Chapter II

REVIEW OF ANCIENT LITERATURE

2.1 Yoga- Scripture based review

Yoga is a mind-body practise based on traditional Indian philosophy, depicting the ideal way of life, and is more than just a physical activity (Kumar et al., 2016).

2.2 Definitions of Yoga

Following are few of the various definitions of yoga:

i. योगश्चित्तवृत्तिनिरोधः ॥२॥

'Yoga chittahvritti nirodhah' ***{Patanjali's Yoga Sutra (Sutra 1:2)}***

- Yoga is cessation of fluctuations of mind

According to Patanjali, yoga is removing fluctuations *(vrittis)* of mind (*chitta*). *Chitta* is made up of three components, *manas*, *buddhi* and *ahamkara*. *Manas* is like the recording faculty which receives impressions gathered by the senses from the outside world. *Buddhi* is the discriminative faculty which classifies these impressions and reacts to them. *Ahamkara* is the ego-sense which claims these impressions for its own and stores them up as individual knowledge. The different components of the mind work together to provide us with information. For example, when a raging Bull approaches towards us, manas reports 'A large animate object is quickly approaching'. Buddhi decides 'That is a Bull. It is angry and might attack someone'. Ahamkara screams, 'It wants to attack *me*'. Further, it is *I* who see this bull. It is *I* who is frightened. And, it is *I* who is about to run away'.

When an event or object in the external world is recorded by the senses, a thought-wave is raised in the mind. Unfortunately, the ego-sense identifies itself with this wave. If the thought-wave or the thought-process is pleasant, the ego-sense

feels '*I* am happy' and if the wave is unpleasant it feels that '*I* am unhappy'. This false identification is the cause of misery- for even the ego's temporary sensation of happiness brings anxiety, a desire to cling to the object of pleasure, and this prepares future possibilities of becoming unhappy. Irrespective of whether the *vritti* is pleasant (*klishta*) or unpleasant (*aklishta*), it has to be stopped. Cessation of the *vrittis* of mind is often misunderstood as 'making the mind blank' without any thoughts, which could rather be a superficial understanding of the *sutra*. It is much more subtle and deeper; it is to unlearn the false identification of the thought-waves with the ego-sense. The *vrittis* mentioned by Patanjali are due to *pramana* (right perception/knowledge), *viparyaya* (false perception/ knowledge), *vikalpa* (fantasy or imagination), *nidra* (sleep) and *smriti* (memory).

ii. योगः कर्मसु कौशलम्

'Yogah karamashu kaushalam' ***{Bhagavat Gita (Chapter 2: 50)}***

- Yoga is skill in action

Kaushalam signifies doing work with devotion and without attachment. Such detached attitude enhances its values, and improves the concentration and skill of the worker. If we work with elegance, fortitude and skill, our body, mind and soul will co-operate with our hands. Any work becomes valuable if carried out with utmost dedication and abilities which would be of help to us and to others in the society.

iii. समत्वं योग उच्यते।

'Samatvam yoga uchyathe' ***{Bhagavat Gita (Chapter 2: 48)}***

- Yoga is equanimity in extreme opposites

A person endowed with equanimity becomes free from virtue and vice. In such a state while living in the world, he detaches himself from the trappings of the world and remains untouched by virtue and sin, from *sukha* and *dukha*, pleasant or pain.

Of the various definitions of yoga, this thesis is built on the definition of *'Samatvam yoga uchyathe'* to explain the effect of yoga in the management of T2DM, and possible prevention of complications of T2DM. Scientific evidence of literature in the yogic management of T2DM are dealt with later.

2.3 Pancha kosha and Diabetes

2.3.1 Pancha kosha (The five layers of existence)

The *Taittiriya Upani*sh*ad* discusses five levels of existence in the human condition. The grossest physical frame is called the *annamaya kosha*, followed by *pranamaya kosha, manomaya kosha, vijnanamaya kosha* and the subtlest, *anandamaya kosha* (Rajesh et al., 2010). The *annamaya kosha* refers to the gross physical body which is a sheath sustained by food. The second subtler sheath is the *pranamaya kosha*, the energy body features by the predominance of *prana*, the life principle which flows through invisible channels called *nadis*. The next sheath in the order of subtlety is *manomaya kosha*, the sheath of sensory capacities where emotions predominate and start governing our actions. Next is the *vijnanamaya kosha*, the sheath of cognitive function and finally *anandamaya kosha*, the sheath of blissfulness (Nagendra, 2010). According to the *panchakosha model*, disease originate at a subtler level. *Manomaya kosha* and *vijnanamaya kosha* endows *manomaya kosha* with unending thought

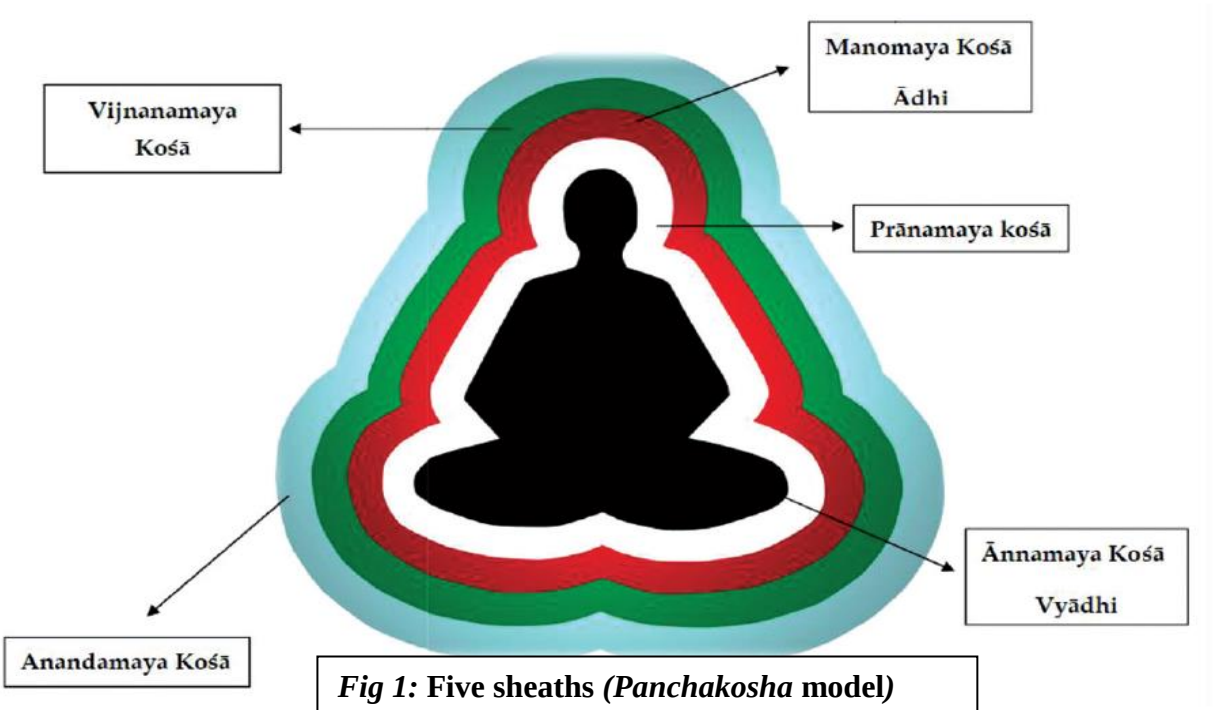

Fig 1: **Five sheaths *(Panchakosha* model*)***

processes and wrong cognition which leads to and manifests as *adhi* (stress). When the *manomaya kosha* is afflicted, the body follows the disturbance completely. Due to these disturbances, flow of *prana* in *nadis* gets vitiated. These imbalances in the flow of *prana* at the *pranamaya kosha* finally culminate as disease at the *annamaya kosha* or physical body level (Rajesh et al., 2014).

2.3.2 Imbalance in pancha koshas and risk of diabetes

The importance of 'equanimity ' ('Yoga is equanimity') in relation to the pathophysiology of type 2 diabetes could be expressed from different aspects and at different levels of *panchakoshas*as as mentioned in the *Taittiriya Upani*sh*ad*.

The role of all five koshas and the importance of '*samatvam*' in these five *koshas* for the prevention and management of T2DM are discussed below.

Annamaya Kosha/ Physical level

युक्ताहारविहारस्य युक्तचेष्टस्य कर्मसु।

युक्तस्वप्नावबोधस्य योगो भवति दुःखहा।।6.17।।

'Yukthaharaviharasya yuktacesthasya karmasu yuktaswapnavabodhasya

Yogobhavati duhkaha' (Bhagavat Gita- Chapter 6: 17)

This *sloka* from *Bhagavat Gita* stresses on 'moderation' at physical level. Moderation in food intake, sleep and even moderation in physical activity is recommended as essential for a true yogi. With respect to T2DM, reduced physical activity is a long known risk factor of T2DM. However, increase in the duration or intensity of physical activity might also increase sympathetic arousal worsening glycemic control. Post prandial excursions result in both acute and sustained

hyperglycemia and in general, acute glucose fluctuations activate oxidative stress. The oxidative stress not only increases after a heavy meal, but also during fasting. For instance, the production of nitrotyrosine, a metabolite derived from nitrosamine stress, was significantly increased during fasting in patients with diabetes, interestingly an additional increase was observed during post meal periods (Monnier et al., 2008). Likewise, both 'low birth weight' (Wang et al., 2016) and 'high birth weight' (Johnsson et al., 2015) increases risk of T2DM at latter part of life, demonstrating the importance of moderation in T2DM.

***Manomaya Kosha/* Emotional level**

The *pancha kosha* model believes that *manomaya kosha* or mind is the root cause of diseases which is in line with the modern concept of 'psychosomatic disorders'. Balancing mind, by maintaining or staying equipoised during times of extreme emotional disturbances and treating *sukha* or *duhka* (happiness or sadness), victory or defeat as one and the same are the attributes of a true yogi. Increased anxiety and stress are risk factors disturbing glycemic control in T2DM management. On the other extreme, depression is also a risk factor which doubles the risk of T2DM (Eaton et al., 1996), showing that the imbalance of extremeness in emotions is a possible contributory risk factor of T2DM.

***Vijnanamaya kosha/* Nervous system level**

Imbalance in the autonomic nervous system level is associated with T2DM. Increased sympathetic tone and reduced vagal activity has been reported in T2DM (Benichou et al., 2018). Studies on yoga have shown that yoga is beneficial in balancing the autonomic imbalance (Singh et al., 2004; Vaishali et al., 2012).

***Pranamaya kosha/* Breathe level**

In yoga, balancing of *ida* and *pingala nadis* through *nadishuddhi pranayama* is believed to help in achieving meditative state, which allows the flow of *prana* through the *sushumna nadi*, the first step in achieving the higher yogic state of '*Samadhi*' or self-realisation. The predominance of either of these *nadis* leads to *tamas* (type D personality) and *rajas* (type A personality) respectively. Type D and type A predominant personality traits are already known to influence the risk of T2DM (Conti et al., 2016; Chauvet-Gelinier et al., 2016). Balancing of these two *nadis* is essential to increase *sattva* and achieve true yogic state, leading into a perfectly balanced '*Anandamaya kosha*'.

Anandamaya Kosha/ Bliss

'*Ananda*' (bliss) is the root of all human life and *anandamaya kosha* can be described as the transcendental body. This is the *kosha* (body) one enters whenever a desire is fulfilled and also in the thought-free state characteristic of *nirvikalpa samadhi* and more familiarly, in deep sleeps (Raina, 2016). Improper sleep is one of the known risk factors for T2DM. A large population based study on 4,82,502 participants showed that, a 'U'-shaped dose-response relationship were observed between sleep duration and risk of T2DM i.e., the risk of T2DM increases when one sleeps more or sleeps lesser than 7-8 hours per day (Shan et al., 2015). A balance or moderation in sleep is essential to prevent the risk of T2DM and its management.

CHAPTER III

SCIENTIFIC LITERATURE REVIEW

3.1. Pathophysiology of Type 2 Diabetes mellitus

Our knowledge and understanding on the pathophysiology of T2DM is ever expanding. The two common pathophysiological abnormalities observed in T2DM are insulin resistance and impaired β-cell function. The pathophysiology of T2DM is believed to commence with insulin resistance, which leads to glucotoxicity and decreased β-cell function (Chang-Chen KJ, Mullur R & Bernal-Mizrachi E, 2008). On the contrary, recently emerging 'β-cell centric' approach (Schwartz et al., 2016) posits β-cell dysfunction as the primary defect in T2DM which leads to Insulin resistance and further complications of diabetes. Beta cells are said to be dysfunctional when there are defects in any one or all the 3 components mentioned below. First, the secretion timing disorder, where there is reduction in the initial acute phase insulin release (AIR). Autonomic nervous system is attributed for greater than 70% of the AIR (Ahren & Holst, 2001). AIR is generally abolished by vagotomy in rats (Berthoud et al., 1981) and by atropine in humans (Teff & Townsend, 1999), suggestive of the pivotal role of vagal activity in AIR. Second is the quantitative disorder, in which there is an increase or decrease in the second phase insulin release. Third, the qualitative disorder, in which there is an increase in the pro-insulin to insulin ratio (Pfutzner & Forst, 2011).

Chronic oxidative stress and increased free radicals observed in T2DM plays a decisive role in inducing β -cell dysfunction, as β -cells possess limited defence against excess ROS due to low levels of ROS-detoxifying enzymes (Prentki & Nolan, 2006; Tiedge et al., 1997). Increase in oxidative stress leads to decreased transcription of the insulin gene by reducing pdx1 and MafA binding (Olson et al., 1993; Olson et al., 1995). Similarly, protein misfolding and resultant ER stress in the human β-cells is a

major pathophysiological event in T2DM which is also associated with oxidative stress (Chang-Chen, Muller & Bernal-Mizrachi, 2008).

Apart from insulin resistance (in muscles & liver) and β -cell dysfunction, the 'ominous octet' model of DeFronzo (2009) infers the involvement of brain, adipose tissue, gastrointestinal hormones, kidney and α-cells in the pathophysiology of T2DM and emphasizes the need for a multiple drug combination to rectify the underlying multiple pathophysiological defects and not simply aim at reducing the Glycated haemoglobin (HbA_1C) levels (DeFronzo, 2009).

3.2 Pancreatic islets

The human pancreas contains approximately 1,000,000 islets that work in a concerted manner to produce bursts of hormone secretion at 5 min intervals (Tengholm & Gylfe, 2009). To generate this secretory pattern, the activity of the insulin-secreting β cells must be in synchronization within the islet and across islets. The secretory activity of other islet endocrine cells such as the glucagon-secreting α cell, which has opposing effects on glucose homeostasis, should also need to be coordinated with that of the β cell. As endocrine cells communicate with each other within the islet they may simultaneously send signals that adjusts blood flow to efficiently deliver islet hormones into the circulation and eventually to the liver, where they help regulate glucose output to maintain glucose homeostasis (Conn *et al*. 1998). Anatomical and functional defects disrupting these coordinated, rhythmic activities probably diminish the efficiency of the islet to a point where they probably contribute to the pathogenesis of diabetes. A loss of pulsatile insulin secretion is indeed characteristic of patients with type 2 diabetes (Tengholm & Gylfe, 2009).

Each islet is a functional unit that has all necessary elements to produce adequate responses to changes in glucose concentration, while influenced by the circulating nutrients, hormones and nervous inputs. Any given islet is a good representative of all the other and includes all pancreatic endocrine cell types, a unique vasculature, and a set of resident macrophages (Rodriguez-Diaz et al., 2014). Islets are self-reliant units whose hormonal responses are small versions of the whole pancreatic output. It is within the structural and functional frame of the islet that the individual endocrine cells coordinate their activities to generate appropriate hormonal responses. It may at first seem counterintuitive that β and α cells, which can be defined as antagonists, are located in the same micro-organ. When isolated, however, β and α cells do not respond appropriately, suggesting that the close association with other endocrine cells within the islet is required to optimize hormone secretion (Wojtusciszyn *et al*. 2008). Paracrine signalling within the islet seems so entrenched that there is a cell population, the δ cells, dedicated to modulate the activity of the neighbouring β and α cells (Taborsky *et al*. 1979; Samols & Stagner, 1990).

Paracrine interactions within the islet may actually be more important than previously thought. It is likely that the roles α and δ cells play in shaping β cell function may have been underestimated because our model of islet biology is mostly derived from studies performed on rodent islets. The rodent islet cyto-architecture differs from that of the human islet in that most β cells only contact other β cells within the core of the islet, far away from α and δ cells located in the periphery of the islet. In rodent islets blood reportedly flows first through β cell-rich regions, implying that β cells are not exposed to signals derived from other endocrine cells (Stagner & Samols, 1992). However, in the human islet, most β cells are surrounded by α and δ cells and there is

no particular cellular arrangement along blood vessels (Brissova *et al*. 2005; Cabrera *et al*. 2006). Thus, in the human islet the different endocrine cells are close enough to influence each other through direct contacts, via the interstitium, or using the vascular route.

Neuroscience of the pancreatic islets

The list of neurotransmitters and neuropeptides that have been suggested to play a role as paracrine signals within the islet is extensive. Most of the small neurotransmitter molecules expressed in the brain have been reported to be present in the islet. To add to the complexity, the hormones released by α and β cells also act locally on neighbouring cells.

The regulation of hormone secretion is one setting in which paracrine signalling is thought to be essential. Many candidate paracrine molecules have been shown to modulate hormone secretion. Prominent examples are GABA and somatostatin, which are produced and released by β and δ cells, respectively. Receptors for somatostatin have been mapped to the different endocrine cells and their activation inhibits all endocrine cells within the islet (Taborsky *et al*. 1979). Although somatostatin is considered a negative regulator of insulin and glucagon secretion, we still know little about how the somatostatin-secreting δ cell is regulated inside the pancreas. Without knowing what controls the δ cell, it is difficult to understand the biological meaning of this paracrine pathway, and thus we can only speculate about the functional role of somatostatin in the islet. GABA has been proposed as a paracrine signal released from β cells to inhibit α cells, which may help explain how an increase in glucose concentration

leads to increases in insulin secretion while simultaneously inhibiting glucagon secretion (Rorsman *et al*. 1989).

Islets are shown to be strongly innervated by parasympathetic and sympathetic axons that probably co-release a variety of neurotransmitters and neuropeptides together with acetylcholine and noradrenaline, in animal models. Acetylcholine has been known for decades to amplify insulin secretion (Gilon & Henquin, 2001). The consensus is that it is released from parasympathetic axons innervating the islet.

Rodriguez-Diaz et al. (2016) examined the effects α cell-derived acetylcholine could have on islet function. Studies had shown that exposure to acetylcholine sensitizes the β cell to subsequent stimuli. To test the hypothesis that α cells release acetylcholine to prime neighbouring β cells, Rodriguez-Diaz et al. subjected isolated human islets to an experimental protocol in which they stimulated α and β cells intermittently while modulating cholinergic signalling. They observed that endogenous acetylcholine sensitized the β cell to subsequent increases in glucose concentration. Based on these results they proposed that in the human islet, acetylcholine serves as a paracrine signal to keep the β cell responsive to future challenges, thus limiting glucose fluctuations.

3.3. *HbA_1C & Glycemic variability*

In addition to HbA_1C and plasma blood glucose levels, glycemic variability (GV), defined by the amplitude, frequency and duration of glycemic fluctuations around mean blood glucose, encompassing both diurnal hyperglycemic peaks and hypoglycemic troughs (Tay, Thompson & Brinkworth, 2015), is an emerging target for diabetes management (Vijayakumar et al., 2018). Glycated haemoglobin (HbA_1C) is the 'gold standard' measure of glycemic exposure during the 6- 8 weeks prior to sampling (Goldstein et al., 1986) and is long being used as a prognostic marker to understand the glycemic status in type 2 diabetes and its associated complications. Randomised controlled trials (RCTs) have demonstrated significant reduction in complications when HbA1C is lowered to 7% or below. However, off late, the application and efficiency of HbA1C as a solitary measure in the assessment of glycemic control is widely debated (Beck et al., 2017). Variations in HbA1C among different ethnic groups have been reported (Bergenstal et al., 2017).These reports suggest that measurement of baseline HbA1C levels alone might not always provide a clear picture on glycemic status of an individual (Lind et al., 2008). For a clinician, a value measured at an appointment alone might not be the best prognostic value for the following years. Fluctuations in values from the recent past might play a far greater role in predicting the risk of complications. Higher the fluctuations in HbA_1C over a period of time, higher would be the risk of complications (Lind et al., 2008).

Moreover, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the intensive glycaemic control arm of the trial was terminated prematurely due to significantly higher rates of mortality (Gerstein et al., 2008). Although it has been difficult to pinpoint the exact cause of higher mortality associated with intensive glycaemic control, higher rates of severe hypoglycaemia or glycaemic variability might

have possibly contributed (Mikus et al., 2012). HbA_1C is an index of long-term glycaemic control and does not provide insight into changes in glycaemic variability or hypoglycaemia (Sacks et al., 2002). Thus, even as HbA_1C is lowered, increase in hypoglycaemia or glycaemic variability may go undetected. Elevated glycaemic variability maybe more damaging or additive to the complications caused by chronic hyperglycaemia, as large fluctuations in blood glucose trigger physiological events which increase microvascular and macrovascular complications associated with T2DM (Mikus et al., 2012). Glucose variability or glycaemic variability is one of the key concepts emerging in the field of T2DM. Hyperglycaemia, hypoglycaemia and increased glucose variability are all independently associated with increased risk of mortality in critically ill diabetes adults (Krinsley & Presiser, 2015). Similarly, hypoglycaemia or hypoglycaemic episodes are as equally harmful as the hyperglycaemia in inducing cardiovascular and neuropathy complications. Unlike heart rate variability, glycaemic variability should be bare minimum and available literature suggests that wide fluctuations in glucose levels reflecting as increased GV may be an independent risk factor for diabetes complication and increased risk of mortality (Hill et al., 2011; Krinsley & Presiser, 2015). Glucose fluctuations or glycaemic variability can induce excessive formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), increasing the risk of diabetes complications and leads to apoptosis related to oxidative stress (Kohnert, Freyse and Salzsieder, 2012). Glucose fluctuations can activate nuclear factor –κB(NFκB) and protein kinase C pathway (PKC) pathway, leading to excess formation of advanced glycation end products than stable high glucose levels (Quagliaro et al., 2003; Hou et al., 2008). There is growing need to identify a safe

and effective intervention to improve glycaemic control while simultaneously reducing glycemic variability and minimising hypoglycaemic events (Mikus et al., 2012).

3.4 Yoga- Scientific literature review

The blood glucose lowering effect of yoga in T2DM could be attributed to the stretching and contraction movements often performed during physical asana postures in yoga, as muscle contraction improves glucose sensitivity and reduce blood glucose (Gurudat & Rajan, 2017). However, randomised controlled trials (RCTs) done in the past found yoga to be as effective or superior to physical exercises (Sinha et al., 2007; Schmidt et al., 1997; Amita et al., 2009) and so, the benefits might not just be limited to the physical movements involved in yoga. For instance, y*oga nidra* ('yogic sleep') is a yogic technique which involves complete body relaxation without any physical movements. A three month study exploring the efficacy of *yoga nidra* in patients with T2DM found a significant reduction in blood glucose levels when compared to control group (Rajesh et al., 2013). The reduction in blood glucose is not due to the physical movements involved, but possibly due to reduction in the stress hormones like catecholamine and cortisol, or due to increased vagal activity (Jyotsna et al., 2013). Reduced breathing rate increases vagal activation and decrease the influence of sympathetic branch of the autonomic nervous system, which is measured by an increase in heart rate variability and baroreceptor sensitivity (Qatanani & Lazar, 2007). Decreased vagal tone contributes to the etio-pathogenesis of T2DM in multiple ways (Ahren & Holst, 2001). Few studies show an improvement in the complications associated with diabetes like improved nerve conduction velocity (Malhotra et al., 2002), cognition (Lazar et al., 2005) and Quality of Life (QoL) (Jyotsna et al., 2012).

Autonomic dysfunction associated with T2DM is reported to be stabilised following yoga (Jyotsna et al., 2013; Agrawal et al., 2003). Thus, yoga shows promising insights of becoming an effective complementary therapy in the prevention and management of T2DM.

Interestingly, few studies even report a reduction in the medication score and insulin intake of T2DM patients in yoga group (Nagarathna et al., 2013; Agrawal et al., 2003), suggesting a possible improvement in β-cell dysfunction, insulin resistance or any of the pathological abnormalities in the ominous octet, which was not observed with the exercise based lifestyle intervention groups (Agrawal et al., 2003).