score (Schulze et al., 2007)

Factors: Age, WC, Height, history of hypertension, smoking, consumption of red meat, coffee, whole-grain bread, and alcohol

Range: 118 – 983

Performance: Area under the curve of ROC was 0.82-0.84

Advantages: Comprehensive multi-variate score taking nutritional factors into account. Excellent at detecting low diabetes risk

Disadvantages: Difficult to deploy in the field due to extensive set of questions. Overestimation of intermediate to high diabetes risk

Cambridge Risk Score (Griffin et al., 2000)

Factors: Age, Gender, BMI, use of steroid and antihypertensive medication, family history of diabetes, smoking history

Range: 0 - 1

Performance: Area under the curve of ROC was 0.8

Advantages: Performs very well in risk estimation that a patient has undiagnosed diabetes

Disadvantages: Unknown performance characteristics for evaluating future diabetes risk (Griffin, 2005). Tested only with White English population

Framingham Offspring Diabetes Risk Score (Wilson et al., 2007)

Factors: FBS, BMI, HDL-C level, Family History of Diabetes, Triglyceride level, BP treatment

Range: 0 - 30

Performance: Area under the curve of ROC was 0.85

Advantages: Performs very well in assessing future diabetes risk

Disadvantages: Unsuitable for field deployment since it requires blood tests (or unreliable patient knowledge of the prior tests). Validated well with white middle aged American population, but substantially underestimated diabetes risk in more general cohort (Nichols & Brown, 2008)

Finnish Diabetes Risk Score (Saaristo et al., 2005; Wilson et al., 2007)

Factors: Age, Gender, BMI, use of BP medication, History of hyperglycemia, Physical activity, Daily consumption of fruits and vegetables, Family History

Range: 0 - 26

Performance: Area under the curve of ROC was 0.73

Advantages: Simple to calculate in the field (See caveat below). Performs well in predicting future diabetes risk and in identifying undiagnosed diabetes in the screened population.

Disadvantages: Maybe unsuitable for field deployment since one of the questions is about history of hyperglycemia. Depending on the circumstances, this data may not be available. Relatively low sensitivity compared to other risk scores

Indian Diabetes Risk Score (Mohan et al., 2005)

Factors: Age, WC, Family History, and Physical Activity

Range: 0 - 100

Performance: AUC of ROC was 0.698

Advantages: Simple to calculate in the field. Performs well in identifying undiagnosed diabetes in the screened population

Disadvantages: Tested only for Indian population. Relatively low AUC compared to other risk scores

It is seen from the above review that these screening models are always in the form of a multi-variate risk score, and most of them include: family history, age, physical activity, and obesity. Clearly, the first three can be determined by merely questioning the individual (instead of needing specialized equipment); for obesity, one can envision either an anthropometric measurement such as WC, BMI etc., or use laboratory equipment such as bioelectrical impedance analysis, hydrodensitometry, dual-energy X-ray absorptiometry (DEXA), etc. (Kuriyan, 2018). A screening score, by its nature, is meant to be used for a quick determination of diabetes risk and therefore is hampered by imposing requirements for laboratory equipment – thus the measure of obesity must necessarily be anthropometric in nature.

Various anthropometric measures of obesity have been proposed, including WC, BMI, Waist-to-hip ratio (WSR), Waist-to-stature (height) ratio (WHR), Skinfold measurements (SKF), etc. (Kuriyan, 2018). Among these, in the context of determining diabetes risk, the most common ones are WC – a measure of central fat, and BMI – a measure of general adiposity.

However, it is not clear whether WC or BMI is better for determining type 2 diabetes risk. Various studies (Alperet et al., 2016; Hartwig et al., 2016; He et al., 2015; Kobayashi et al., 2018; McKeigue et al., 1991; Nyamdorj, 2008; Okosun et al., 2000; Qiao & Nyamdorj, 2010; Wannamethee et al., 2010; Yang et al., 2018) have been done in this area and have drawn conflicting conclusions. Some studies have found that WC is a better measure of risk (Alperet et al., 2016; He et al., 2015; McKeigue et al., 1991; Wannamethee et al., 2010). Other studies have drawn the opposite conclusion (Okosun et al., 2000; Yang et al., 2018). At least one study has found both measures to be equally good (Qiao & Nyamdorj, 2010). The studies have been done across multiple ethnicities such as Chinese (Alperet et al., 2016; He et al., 2015; Nyamdorj, 2008; Qiao & Nyamdorj, 2010), Malays (Alperet et al., 2016; Nyamdorj, 2008), Asian Indians (Alperet et al., 2016; He et al., 2015; McKeigue et al., 1991; Nyamdorj, 2008), Germans (Hartwig et al., 2016), Japanese (He et al., 2015), and multiple ethnic groups in the USA (Kobayashi et al., 2018; Okosun et al., 2000). The studies have been done with varied designs (cross-sectional and prospective) and methods (independent, collaborative, and pooled analyses), measures (risk association, positive predictive values, area under the curve), and outcome (T2DM incidence, insulin resistance). Given the great breadth and depth of these studies, these conflicting conclusions probably point to the fact that each metric only partially captures the etiological association between obesity and type 2 diabetes.

Probably because of this evidentiary ambiguity, there is no consistency among the diabetes screening scores in terms of the obesity measure they use. WC is the obesity metric in the most commonly used model in India (Indian Diabetes Risk Score or IDRS (Mohan et al., 2005)), Germany (German Diabetes Risk Score (Schulze et al., 2007)) and France (Diabetes Risk Score derived from the DESIR study (Balkau, Lange, Fezeu, & Tichet, 2008). BMI is the obesity metric in the most commonly used model in the UK (Cambridge Risk Score (Schulze et al., 2007)) and the USA (Framingham Offspring Diabetes Risk Score (Griffin et al., 2000)) and the Finnish Diabetes Risk Score (Lindström & Tuomilehto, 2003).

3.3 DIABETES PREVENTION AND GLYCEMIC CONTROL THROUGH YOGA

3.3.1 Potential pathways for Yoga to bring about diabetes prevention/glycemic control

We recall from Chapter 2 that the accepted model for diabetes progression according to the latest medical evidence starts with insulin resistance, leading to hyperinsulinemia; when hyperinsulinemia is accompanied by β-cell dysfunction, it leads to T2DM. Insulin resistance has various risk factors including: obesity, high nutrient availability (leading to increased caloric load), a sedentary lifestyle, age, stress, and generic programming. β-cell dysfunction is the result of either the inability of β-cells to produce enough insulin and/or the loss in β-cell mass (due to autoimmune conditions). If Yoga is the intervention, then it could act on the underlying pathologies (insulin resistance, β-cell dysfunction) either directly, or indirectly by mitigation of the risk factors. These possibilities are shown in Fig 6.

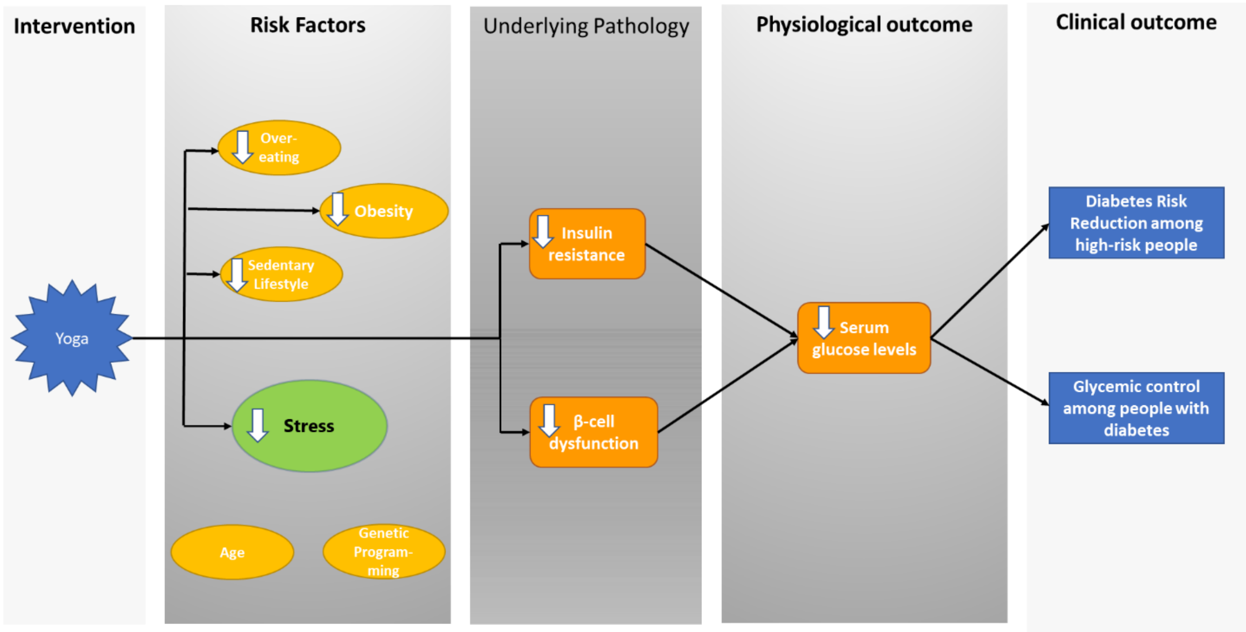

Fig 6: Potential ways in which Yogic intervention might bring about diabetes risk reduction and glycemic control

Therefore, our scientific literature review will encompass each of these areas, to see if there is evidence that Yoga will (a) decrease insulin resistance (b) reduce obesity (c) bring about sustained changes to bad dietary habits (d) reduce stress (e) overcome the sedentary lifestyle habit (f) potentially encourage insulin production in the pancreas, thereby reducing β-cell dysfunction

3.3.2 Yoga and Obesity

Many studies have shown that Yoga is helpful in reducing obesity, as measured by anthropometric parameters. In an RCT involving 60 women to study the effects of a 12-week yoga intervention showed moderately strong positive effects on anthropometric and self-reported variables (WC, BMI, self-esteem, etc.) in women with abdominal obesity (Cramer et al., 2016). A study involving 80 overweight to obese men showed that 3 months of Yoga training showed significant improvement in weight and percentage of body fat (Rshikesan et al., 2016). A study of 20 overweight or obese boys concluded that an 8-week Yoga practice showed significant reductions in body weight and BMI (Seo et al., 2012). A pre-post assessment of 47 individuals who participated in a 6-day yoga and diet change intervention found a significant decrease in BMI and fat-free mass (Telles et al., 2010).

One of the hallmarks of metabolic syndrome is a gradual but continual weight gain in individuals beyond 50 years of age. A post-hoc analysis of 15,550 adults aged 53-57 years the Vitamin and Lifestyle (VITAL) cohort study showed that yoga practice for four or more years was associated with 3.1lb lower weight gain among normal weight (BMI < 25) participants, and 18.5lb lower weight gain among overweight participants (Kristal et al., 2005).

A systematic review and meta-analysis of 30 RCTs concluded that yoga can be "preliminarily considered a safe and effective intervention to reduce BMI in overweight or obese but otherwise healthy adults" (Lauche, Langhorst, Lee, Dobos, & Cramer, 2016).

3.3.3 Yoga and proper nutrition

Several studies have analyzed the relationship between participation in Yoga and healthy eating behaviors. An analysis of data (n=1820) from wave 4 of Project EAT (Eating and Activity in Teens and Young Adults) found that regular practice of Yoga was associated with more servings of fruits and vegetables, fewer servings of sugar sweetened beverages and snack foods, and less frequent fast food consumption (Watts et al., 2018). In a study intended to compare the dietary intakes and antioxidant status among pre- and postmenopausal women, it was found that yoga practitioners had both lower BMI and lower fat intake than their counterparts who did Tai Chi or were sedentary (Palasuwan et al., 2011). A 2010 study designed to assess mind-body health of yoga practitioners against a reference group of college students found that Yoga practitioners reported consuming a significantly higher proportion of recommended servings from each food group than did a comparison group of college students (Monk-Turner & Turner, 2010). It was reported in 2013 that when 47 Yoga practitioners were compared against 46 runners and 52 sedentary individuals, the Yoga group significantly less tendency to eating meat compared to runners and sedentary individuals (Satin et al., 2014).

Relatively fewer studies have explored the relationship between duration, frequency, and type of Yoga. A 2012 cross-sectional survey of 1045 yoga practitioners found that frequency of yoga practice favorably predicted both fruit and vegetable consumption and vegetarian status; it was also found that more frequent practice of gentle poses and a study of yoga philosophy were positively linked to vegetarian status (Ross et al., 2012). A post-hoc analysis of 15,550 adults aged 53-57 years the Vitamin and Lifestyle (VITAL) cohort study showed, it was found that people who practiced yoga for four or more years had 11% lower percentage of energy from fat and 45% higher consumption of fruits and vegetables (Kristal et al., 2005).

3.3.4 Impact of Yoga on sustaining an active lifestyle

The motivation to transition from sedentary to an active lifestyle can either be extrinsic, e.g. peer pressure, or a health crisis; or it can be intrinsic, which is based on outcomes such as satisfaction, pleasure, and curiosity. According to self-determination theory (Deci & Ryan, 2000), if motivation is intrinsic in nature the resulting activity is more likely to be sustained (because they would perform it voluntarily), and is more likely to yield positive results, when compared to extrinsic motivation. In a cross-sectional study conducted among 109 individuals in Malaysia, it was found that participants who practiced Yoga ranked intrinsic motivation the highest, with an overall mean score of 4.2 (measured on the Self-Motivation Scale SMS28) as compared to extrinsic motivation (SMS28 $\mu=3.6$) (Lian et al., 2017). A similar result was found by a study in Romania which analyzed the motivations of 29 Yoga practitioners and 29 Pilates practitioners: Yoga practitioners ranked intrinsic motivation as higher (SMS28 $\mu=4.74$) than extrinsic motivation (SMS28 $\mu=3.25$) (Petracovschi, 2017).

An analysis of data (n=1820) from wave 4 of Project EAT (Eating and Activity in Teens and Young Adults) found that 75% of the participants indicated that the practice of Yoga had a positive impact on how active they were. The researchers concluded that Yoga impacted physical activity in four ways: (a) Activity due to yoga practice (b) motivation to do other forms of physical activity (c) improved capacity to be active and (d) complemented an already active lifestyle (Watts et al., 2018).

3.3.5 Yoga and stress

Reducing the effects of stress has always been one of the widely recognized and studied benefits of Yoga. It is beyond the scope of this report to survey the entire field of Yoga and stress; instead, we focus on studies which have explored the effects of Yoga on stress as it relates to serum glucose levels in the blood.

Stress, commonly defined as the real or perceived threat to homeostasis, results in the activation of a complex range of responses involving the endocrine, nervous, and immune systems. Collectively, this is known as the stress response (Chrousos & Gold, 1992). Stress response includes behavioral changes (increased awareness, improved cognition, euphoria, enhanced analgesia) and physiological changes (increased cardiovascular tone, serum glucose levels, respiratory rate, and inhibition of digestion, growth, reproduction, and immunity). Due to the potentially pathogenic effects of stress response, a number of neuronal and endocrinal systems work together to tightly regulate this process (Smith & Vale, 2006).

The physiological response to stress is transmitted through the hypothalamic-pituitary-adrenal (HPA) axis, whose end result is to induce the adrenal cortex to release glucocorticoids like cortisol. Cortisol regulates physiological changes through ubiquitously distributed intracellular receptors (Dunlavey, 2018). Specifically, cortisol acts to increase levels of serum glucose in the blood (a) stimulating gluconeogenesis (b) decreasing insulin sensitivity in peripheral tissue

(c) having a permissive effect on the actions of other hormones, such as glucagon and adrenaline, which increase glucose production (Willms, Schumm-Draeger, & Siegmund, 2016). When investigating the effects of Yoga on stress in the context of diabetes prevention and glycemic control, it is thus important to review scientific literature on the studies involving Yoga and cortisol.

A 2011 study of breast cancer survivors on a 90 min, twice weekly yoga intervention found that the yoga group had lower morning and 5 pm salivary cortisol and improved emotional well-being and fatigue scores after 8 weeks (Banasik et al., 2011). A 6-week study of an integrated yoga program and supportive therapy in stage II and III breast cancer outpatients found decreased morning salivary cortisol levels (Vadiraja et al., 2009). A study of 26 individuals, divided into equal groups of control and yoga intervention, with the yoga group participating in 3 months of Kundalini Yoga classes, found that the Yoga group had significant decrease in salivary cortisol levels and levels of perceived stress (García-Sesnich et al., 2017). In 2016, a study intended to find the association of yoga practice with periodontal disease by measuring serum cortisol levels, found that individuals practicing Yoga regularly had low cortisol levels as compared to the control group (Katuri et al., 2016). In another study designed to investigate the antidepressant effects of Yoga (hypercortisolemia is well known in depression) demonstrated that depressives who began with higher cortisol levels as compared to controls at baseline, showed significantly decreased cortisol levels at the end of three months of Yoga practice (Thirthalli et al., 2013).

The studies cited above have used a combination of Yoga *asanas*, along with meditation, and *pranayamas*. Other studies have examined the effect of meditation alone to adrenocortical activity. A study of young adult volunteers in 1978 found that long-term practitioners of Transcendental Meditation (TM) showed significantly decreased cortisol levels when compared to control, leading the authors to conclude that the practice of TM is associated with psychophysiological response(s) which acutely inhibit pituitary-adrenal activity (Jevning et al., 1978). A 1991 study of 52 Dhammakaya Buddhist meditators found that after meditation, the levels of serum cortisol was significantly reduced (Sudsuang et al., 1991).

3.3.6 Yoga and insulin resistance

The term insulin resistance refers to resistance to the metabolic effects of insulin: (a) suppressive effects of insulin on endogenous glucose production (b) stimulatory effects of insulin on peripheral (mainly skeletal muscle) glucose uptake and glycogen synthesis and (c) inhibitory effects of insulin on adipose tissue lipolysis. As each of these result in increased levels of serum glucose in the blood, the net effect of insulin resistance, when not regulated by other mechanisms (such as increased insulin levels), is to cause hyperglycemia (Joslin & Kahn, 2005).

Studies on the effects of Yoga on insulin resistance have focused on four areas: (a) measuring bio-markers of insulin resistance (b) measuring clinical markers of insulin resistance such as increased blood pressure, lipid profiles, and cardiovascular function (c) measuring phenotypic manifestations such as body weight and composition and (d) measuring indirect biological effects such as oxidative stress, markers of sympathetic activation, etc.(Innes et al., 2005).

Since our interest here is to look for evidence that Yoga might increase insulin sensitivity, we will focus on area (a): studies which have explored changes in biomarkers of insulin resistance as a result of doing Yoga. Various studies have measured one or more of the following biomarkers: Fasting glucose (FBG), post prandial glucose (PPG), fasting insulin, and fasting glycated hemoglobin (HbA1c). In a 2001 study of 19 individuals with T2DM, it was found that at the end of a 40-day Yoga intervention, significant reductions were seen in FBG, PPG, and HbA1c (S. Singh et al., 2001). A 1991 study of 29 individuals found that the practice of Yoga produced significant reductions in FBG, and that the mean reduction in FBG increased with the duration of Yogic intervention (V. Sharma, Mishra, & Kulshreshta, 1991). A 2012 study of 90 adolescent individuals with polycystic ovary syndrome (PCOS), divided equally into Yoga and Exercise groups, found that 12 weeks of Yoga practice resulted in a statistically significant decrease in FBG, which was higher than the corresponding decrease in FBG for the exercise group (Nidhi et al., 2012). A study of 21 individuals with T2DM conducted at the Royal Free Hospital in London found that that Yoga group had significant reductions in FBG and HbA1c when compared to controls, after 12 weeks of Yoga (Monro, Power, Comar, Nagarathna, & Dandona, 1992)

There have been relatively fewer studies of the effects of Yoga on fasting insulin, and the results haven't been very conclusive. In a 2002 study of 34 high-risk (CVD) individuals split into 14 (control) and 20 (TM and Yoga), it was found that the mean fasting insulin in the Yoga group reduced when compared to control, but the results were not statistically significant (Fields et al., 2002). In the PCOS study mentioned above, researchers found a statistically significant decrease in fasting insulin; but the exercise group showed a greater decrease (also statistically significant) (Nidhi et al., 2012).

3.3.7 Yoga and β-cell dysfunction

Our review failed to find any studies that examined the effects of Yoga on mitigating β-cell dysfunction. Although we found several mentions of *kapalabhati pranayama* (a breathing technique involving sharp exhalations with automatic inhalations) improves the efficiency of β-cells of the pancreas (e.g. in (Raveendran, Deshpandae, & Joshi, 2018)), we were unable to find any cited study where this was explored.

However, when gene expression studies are examined, one finds compelling evidence of the salutary effects of Yoga in restoring β-cells' ability to secrete insulin at normal levels. This evidence comes from two separate causal pathways: oxidative stress and chronic inflammation.

Ever since the proposal that impaired insulin secretion could be the result of oxidative stress and stress-activated signaling pathways (Evans, Goldfine, Maddux, & Grodsky, 2002) evidence has been accumulating in its favor, e.g. (Ma & Zheng, 2018). This study performed a single-cell gene expression analysis of Islet cells and showed that β-cells are normal in insulin gene expression in the scenario of low cellular stress (especially oxidative stress), but appear dysfunctional under high cellular stress. Several studies have examined the effects of Yoga on oxidative stress: it was found that yoga is an effective means to reduce oxidative stress and to improve antioxidant defense in elderly hypertensive patients (Patil, Dhanakshirur, Aithala, Naregal, & Das, 2014); a 16-week Yoga practice plasma decreased malondialdehyde (MDA) concentration and increased superoxide dismutase activity (SOD) in female patients with shoulder pain; and in a study involving patients with end-stage renal disease (ESRD), the Yoga group showed decreased MDA concentrations and increased SOD activity (Gordon, McGrowder, Pena, Cabrera, & Lawrence Wright, 2013). Taken together, these findings support the idea that Yoga can have a salutary effect on β-cell dysfunction by reducing the effects of oxidative stress and increasing antioxidant activity.

Separately, it has been shown chronic Islet inflammation, in addition to its key role in the pathogenesis of type 1 diabetes, also plays an important role in β-cell dysfunction and failure in T2DM (Marzban, 2015). Specifically, increased expression of interleukin (IL)-1β have been reported in the pancreatic islets from patients with T2DM (Ehses et al., 2007; Maedler et al., 2002), and depletion of islet macrophages reduced IL-1β expression in these cells and improved insulin secretion (Westwell-Roper, Ehses, & Verchere, 2014). In a study of Yoga's effect on breast cancer survivors found that a 12-week practice of Yoga reduced levels of IL-1β; this effect was observed post-treatment and at 3-months post-treatment; study authors concluded that regular practice of Yoga dampens or limits inflammation (Kiecolt-Glaser et al., 2014). These findings offer additional evidence to the idea that Yoga can restore β-cells' ability to secrete insulin.

3.4 CONCLUSION

This review concludes that there the salutary effects of Yoga on the risk factors for insulin resistance provides a strong support to the hypothesis that Yoga can be effective in reducing risk of diabetes among high-risk individuals. Evidence also points to Yoga's potential efficacy as a complement to standard care for maintaining glycemic control among individuals who have diabetes.