CHAPTER I

INTRODUCTION

Effect of Yoga on Ambulatory Glucose Profile in Type 2 Diabetes mellitus

1.1. INTRODUCTION

Diabetes is a metabolic disorder characterized by elevated blood glucose concentration, which occurs either because of insulin resistance, or due to insufficient secretion of insulin, or both. Diabetes mellitus is a Greek word, which means sweet fountain (Diabetes- fountain, mellitus-sweet).

Diabetes is known from ancient times. Diabetes has been affecting lives for thousands of years. It was recognized by the Egyptians in manuscripts dating to 1550 BCE. An Egyptian manuscript from 1500 BCE also tells about the diabetes and describes as "too great emptying of the urine". At the same time Indian physicians identified the disease in which the urine attracts the ants and flies and classified it as *madhumeha* or "honey urine"(Porestsky, 2007). The prevalence and incidence of diabetes mellitus is increasing worldwide at an alarming pace. The number of adults with diabetes was 194 million in 2006 and was predicted to reach 333 million by 2025 (IDF Diabetes Atlas, 2006). But already, an estimated 425 million adults have diabetes and another 352.1 million adults have impaired glucose tolerance (IDF Diabetes Atlas, 2017).

Annual expenditure for the management of diabetes is US$ 727 billion, of which major portion is spent on the direct and indirect costs related to the ‘complications’ of diabetes (IDF atlas, 2017). Current guidelines focus on multiple drug treatments to reduce blood glucose and associated complications of diabetes, but life expectancy and quality of life remains substantially low (Lean et al., 2017). There is growing interest in

alternative and holistic model of care which is cost-efficient, sustainable and effective, with little or no adverse effects. Devising novel prevention and management strategies for metabolic disorders and its complications will depend in part on the careful elucidation of the common pathways involved (Wulsin, Herman & Thayer, 2018), which are dealt with in the later sections.

1.2 Classification of Diabetes Mellitus

Considering the basic defects, a large proportion of the diabetes can be classified into following broad categories:

i. Type 1 diabetes

Type 1 diabetes is the result of an absolute deficiency of insulin in the body, mostly as a result of autoimmune destruction of the pancreatic islet cells.

ii. Type 2 diabetes

Type 2 diabetes is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion.

iii. Gestational Diabetes

Apart from these two broad categories, women developing diabetes during pregnancy are classified as having gestational diabetes. Other uncommon and diverse types apart from these, also exist, and are caused by plethora of factors such as infections, drugs, endocrinopathies, destruction of pancreas and genetic defects.

Though it might appear simple, assigning a category might be complex at times and are often be guided by the clinical features at the time of presentation. An appropriate example would be steroid induced diabetes, which usually disappears once the steroids are reduced or withdrawn but the patient can again develop diabetes years later and may be classified as a type 2 diabetic. Similarly, gestational diabetes may continue as type 2

diabetes in a woman, if she is hyperglycaemic even after her pregnancy or may resolve and recur years later as type 2 diabetes.

iv. Other types

Specific types of diabetes due to other causes eg. Monogenic diabetes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), disease of the exocrine pancreas (Fibro calculus pancreatopathy), and drug-or chemical-induced diabetes (such as with glucocorticoid, ACTH, pentamidine, etc.)

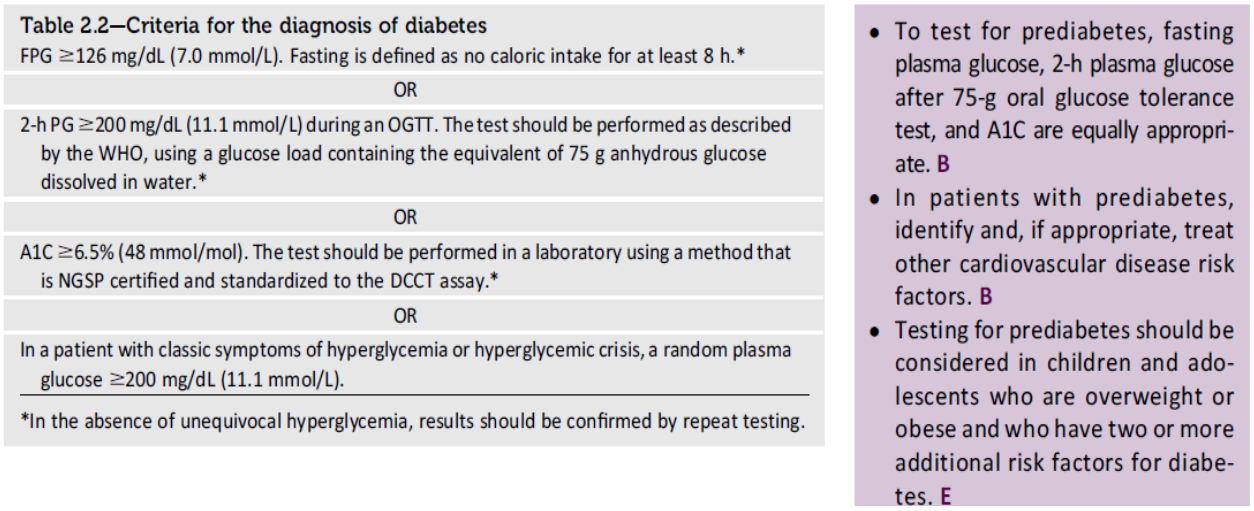

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

- To test for prediabetes, fasting plasma glucose, 2-h plasma glucose after 75-g oral glucose tolerance test, and A1C are equally appropriate. B
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease risk factors. B
- Testing for prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. E

Fig. 1 Criteria for the diagnosis of diabetes (American Diabetes Association 2017)

1.3 Pathophysiology of type 2 diabetes

Insulin Resistance as the primary defect

Hyperinsulinemia and insulin resistance often precede the development of impaired glucose tolerance (IGT). Impaired Glucose Tolerance represents the transient

stage between normal glucose tolerance and type 2 diabetes. The hyperglycemia to insulin resistance occurs in three phases (Seshiah and Balaji, 2010).

First Phase - Plasma glucose remains normal despite demonstratable insulin resistance because the insulin levels are increased.

Second phase - Insulin resistance tends to worsen so that post-prandial hyperglycemia develop despite elevated insulin concentration.

Third phase – Insulin resistance does not change but declining insulin secretion causes fasting hyperglycemia.

Because of insulin resistance, the beta cells produce excess insulin. As the resistance progresses the muscle glucose uptake becomes impaired, but the insulin produced is sufficient enough to maintain the hepatic glucose output in the normal range (i.e. fasting blood glucose is still normal). At this stage, the time taken to achieve normoglycaemia post-meal is the only defect noticed. Eventually, as the hyperglycaemia becomes sufficiently severe, the compensatory hyperinsulinemia is no longer adequate to maintain the fasting plasma glucose in normal level. The development of fasting and postprandial hyperglycemia stimulates beta cells further, with the resultant hyperinsulinemia leads to down regulation of the receptor number and the post-receptor events, exacerbating the insulin resistance further leading to chronic hyperglycemia, which is toxic ‘glucotoxicity’ to the beta cells and is responsible for the acquired defect of impaired insulin secretion.

Insulin secretory defect as the primary defect in type 2 diabetes

In the evolution of the disease in those who are prone to or at increased risk of type 2 diabetes, the primary defect might also be in the beta cells (Schwartz et al., 2016). Even when the blood glucose is normal, the earliest abnormality noted might be the loss of ultradian oscillation of insulin secretion, with decreased acute phase insulin secretion. Reduction in the acute phase insulin release is one of the earliest signs, which is found reduced in the first degree relatives of patients with type 2 diabetes (Pal et al., 2013).

The impairment of insulin secretion will lead to excessive and prolonged increase in the plasma glucose concentration. This increase in glucose concentration has a glucotoxicity effect and reduces insulin release from the beta cells. Though the acute phase insulin release is diminished, the total amount of insulin secreted in response to a meal may actually be increased. The post prandial hyperinsulinemia may be sufficient to return the fasting plasma glucose level to normal, but longer periods are required to restore euglycemia. This elevated insulin concentration leads to down regulation of the insulin receptors and the post receptor events in the insulin sensitive tissues and results in the emergence of insulin resistance.

Thus, both insulin resistance and insulin deficiency may lead to or induce the other resulting in hyperglycemia. Whether the primary defect initiating the glucose tolerance resides in the beta cell or in the peripheral tissues, development of insulin resistance will eventually ensue or become aggravated respectively. By the time overt fasting hyperglycemia (>140mg/dL) develops both impaired insulin secretion and insulin resistance are present. Thus hyperglycemia due to either of the primary

abnormality may secondarily involve the other abnormality. The sensitivity and maximum responsiveness to insulin are reduced (insulin resistance) in the target tissues by prolonged elevation of the plasma glucose. Hyperglycemia is also toxic to the beta cells and further diminishes their capacity to respond to stimulation (insulin deficiency). Hence, hyperglycemia is not only manifestation of diabetes, but also its cause (Seshiah and Balaji, 2010).

1.4 Clinical features of type 2 diabetes

Though the symptoms vary from person to person, the most common symptoms are caused due to hyperglycemia where polyuria, polyphagia and polydipsia are seem. The classical symptoms of diabetes like thirst, polyuria, nocturia and rapid weight loss are prominent in type 1 diabetes than type 2 diabetes, although diabetic coma might be the first event due to acute metabolic compensation in type 1 diabetes.

T2DM usually begins in the middle or late life with obesity being a typical presentation seen in affected individuals. Type 2 diabetes patients might not develop ketoacidosis (a serious complication in type 1 DM), though they are susceptible to hyperosmolar, non-ketotic coma. Many type 2 diabetes patients complaint of non-specific conditions like chronic fatigue and malaise and uncontrolled cases are often associated with increased susceptibility to infections.

1.5 Risk factors for type 2 diabetes

In Type 2 DM, high calorific diet, physical inactivity and obesity are the major predicators. Overweight and obese individuals are at an increased risk of developing T2DM. Moreover, susceptibility for diabetes mellitus is seen to occur in individuals with extensive central adiposity in comparison to those with a more distribution of body fatness. The importance of risk factors in Indian population is not known and migrant studies provide evidence of western (United States) risk factors occurring in the Indian population (Vijayakumar et al., 2017). With respect to physical activity, it was further shown that sedentary lifestyle is associated with higher risks of diabetes, metabolic syndrome and its components, in comparison to moderate to high intensity physical activity.

1.6 Complications for type 2 diabetes

Type 2 diabetes patients risk developing cardiovascular diseases, cerebrovascular diseases and renal diseases much more than the general population. The resistance to insulin stimulated glucose uptake is associated with other phenomenon like glucose intolerance, dyslipidemia, high blood pressure and coronary heart disease which have the tendency to cluster together in the same affected individual.

Prospective studies in type 2 diabetes mellitus have shown an association with hyperglycemia and increased risk of microvascular complications, sensory neuropathy, stroke, myocardial infarction and macrovascular diseases.38 The hallmark of macrovascular disease in diabetics comprises of coronary artery disease with its complications of myocardial infarction and congestive heart failure, cerebral and carotid arteriosclerotic vascular diseases with its complications of stroke and cerebral ischemia and finally peripheral vascular diseases leading to claudication, ischemia and amputation.

The microvascular complications include retinopathy, nephropathy and neuropathy. Diabetic retinopathy is one of the leading cause of blindness. Glaucoma, cataract, optic neuropathy and ocular palsies are the other eye disorders seen in diabetes. In case of diabetic nephropathy, it still stands to be the major cause of mortality and morbidity in type 2 diabetes inspite of the improvements made in early detection, prevention and treatment. Neuropathy is a condition seen in both type 1 as well as type 2 DM, though it may be present in the latter at the time of diagnosis itself and not so for the former. The commonest form of neuropathy to affect type 2 diabetes is peripheral sensorimotor neuropathy affecting the feet initially and this condition is seen to be exacerbated with poor hyperglycemic control, uncontrolled hypertension and

dyslipidemia. Also, foot complications are a serious threat to diabetic patients and the main factors responsible for this are vascular insufficiency, peripheral neuropathy along with ulcerations and pedal deformities. Diabetes is the main cause for amputation and increases the risk by 10 folds when compared to non-diabetics (Hoffstad et al., 2015).

1.7 Treatment and management in type 2 diabetes mellitus

Type 2 diabetes is a progressive disorder. Medications usually begin as a monotherapy and due to the progressive nature of diabetes, other agents may need to be added and many patients may require to be started on insulin therapy on the long run. The goal of therapy is to maintain near-normal glucose levels to prevent the development of diabetic complications, however majority of the patients suffering from type 2 diabetes require a combination of multiple therapies to manage the disorder.

As per the American Diabetes Association Guidelines (ADA, 2018), metformin remains the optimal drug for monotherapy. Its low cost, proven safety record, weight neutrality, and possible benefits on cardiovascular outcomes have secured its place as the favoured initial drug of choice. While sodium glucose co-transporter-2 (SGLT-2) inhibitors are approved as monotherapy, they are mainly used in combination with metformin and/or other agents. Initial combination therapy of metformin along with any of the below mentioned (Fig 1) second agent might allow patients to achieve better HbA1C. In certain patients, glucose control remains poor despite the use of three anti-hyperglycemic drugs in combination. With long-standing diabetes, a significant diminution in pancreatic insulin secretory capacity dominates the clinical picture. In any patient not achieving an agreed HbA1C target despite intense therapy, insulin therapy should be considered as an essential component of the treatment strategy. Over the past few years, however, the effectiveness of combining GLP-1 receptor agonists with basal

insulin has shown equal or slightly superior efficacy to the addition of prandial insulin and with increased weight loss and lesser risk of hypoglycaemia (Inzucchi et al., 2015).

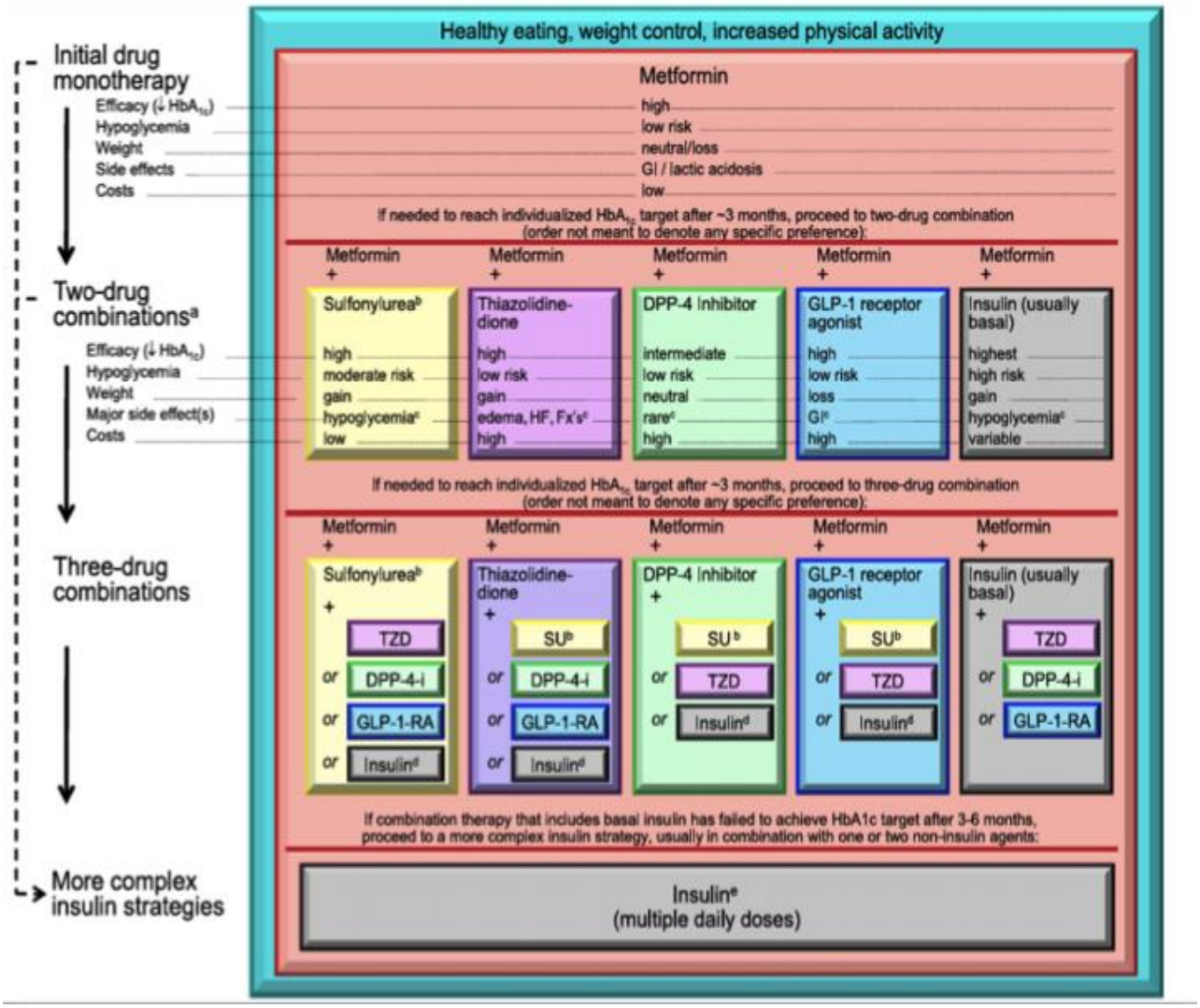

Fig 1– Antihyperglycemic pharmacotherapy for type 2 diabetes management (ADA)

The current therapeutic approaches could face several problems due to multiple features of type 2 diabetes like beta cell failure, post-prandial hyperglycemia, insulin resistance along with other side effects of modern medications like gastro-intestinal

disorders with metformin and alpha-glycosidase inhibitors, fluid retention and osteopenia with thiazolidinediones and hypoglycemia and weight gain for sulfonylureas. Insulin therapy is very common amongst type 2 diabetes patients as the disease is progressive in nature and beta cell deterioration occurs constantly. However, prolonged insulin therapy may worsen insulin resistance as well.

1.8 CAM therapies (Complementary and Alternate Medicine) in type 2 diabetes management

The chronic nature of diabetes, harmful side effects of synthetic drugs, enormous cost of modern drugs, inability of the existing modern therapies to prevent the progression of diabetes and to control few of the pathological aspects of diabetes, and also due to the potential threat caused by diabetes to the quality of life, there is an urgent need for some alternate strategies to the current pharmacotherapy used to treat diabetes (Mowla, Alauddin, Rahman and Ahmed, 2009). Many patients with diabetes have started using Complementary and Alternative Medicine (CAM) to have a better glycaemic control (Aljasir, Bryson and Al-shehri, 2010). Approximately, 70% of the Canadian population and 80% of the German population use CAM therapies (WHO, 2010) and amongst diabetics, 48% of type 2 diabetes patients in United States of America (USA) use CAM therapies with or without the knowledge of their General Practitioners (GP's) (Bradley, Kozura, Buckle, Kaltunas, Tais, and Standish, 2009). This high number of CAM therapy users does make it clear that, all of us, including the conventional medical practitioners and the 'Nay- Sayers' to the complementary medicine should be aware and have some knowledge about the complementary medicine to give effective treatment to the patients, and to avoid any possible drug

interaction between the conventional medicine given and the herbal medicine taken by the patients (Lee and Kemper, 2000). The American Diabetes Association (ADA) has responded to the increasing use of CAM therapies by issuing a position statement which states that the usage of adjuvant therapies should be evidence based and the evidence of which would be obtained from the clinical research trials (ADA, 2004).

In CAM, the term "complementary" refers to therapies which are used in conjunction with conventional medicine and "Alternative" medicine refers to therapies that are used to replace the conventional medicine (Birdee and Yeh, 2010). The National Centre for Complementary and Alternative Medicine is a federal scientific agency for CAM research in United States of America (USA), which has categorised CAM into five domains, namely, biologically based practices, mind-body medicine, manipulation and body- based practices, energy medicine and whole- medical systems. Yoga comes under the domain of mind-body medicine and therapies like Naturopathy comes under whole-medical systems (Birdee and Yeh, 2010) and includes many treatment modalities within it.

1.8.1 Acupuncture

Acupuncture is believed to be effective not only in controlling hyperglycaemia in type 2 diabetes, but also in preventing and managing the complications arising due to diabetes (Dey *et al.*, 2002).

Acupuncture points for Diabetes:

Four commonly used acupuncture points (Dey *et al*., 2002) in diabetes are (see Appendix 1):

1. *Zusanli* (St 36) – the acupuncture point is located 3 inches below the lateral knee depression, one finger breadth from the lateral side of the anterior crest of tibia.
2. *Sanyinjiao* (Sp 6) – the acupuncture point is located 3 cun above the tip of inner ankle, on the posterior margin of the metatarsal bone.
3. *Feishu* (UB 13) – the acupuncture point located 1.5 cun lateral and inferior to the spinous process of the third thoracic vertebra in prone position.
4. *Shenshu* (UB 23) – the acupuncture point located 1.5 cun lateral and inferior to the spinous process of the second lumbar vertebra in prone position.
5. *Zhongwan* (CV 12) – the acupuncture point is located on the upper abdomen and on the anterior abdominal wall, 4 cun above umbilicus. CV 12 was reported to lower plasma glucose concentration regardless of the presence of hypoglycaemia (Jang, Shin, Kim, Kim, and Kim, 2003)

The search results for acupuncture treatment for diabetes, published in English language yielded 7 results, all being studies carried out on experimental animals. One such animal experiment had shown that acupuncture can activate glucose- 6- phosphatase

(Dey *et al.*, 2002) an enzyme which completes the final stage of gluconeogenesis and glycogenolysis.

Clinical Trials and Discussion

The most relevant of the animal trials was the one which analysed the effect of acupuncture on the synthesis of Nitric Oxide Synthase (NOS) and specifically, the neuronal NOS (nNOS) in the cerebral cortex was studied on streptozin (STZ)- induced diabetic rats (Jang *et al.*, 2003). Animals were divided into 4 groups, the control group, the non- diabetic and acupunctured group, the STZ- induced diabetes group and the STZ- induced diabetic and acupunctured group. Data of number of rats in each group are not available. Diabetes was induced in rats by administering STZ intra-peritoneally (50 mg/ kg of body weight). Stainless steel acupuncture needle of 0.3mm diameter was inserted at the point corresponding to St 36 (Zusanli) in human beings, and left in place for 20 minutes for 5 consecutive days. After 5 days, the animals were sacrificed and there brain histochemistry showed that there was an increase in the number of various nNOS positive neurons ($p<0.05$) to the levels of the normal non-diabetic group in the STZ-induced diabetic and acupuncture treated group of rat, which had initially been lowered due to the administration of STZ ($p<0.05$) (Jang *et al.*, 2003). NOS is believed to be significant in patients in diabetes mellitus, as a decrease in the NOS activity is thought to increase vessel resistance resulting in reduced blood flow, impaired learning, memory and cognition being affected as well (Biessels *et al.*, 1998). NOS is significant as it also endogenously generates nitric oxide (NO) from L-arginine, which is a potent vasodilator and a key metabolic regulator found to be reduced in type 2 diabetes patients (Tessari *et al.*, 2010). Though the outcome measure of nNOS was significantly increased both clinically and statistically ($p<0.05$), increasing the nNOS value similar to

the non-diabetic state), its application in human subjects is yet to be verified. Large trials with human subjects has to be conducted to confirm its efficacy on human type 2 diabetes patients, as the authors of the trial have only tentatively suggested that acupuncture 'may' help to increase the nNOS activity in diabetic condition.

A pilot study to prove the efficacy of acupuncture on diabetic neuropathy was conducted on 7 patients (Ahn, Bennani, Freeman, Hamdy and Kaptchuk, 2007) for 10 weeks (once a week). All the participants reported limited relief with their pain relief medication prescribed for their neuropathy (like gabapentin), and were told to continue with their medication. A Short form McGill Pain Questionnaire (SF-MPQ) was used to measure the outcome measure of pain (Ahn *et al.*, 2007). On a scale from 0 to 45, where at 45 the pain felt is 'worst', the Traditional Chinese Medicine (TCM) acupuncture group reduced pain by 4.7 points from baseline (19 vs. 14.3), while in the Japanese acupuncture group the pain reduced by 4.3 points from baseline (17.8 vs. 13.5) and p values were not provided for both the group. It was interesting to note that the 10 week intervention program had not any clinically significant difference in HbA1C in both groups, decreasing by 0.1 % (6.6% vs. 6.5%) in Japanese acupuncture group while it increased by 0.4 % (8.8% vs. 9.2%) in the TCM acupuncture group. The crucial point to be noted while giving acupuncture treatment for diabetes and especially this trial which had used 15-24 needles for the Japanese group and 6-14 in the TCM group, is the likelihood of contracting an infection, the chances of which are greater especially with diabetes patients. The high number of needles used could be disturbing and in fact, might create panic for the first time users of acupuncture and might possibly lead to the serious complications causing 'necrotising fasciitis' (reported by Saw, Kwan and Sengupta, 2004), which could arise due to the combination of needle usage and the

nature of diabetes, as the diabetes patients are more prone to infections. In the case study reported by Saw *et al.* (2004), although the needle was sterilised by candle flame, the site of injection was not sterilised at all which had led to the 'life-threatening' condition of necrotising fasciitis. So, it must always be kept in mind to sterilise the needle and the site of injection before carrying out the acupuncture treatments, and its also advisable to use the disposable acupuncture needles.

1.8.2 Botanical medicine

Many drugs used in the conventional medicine have been derived from the prototypic molecules obtained from the medicinal plants, for example, metformin which is being used as one of the most efficacious oral glucose- lowering agent is derived from the plant *Galega officinalis* which is used to treat diabetes (Dey, Attele and Yuan, 2002). *Charaka samhita*, an ancient text in *Ayurvedic* system of medicine, mentions that a single herb exerts different actions on many diseases, but every herb might have one dominating effect, with other effects being comparatively subsidiary (Saxena and Vikram, 2004). According to the ethno botanical information, more than 800 plants have been used as traditional remedies to treat diabetes in some form or the other (Alarcon- Aguilara et al., 1998; cited in Saxena and Vikram, 2004). However, in this review only a few of those herbs that had been scientifically evaluated in the past on human or animal subjects are considered.

Allium sativum (Garlic):

Found in many kitchens, *Allium sativum* is commonly used for medicinal purposes (Birdee and Yeh, 2010). The search results showed that much of the clinical literature on garlic focused on the potential antioxidant property and its microcirculatory

effects, which helps to reduce hyperlipidaemia and hypertension which helps to prevent or delay complications associated with diabetes mellitus and only a few studies examined its effects on insulin and glucose metabolism (Yeh, Kaptchuk, Eisenburgh and Philips, 2003). In fact, the highest quality RCT of garlic was designed to examine the thrombocyte aggregation in healthy non-diabetic individual, but the investigators accidentally discovered the anti-glycaemic property of garlic while measuring the outcome measures (Yeh *et al.*, 2003). Considering the fact that amongst all the possible risk factors for atherosclerosis, diabetes is the most potent one (Sobenin, 2008), as insulin resistance leads to overproduction of very low density lipoprotein (VLDL), reduced lipoprotein lipase activity and eventually leads to dyslipidaemia (Mang, Wolters, Schmitt, Kelb, Lichtinghagen, Stichtenoth, and Hahn, 2006) and the usage of garlic thus would help to prevent and could possibly treat the cardiovascular complications of diabetes.

Active Medicinal Components

Allicin is believed to be the main active medicinal component of garlic (Dey *et al.*, 2002; Yeh *et al.*, 2003; Karel, 2008). However, garlic extracts made in capsule form should contain the enzyme allinase to convert the inactive allicin into an active component to be used by the body (Karel, 2008).

Aged garlic extract (an extract of garlic aged for a period of 20 months), is reported to have antioxidant property helping to control the formation of Advanced Glycation End products (AGE) and thereby could possibly prevent the complications of diabetes (Ahmad and Ahmed, 2006).

**Allium sativum (*Garlic)

Clinical Trials and Discussion

The double- blinded RCT on human subjects with type 2 diabetes measuring plasma glucose level involved 60 type 2 diabetes patients over a four week period with the garlic extract in powder form (300 mg, twice daily). It was given as a mono-therapy or as an alternate therapy to sulfonylurea drugs and was found to reduce fasting plasma glucose level by 25.2 mg/dL with a significant p value of $p<0.05$ from baseline value and if given as combined therapy along with sulfonylurea drugs, it reduced the fasting plasma glucose level by 12.6 mg/dL with an insignificant p value of $p>0.05$ (Sobenin et al., 2008). Garlic extract also significantly reduced the triglyceride levels by 16 mg/dl (Sobenin *et al.*, 2008).

Another single-blinded RCT carried out in Pakistan measured 'lipid profile' as the outcome measure in the type 2 diabetic patients (Ashraf, Aamir, Shaikh and Ahmed, 2005), involving 70 type 2 diabetes patients, and found that the 300 mg garlic powder (twice daily) taken for 12 weeks reduced the total cholesterol by 27.46 mg/dl and LDL (low density lipoprotein) by 30.15 mg/dl, both having significant p values of $p<0.001$. HDL (high density lipoproteins) increased by 3.35 mg/dl (10% of baseline value) with a significant p value (Ashraf *et al.*, 2005). Thus, Garlic proved to be an effective adjuvant

botanical medicine that can be used during the early stages of diabetes, when there is moderate increase in FPG and is also effective in improving the lipid profile. Both the trials showed significant improvement in glycaemic control and lipid profile, more trials on Garlic would be of greater value to conclude it to be effective to be used in diagnosed type 2 diabetes patients.

Mechanism of Action and Dosage

Reported mechanisms of action being increased secretion of insulin or decreased degradation of insulin, improved liver glycogen storage (Karel, 2008) and increased glutathione peroxidise activity (Yeh *et al.*, 2003). Experiments on animal models have established moderate reduction in blood glucose levels, but not in pancreatectomized animals (Yeh *et al.*, 2003), confirming that the anti-glycaemic activity of garlic is mediated through the pancreas and is pancreas- dependent (Dey *et al.*, 2002).

Dey *et al.* (2002) postulated that the diallyl sulphide compound in garlic replaces insulin (which is also a disulfide) for the insulin inactivating sites in liver, thereby resulting in an increase of (free) insulin in the blood stream (Dey *et al.*, 2002). Dosage used for fresh garlic is between 2-4 g/day or 400-600 mg capsule/ day (Karel, 2008; Dey *et al.*, 2002; Sobenin *et al.*, 2008).

Adverse Events and Possible Drug interaction

A few of the case reports highlighted its potential to increase the risk of post-operative bleeding, due to its anti-coagulant property (Izzo and Ernst, 2001). Therefore, garlic should be given with caution (if given more than 5 g/day) while taking anti-coagulants and anti- platelet drugs like warfarin, aspirin, etc. (Birdee and Yeh, 2010).

***Cinnamom zeylanicum* (Cinnamon):**

Though mainly known just as a spice in the western countries, Cinnamon is being used as an herbal medicine widely in Asia (Mang *et al.*, 2006).

* *Cinnamom zeylanicum* (Cinnamon)

Active medicinal component

Major medicinal components of Cinnamon like the cinnamaldehyde, cinnamic acid, coumarin and eugenol were found not to have any influence on the insulin-enhancing activity in epididymal fat cells *in vitro*, whereas, a class of water-soluble type A Cinnamon polyphenol compounds displayed antioxidant, insulin- potentiating and related activities (Qin, Panickar and Anderson, 2010).

Clinical Trials and Discussion

Khan, Khattak, Safdar, Anderson and Khan (2003) conducted a randomised controlled trial with 60 diagnosed type 2 diabetic patients in Pakistan. After matching for age and gender in the placebo and intervention groups, subjects in the intervention groups were given 1g, 3g and 6g/day of Cinnamon for 40 days. The results in all the 3 dosages of Cinnamon were positive and significant as well, the FPG reduced by 18-

29%, triglycerides by 23-30% and LDL by 10-24% (in 3g and 6g groups), with significant p values of $p<0.05$. Of all the trials reviewed here on Cinnamon, Khan *et al.* (2003) had shown the highest decrease in the plasma glucose level. This significant decrease might be attributed to the high baseline FPG values of the subjects which varied between 140.4 and as high as 399.6 mg/dL, with average FPG of subjects included under the intervention group being 216±32.4 mg/dL.

Another randomised controlled trial, a double blinded RCT study involving 79 type 2 diabetes patients conducted in Germany which compared 3g/day of Cinnamon powder extract against a placebo for 4 months (Mang, Wolters, Schmitt, Kelb, Lichtinghagen, Stichtenoth, and Hahn, 2006). The mean FPG reduction in the intervention group was 19.98 mg/dL (10.3% of baseline value) with a significant p value from baseline of $p<0.001$, and $p<0.05$ when compared to the placebo group which had a mean FPG reduction of 3.37%. As the baseline HbA_1C value was already < 7%, which was on a par with the current recommended guidelines for treating diabetes (ADA, 2005), no further reduction in HbA_1C was observed. On the whole, a moderate reduction of FPG was observed in this trial without any reported adverse effect.

Crawford (2009), in a randomised control trial carried out for 90 days on 109 type 2 diabetes patients, compared 1g of Cinnamon extract/ day with placebo. The outcome measure of interest was HbA_1C, which decreased by 0.83% with p value from baseline being $p<0.001$. This trial also proves to be the largest trial carried out on Cinnamon with type 2 diabetes patients (till June, 2011). It is worth mentioning here the work of Fairman and curtiss (2009), who evaluated Crawford's (2009) trial, in which they had stated that the effect of supplemental cinnamon (along with the usual care) on HbA_1C levels is so effective, that they found it to be only slightly (exact data not

provided) less effective than the placebo-adjusted reductions reported for the two popular drugs, sitagliptin and saxagliptin, used to treat type 2 diabetes mellitus, but, Cinnamon has the added benefit of able to treat without any side effects and can be used to treat more than 25 times as many patients with the same amount of money to treat with the gliptins (Fairman and curtiss, 2009; cited in Qin *et al.*, 2010). Thus, Cinnamon proves to be an efficient and cost effective treatment mode to treat type 2 diabetes as a complementary therapy.

The first ever study conducted in USA on Cinnamon with 60 type 2 diabetes patients, concluded stating that Cinnamon cannot be generally recommended for treatment of type 2 diabetes in the 'American population' (Blevins, Brown, Wright, Scofield, and Aston, 2007), as they confined the significant reduction in outcome measures observed with Cinnamon in Khan *et al.* (2003) as applicable only to the particular ethnic population in Pakistan and not to the western diabetic population. No significant reduction in fasting plasma glucose or HbA_1C was observed. An insignificant reduction of only 9.72 mg/dL in FPG and 0.2% in HbA_1C was observed. However, when the baseline values in Blevins *et al.* (2007) are analysed, it is obvious that the subjects recruited for the trial already had a strict glycaemic control of mean HbA_1C- 7.2%, closer to the ADA guidelines of 7.0% (ADA, 2005) and FPG value of 140.94 mg/dL which is much lesser than the baseline value of other 2 trials reviewed before.

A similar effect was also observed by Vanschoonbeek et al., (2006), in which 25 post-menopausal type 2 diabetic women, given 1.5g of Cinnamon extract/day for 6 weeks, did not show any significant reduction in plasma glucose or insulin concentration. Though the mean baseline value of plasma glucose is comparatively

higher with 150.66 mg/dL, the FPG reduced by an insignificant 8.28 mg/dL, with p value of $p>0.05$ (Vanschoonbeek *et al.*, 2006). Cinnamon (1.5 g dosage) proved to be ineffective in reducing the plasma glucose level of the post-menopausal women.

Akilen, Tsiami, Devendra and Robinson (2010) conducted a double- blinded RCT with 58 type 2 diabetes patients for a period of 12 weeks. At the end of 12 weeks, HbA_1C reduced by 0.36% ($p<0.005$), but no significant reduction in FPG (14.04 mg/dl; $p=0.88$). The most clinically significant finding was the decrease in systolic and diastolic blood pressure (BP) by 4 mmHg ($p<0.001$). A starch- filled capsule (80 % amylose and 20% amylopectin) was used as placebo which would reduce gastric emptying (Akilen *et al.*, 2010).

Though it can be tentatively postulated that Cinnamon demonstrates its anti-glycaemic effects only in hyperglycaemic states and thus will not be cause hypoglycaemia in patients, but, it is worth considering the fact that Khan *et al.* (2003) recruited subjects who were under the prescription of sulfonylurea derivatives, while all other trials had subjects under prescription of various other drugs like metformin, TZD, etc. Thus, Cinnamon could possibly act through a pathway similar to that of sulfonylurea derivatives to bring about glycaemic control.

Larger double-blinded scientific trials, without any possible bias are needed, to answer all the doubts that arise regarding the efficacy of Cinnamon on glycaemic control. The trials which are reviewed here were found to be evaluating the benefits of Cinnamon only as a complementary therapy, as the subjects were asked to continue their medication in all the studies and Cinnamon was just given as an add-on to the conventional medicine.

Mechanism of Action and Dosage

Cinnamon extracts were reported to increase the insulin receptor β proteins and the glucose transporter 4 (GLUT 4) proteins which are involved insulin receptor activation and insulin-regulated glucose transportation (Akilen *et al.,* 2010). Cinnamon is suggested to increase glycogen synthesis by activating glycogen synthase, increase glucose uptake and down-regulate glycogen synthase kinase-3β which is involved in phosphorylation and inactivation of glycogen synthase (Khan *et al.*, 2003).

Cinnamon is also reported to decrease inflammation and prevent the complications of diabetes by inhibiting the formation of advanced glycation end products (AGE), and control the vascular endothelial growth factor (VEGF) formation which is the involved in the development of diabetic retinopathy (Qin *et al.*, 2010).

Even though the therapeutic dosage varied with every study, 1-6 g/day was uniformly used and is found to be effective without producing any serious adverse events and therefore, 1-6g/day is recommended (Karel, 2008).

Adverse events and possible drug interactions

None reported.

Momordica charantia (Bitter gourd)

Active medicinal component

Bitter gourd (also known as bitter melon) contains hypoglycaemic compounds like charantin, protein polypeptide P- which is structurally similar to the animal insulin (Dans *et al.*, 2006) and is regarded as 'plant insulin' (Saxena and Vikram, 2004) and seeds contain the hypoglycaemic alkaloid, vicine (Paul and Raychaudhuri, 2010).

***** *Momordica charantia* (Bitter gourd)

Clinical Trials and Discussion

A RCT conducted in India on 50 type 2 diabetes patients found no reduction in FPG. Even though, the fructosamine level reduced by nearly 10% from the baseline value and PPG reduced by nearly 15% (1.89 mmol/L), all the outcome measures measured were insignificant (p value not specified) (John *et al.*, 2003). 6 g/day of dried bitter gourd extract was given to the intervention group, which is more than the dried weight of 1 whole fruit (5 g) (John, Cherian, Subhash, Cherian, 2003). This is one classic example of the inefficacy of the dried powder form of bitter gourd in bringing about the glycaemic control, which would be discussed in the later sections below. Bitter melon was reported to have insulin secretagogue effect (Platel and Srinivasan,

1997; cited in John *et al*., 2003) and as the insulin levels are not measured, it was not possible to observe whether dried extract of bitter gourd have any effect on insulin or on beta cells.

A double-blinded RCT was conducted on 40 type 2 diabetes patients (Dans, Villarruzb, and Jimenoa, 2006) with *Momordica charantia* in Philippines, comparing placebo with 3g/day of bitter gourd extract, reported a very slight reduction in HbA_1C of 0.28% and a reduction of FPG by 0.41 mmol/L, both with insignificant p values of $p>0.5$ (Dans *et al*., 2006). The placebo controlled group had a better reduction in HbA_1C (0.58%), than the intervention group. The type of placebo used has been explained and the dosage of bitter gourd has also not been mentioned, making it harder to analyse.

Anti-hyperglycaemic effects have been observed in the animal trials and even hypoglycaemic events being reported in human subjects, no standard human trials had yet proved that bitter melon is effective enough in reducing hyperglycaemia (Biyani *et al.*, 2003). Standardized extract preparations of *Momordica charantia* is needed as dried extracts are found to be relatively inefficient that the aqueous extracts of bitter gourd. Therefore, the method and form of extraction also seems to affect the efficacy and therapeutic value of Momordica charantia.

Mechanism of Action and Dosage

Insulin secretagogue effect and extra pancreatic effects in reducing plasma glucose have been reported (John *et al.*, 2003). The 'plant insulin' (protein polypeptide-P) is reported to how insulin mimetic effect and the fruit extract also improved the number of β- cells in diabetic animals (Saxena and Vikram, 2004). It is also believed to

activate the AMP- activated protein kinase pathway, just like metformin, thereby overcoming insulin resistance as well (Zhang, Zhou and Li, 2009).

Dosage varied between 3-6 g/day with mixed results. Therefore, it is rather inconclusive of the dosage at which bitter gourd is most effective.

Adverse events and possible drug interactions

Hypoglycaemic episodes on taking bitter gourd have been reported in the past. Hypoglycaemia is the main adverse event reported in both animal and human subjects (Ooi *et al.*, 2010)). This adverse event of hypoglycaemia seemed to be potentiated by the use of glitazones (Nivitabishekam *et al.*, 2009; cited in Ooi *et al.*, 2010), metformin and sulfonylurea (Tongia *et al.*, 2004). Abortifacient effect of bitter gourd had also been reported, therefore the raw fruit is better avoided during pregnancy (Ooi *et al.*, 2010).

Panex ginseng **and** ***Panex quiquefolius*** **(Ginseng):**

Amongst the several species of Ginseng, *Panex ginseng* (Asian Ginseng, Korean or Chinese Ginseng) and *Panex quiquefolius* (American Ginseng) are the most studied species (Birdee and Yeh, 2010) and studies on both of these species are considered for this review.

Active medicinal component

Ginsenosides (triterpenoid saponin glycosides) in Ginseng are believed to bring about the hypoglycaemic effects (Yeh *et al.*, 2003) To be more specific, ginsenoside Rb-2 is attributed to the glucose lowering effect in type 2 diabetes patients (Dey *et al.*, 2002) and ginsenoside Re helps to overcome the insulin resistance (Reeds *et al.*, 2011). Ginsenoside has been proved to be the hypoglycaemic component in Ginseng by

Sievenpiper *et al.*(2003), when they found that the depressed ginsenoside profile in the American Ginseng did not produce any glucose lowering effect on the subjects.

*** Ginseng**

Clinical Trials and Discussion

Vuksan, Sievenpiper, Vyy, Francis, Beljan-Zdravkovic, Xu and Vidgen, (2000a) conducted a cross over study with 9 type 2 diabetes patients and 10 non-diabetic patients to compare the effects of consuming a 3 g equivalent of Ginseng extract with a placebo, taken 40 minutes before a meal and if taken along with the meal. The observations at the end of this short term clinical trials were the post Prandial plasma glucose (PPG) of the diabetic patients decreasing by 19% if taken before meal and decreased by 22% if taken along with the meal with significant p values $p<0.05$, whereas the PPG decreased by 18% if ginseng is taken before the meal and had no effect if taken with meal. Therefore, the authors suggested the administration of extract along with the meal rather than before food. This is not just because of the better reduction in the PPG of type 2 diabetes patients, but to also prevent the hypoglycaemia in people with normal glycaemic levels.

Vuksan, Stavro, Sievenpiper, Beljan-zdravkovic, Leiter, Josse, and Xu (2000b), conducted another trial with ten type 2 diabetes patients in a placebo controlled crossover study, to find out whether the result obtained used in their previous researches

giving a 3 g/day dosage of American Ginseng can be bettered by increasing the dosage of Ginseng, but discovered that all 3 dosages of 3g, 6g and 9 g/day used in the trial are equally effective which reduced PPG by 59.1%, 40.9% and 45.5% respectively and therefore, no more than 3 g/day is needed for type 2 diabetes patients.

A relatively larger double blinded RCT, with 36 type 2 diabetes patients, comparing placebo with 100mg or 200mg of extract was conducted by Sotaniemi, Haapakoski and Rautio (1995). FPG was reduced only in the 200mg Ginseng group with a p value of $p<0.05$ and HbA_1C in 200mg reduced as well ($p<0.05$). Lipid levels remained unaltered. Subjects reported an improvement in mood, vigour, well-being and psychomotor performance (Sotaniemi *et al.,* 1995).

There are contrasting evidences about the effectiveness of Ginseng in type 2 diabetes or simply as a blood glucose lowering agent. Reeds et al., (2011) did a RCT with 15 overweight or obese subjects who are either newly diagnosed type 2 diabetic or had Impaired Glucose Tolerance (IGT). A very high dose of 8 g/day (1-3 g/day is reported to be normal by Dey *et al.,* 2002) of Korean (Asian) red Ginseng was given to the subjects for 4 weeks. They were given orally to the patients after testing and proving that the extract is effective enough *in vitro* on animal and human tissues. But interestingly, the Re 2 ginsenoside, the most potent ginsenoside in reducing plasma glucose level is not found in the circulation in spite of the excess dosage and thus the authors concluded that the bio-availability of the oral Ginseng is very low when compared to the intraperitoneal administration carried out on animal models due to the enzymatic conversion of the ginsenoside in the stomach after consuming (Reeds *et al.*, 2011). This proves to be an interesting discovery, because most of the supplements of Ginseng are administered orally to the human beings and a low bio-availability means

they could not be benefitted by the medicinal properties of the Ginseng by consuming it in oral form. The result of this trial rises a curious question that, in case if the active hypoglycaemic component does not get absorbed into the human system, then how did the other trials proved Ginseng is beneficial enough in bringing about a glycaemic control. However, the systematic quantitative analysis carried out by Sievenpiper *et al.* (2004) on the different species of Ginseng discovered that not all species of Ginseng has got hypoglycaemic effect. In fact, they had mentioned that the American Ginseng (*Panax quinquefolius*) is effective in reducing blood glucose levels, whereas Asian Ginseng was found to increase the glucose level (Sievenpiper *et al.*, 2003). Various factors like selection of species, harvesting period, method of extraction and dosage – all seem to have some effect or the other on the hypoglycaemic effect of Ginseng in the blood.

Mechanism of Action and Dosage

Insulin secretagogue, prevents β- cell apoptosis, PPAR (Peroxisome Proliferator Activated Receptor) modulator- thereby helps to overcome insulin resistance (Karel, 2008). Treatment dose considered to be safe and effective is 1-3 g/ day of crude root or 200-600 mg of standardised extract (Dey *et al.*, 2002).

Adverse events and possible drug interactions

Ginseng was reported to cause hypoglycaemia (Birdee and Yeh, 2010), therefore caution is required while taking with other hypoglycaemic agents. Ginseng is contraindicated to use along with the monoamine oxidase inhibitors (MAO inhibitors) (Karel, 2008). Interaction between *Panex quinquefolius* and warfarin had also been documented in the past (Karel, 2008) and therefore had to be used with caution.

Table 2: Summary of the characteristics of Botanical medicine

Name	**Hypothesised Effect(s)**	**Reported Adverse Effects**	**Possible Drug Interaction(s)**
Allium sativum (Garlic)	·Insulin secretagogue ·Blood thinner	Dyspepsia on higher doses.	With anti-coagulant and anti-platelet drugs (like aspirin, warfarin, etc.)
Cinnamomum zeylanicum (Cinnamon)	·Insulin sensitizer (increased GLUT4) ·Insulin mimetic	None reported	None
Gymnema sylvestre (Gymnema)	·Insulin secretagogue	Suppression of sweet taste in mouth	None
Momordica charantia (Bitter gourd)	·Insulin mimetic ·Decreased hepatic glucose production .Insulin sensitizer	·Glucose-6-phosphate deficiency ·Possible hypoglycaemia	Caution needed while taking with insulin secretagogues.
Panex Ginseng, Panex quiquefolius (Ginseng)	·Insulin mimetic ·Alters hepatic glucose metabolism	·Oestrogenic effect with breast tenderness, amenorrhea, vaginal bleeding, impotence · Hypertension · Insomnia	With anti-coagulant and anti-platelet drugs (like aspirin, warfarin, etc.)

1.8.3 Dietary Management

The commonly used diets to control blood glucose levels in diabetes patients include diet with low fat (especially animal fat) and high unrefined carbohydrates (which derives 25-30 % of total energy from fat and around 50% of energy from unrefined carbohydrates), or diet with low glycaemic index (foods like pasta products, oat bran, oats, beans, fruits and vegetables), both in combination with the advice in reducing the excess weight (Nield *et al.*, 2009). Though everyone would agree that diet plays a major role in glycaemic control of type 2 diabetes (Wolever et al., 2008), it is not an easy task to pick and choose the right kind of diet which would act efficient enough in controlling hyperglycaemia out of the various diets like- diet with low glycaemic index (GI) foods, low carbohydrate, high protein, high/ low fat diet, high fibre diet, whole grain/ cereal diet, vegetarian diet, Mediterranean diet or any other diet. The following section will briefly analyse the available literature and help the care provider's and the patients in choosing the kind of diet which are most effective in controlling the hyperglycaemia with least adverse events and no fad diets are discussed due to their heterogeneity and lack of suitable evidences to back their claims.

Clinical Trials and Discussion

To begin with, the significance of vegetarian diets in reducing the metabolic risk factors associated with diabetes (like triglycerides, total cholesterol, High density lipoproteins (HDL), blood pressure (BP)) and in preventing metabolic syndrome was demonstrated by Rizzo, Sabate, Jaceldo-Siegl and Fraser (2011). The study is a cross-sectional study, with 773 subjects being randomly selected out of the 96,000 from 'the Adventist Health Study 2' (Rizzo *et al.*, 2011). The subjects were classified as vegetarian (those consuming meat, poultry or fish < 1 time/month), semi-vegetarians

(consuming fish at any frequency; and other meats ≥ 1 time/month, but <1 time/week) and non-vegetarians (consuming meat or poultry ≥ 1 time/week and ≥ 1 time/month). The results, after adjusting to the physical activity, were in favour of the vegetarian diet and showed that metabolic syndrome was highest in the non-vegetarian population (39.7%), followed by semi-vegetarians (37.6%) and least in the vegetarians (25.2%) with a very significant p value of <0.001 for all the values. The Odds Ratio (OR) for metabolic syndrome of those adhering to vegetarian diet was 0.44 when compared to the non-vegetarians. Apart from that, the metabolic risk factors (MRF) associated with diabetes like triglycerides, blood pressure, waist circumference, and blood glucose levels were significantly lower in vegetarians than non-vegetarians and the semi-vegetarians had a significantly lower waist circumference and BMI when compared to non-vegetarians. This cohort study has shown that vegetarian diet is the best to prevent and to treat T2DM. The random selection of 773 subjects, from a total of 96,000 could possibly make the study reliable and might possibly be applicable to the whole general or diabetic population, but more research has to be carried out to confirm whether the results obtained are solely because of the vegetarian diet consumed by the subjects or any other confounding factors which were not of interest in the study has affected the outcome measures.

High protein diet was found to increase the risk of diabetes by the study conducted by Sluijs et al. (2010), irrespective of the fat content, but vegetable protein was not found to be related with risk of diabetes. The prospective cohort study was carried out on 38,904 participants, who were followed up for 10 years. The results discovered that, the risk of diabetes increased with higher animal protein intake (62.9 vs. 35.2 g/day) by more than 2 times (2.18 times - Hazard ratio (HR)) and total protein

(animal and plant source) by 2.15 times. The study also demonstrated that replacing 5% energy of proteins in diet with 5% energy from fats, increased the risk of diabetes by 1.31 times and replacing 5% energy of carbohydrates with proteins increased risk of diabetes by 1.28 times as well. The authors postulated several mechanisms through which high protein diet could cause diabetes like, insulin resistance may arise due to the inhibition of glucose transport and phosphorylation. The amino acids in these high protein diets intervening with the glucose metabolism by acting as a substrate for the gluconeogenesis and might even be due to the increased iron load (Forouhi et al., 2007; cited in Sluijs *et al*., 2010). This study thus broke the common belief that a high protein diet instead of a high carbohydrate could possibly help in managing diagnosed type 2 diabetes. This study once again emphasised the importance of vegetarian diet in diabetes prevention and could possibly in the management, as non-vegetarian diet could cause insulin resistance due to the high animal protein content (Sluijs *et al*., 2010).

Tao, McDowell, Saydah, and Eberhardt (2008) discovered the association between the polyunsaturated fatty acid (PUFA) - linolenic acid and peripheral neuropathy and concluded that, the intake of linolenic acid is associated with lowered risk of peripheral neuropathy in patients diagnosed with type 2 diabetes. The study analysed the data of 1,062 diabetic patients in U.S., and the dietary intake of PUFA was estimated with one-one interview and obtaining details of their 24-hr dietary intake and supplements taken in the past 30 days were also considered. The results showed that diabetic patients with peripheral neuropathy were consuming significantly lesser amounts of PUFA (14.60 Vs 16.82 g/day) and linolenic acid (1.25 vs. 1.45g/day) when compared to patients having diabetes without peripheral neuropathy (Tao *et al.*, 2008).

The trial claims that an increase in PUFA intake as little as 0.25 g/day could help lower the risk of peripheral neuropathy in diagnosed type 2 diabetes patients.

The effect of mono unsaturated fatty acids (MUFA) was studied by Salas-Salvado et al., 2011, comparing the MUFA rich Mediterranean diet group with the low-fat diet group, which is commonly prescribed for diagnosed type 2 diabetes patients. In a cohort study, carried out on 418 non-diabetic subjects for 4 years, the subjects were divided into 3 groups – low fat diet (control) group, Mediterranean diet (MedDiet) with free virgin olive oil (1 litre/week) or mixed nuts (30 g/day). Apart from the virgin oil and nuts, MedDiet advice to subjects of both groups include increased consumption of fruits and vegetables, lesser consumption of total meat, consuming white meat instead of red meat, preparation of home-made sauce and avoidance of butter, cream, fast food, sweets, pastries and sugar sweetened beverages. Subjects in low fat group (control group) were recommended to reduce all types of fats, both from vegetable and animal source. Results were varying, like, the weight loss sustained to >5% in all the three groups and only a few changes in medication in all the groups. 54 participants progressed to develop type 2 diabetes. After adjustments to various confounding factors, diabetes incidence was reduced by 51% in MedDiet with olive oil group and 52% in MedDiet with mixed nuts group (Salas-Salvado *et al.*, 2011) when compared to the control group. However, considering the small number of just 54 participants (out of 420 participants) developing diabetes within the 4 year period of research, generalising the benefit obtained by using MUFA of reduction the incidence of diabetes to a large population is not plausible.

In a randomised parallel group trial, 40 poorly controlled type 2 diabetes patients were randomised to either low GI group or ADA (American Diabetes Association) diet

group. Subjects in ADA diet group were educated on carbohydrate counting and to consume 55% of their daily energy requirement through carbohydrates, while the low-GI group were educated on how to choose the predominantly low glycaemic index foods (Ma et al., 2008). The trial was conducted for one year. Decrease in HbA_1C of 0.7% was observed in both the groups in the first 6 months, but were attenuated at 12 months. HDL, blood pressure and body weight remained the same throughout in both the groups. Though the reduction of 0.7% is clinically significant (not statistically significant), the authors mentioned that the other factors were almost least affected but the exact numbers and the possible reasons behind it had not been explained about anywhere in the research paper. But, the authors concluded saying that, both the ADA recommended diet and the low- GI diets are equally effective.

Another randomised, parallel group study (Jenkins et al., 2008) was carried out with 210 diagnosed type 2 diabetes patients comparing low- glycaemic foods with the high-cereal fibre diet for a period of 6 months. Subjects from high-cereal fibre diet were requested to consume "brown" food option (Jenkins *et al.*, 2008) (like brown rice, brown bread- whole wheat and whole grain, potatoes with skin, crackers and breakfast cereals) and low-glycaemic diet group consumed specially made low glycaemic foods available in market (like low glycaemic index breads, rye pita, red river cereal, large flake oat meal), oat bran, pasta, parboiled rice, peas, beans, lentils and nuts. Three servings of fruits and 5 servings of vegetables were advised in both groups. Interestingly the low-glycaemic diet seemed to be much more effective in controlling HbA1C when compared to the high-cereal fibre diet ($p<0.001$). HbA_1C reduced by 0.5% in low-glycaemic index diet, while it reduced by 0.18% in the high fibre diet group. The difference in HbA_1C reduced was independent of the reduction in body

weight (Jenkins *et al*., 2008). Another outcome measured was the HDL level, which increased 1.7 mg/dl in the low-glycaemic index group, whereas surprisingly, it decreased by 0.2 mg/dl ($p<0.005$), therefore low glycaemic diet would also be helpful in preventing the cardiovascular complications associated with diabetes. One of the most important factor worth noting in this trial is the hypoglycaemic episodes encountered by the 6 participants, all of whom were from the low glycaemic index diet group, therefore low-glycaemic diet seemed to have a very strong influence in lowering the blood glucose level, therefore if used with caution, it can be used for effective controlling of hyperglycaemia.

Another randomised, parallel group trial conducted in Canada concluded that low GI diet has no effect on HbA_1C (Wolever et al., 2008). In this 1 year trial, 162 subjects were randomly assigned to the high- GI, low- GI and low carbohydrate diet groups. The high- GI, low- GI and low carbohydrate diets contained 47%, 52% and 39% of carbohydrates respectively and GI of 63, 55 and 59, respectively. The low carbohydrate group were made to exchange the carbohydrates in their diet with the MUFA rich foods. None of the 3 groups showed any improvement in the HbA_1C level. In fact, the HbA_1C of all the 3 groups increased from the baseline value of 6.1% to 6.3% after 1 year. The FPG remained normal throughout in the high-GI group, but in the other 2 groups, FPG initially reduced but raised again to end up higher than the mean FPG level of the high- GI group (data not provided), which the author themselves report as 'shocking' (Wolever *et al*., 2008). But, the results of FPG were in fact complementing the results obtained from Ma *et al*. (2008) who also observed an initial decrease in FPG in the first 6 months, while increasing again at the following 6 months. This puts a big question on the efficacy of low- GI in reducing the FPG over a long

term. But, on the positive note, low- GI was effective enough in reducing the PPG, which is a more important indicator of cardiovascular risk than FPG. The trial showed a reduction of 18 mg/dL reduction in PPG in the low- GI group, than the other 2 groups under study which was associated with 6- 15% reduction in the cardiovascular events. Low glycaemic diet was also found to decrease the triacylglycerol levels in blood (Willet, Manson and Liu, 2002), but it was not observed so in the trial carried out by Wolever *et al.* (2008).

Another trial claimed low carbohydrate diets to be much more effective than low glycaemic index foods in bringing about glycaemic control (Westman et al., 2008). The trial conducted on 84 obese diagnosed type 2 diabetes patients was a randomised, parallel group study. Subjects were randomly assigned to either low carbohydrate, ketogenic diet (< 20g carbohydrate per day) group or low glycaemic index, reduced calorie diet (500 kcal/day lesser). Though both groups showed improvements in their glycaemic control, the low carbohydrate group showed much greater reduction in HbA_1C (-1.5% vs. -0.5%), body weight (-11.1 kg vs. -6.9 kg) and HDL (+5.6 mg/dl vs. 0 mg/dl), when compared to the low glycaemic index diet group. It is worth mentioning here that, in this trial the low glycaemic diet did not underperform in its glycaemic control, as it reduced the plasma glucose level, body weight, BMI and fasting insulin with a significant p value of <0.05. It is rather the low carbohydrate diet, which had proven to be much more effective than low glycaemic index diet.

One of the trials which has caused a lot of hope and expectation amongst the diabetes patients and health professionals was the trial conducted to assess the efficacy of restricted energy intake of 600 Calories per day, which was claimed to reverse type 2 diabetes (Lim et al., 2011). This RCT was conducted on 20 (11 intervention and 9

controls) subjects with diagnosed type 2 diabetes for a period of 8 weeks. During the trials, the subjects consumed a liquid diet formula (which includes 46.4% carbohydrates, 32.5% proteins and 20.1% fat, with traces of vitamins and minerals; from Optifast®) which constituted 510 calories, and the remaining 90 calories was provided from three portions of non-starchy vegetables. After 8 weeks, the FPG reduced significantly by 63 mg/dL, HbA_1C decreased by 1.4% and total cholesterol reduced by 14.4 mg/dL. Plasma insulin also decreased from 151 pmol/L to 65 pmol/L. No significant increase in HDL or insulin sensitivity was observed. But, the most crucial outcome measure of this research was the triacylglycerol, which decreased from the initial baseline value of 43.2 mg/dL to 23.4 mg/dL ($p<0.05$). Triacylglycerol is quite a significant marker as it is believed to cause insulin resistance and thus, induce diabetes. Prior to the onset of spontaneous diabetes in rodents, total pancreatic fat and pancreatic triacylglycerol were found to increase (Lee et al., 2010; cited in Lim *et al*., 2011) and this particular trial has thrown lime-light on triacylglycerol and the reduction of it through natural means, which could possibly restore the pancreatic beta cell function (Lim *et al*., 2010) and 'might' possibly reverse diabetes. The authors made it clear in the acknowledgement section that the study was funded by Diabetes UK and 'NOT' by Optifast®, which had provided the liquid formula only on request from the researchers. The next obvious question would be how effective would this 600 calorie be in the long term and this question was also answered by the researchers by doing a follow up of 12 weeks post-intervention and found that, though there was a mean increase in weight of 3.1 kg, the FPG (102.6 vs 109.8 mg/dL), HbA_1C (6.0 Vs 6.2 %) and hepatic triacylglycerol (2.9 Vs 3.0%) continued to be almost the same 12 weeks after intervention. The pancreatic triacylglycerol remained the same, in fact, decreased

further (6.2 Vs 5.7%) to a small extent. Though the 12 week follow up has the proved the efficacy of negative balance diet in lowering the triacylglycerol and thereby restoring the beta cell function. A larger RCT is underway to strongly suggesting it to be efficient enough in reversing diagnosed type 2 diabetes and a longer follow up would also be more useful in establishing the efficacy of the 600 calorie diet.

All these trials and analysis of the trials are just to give an overall idea about the efficacious dietary treatment options available, for the health professional to consider while treating the diabetes patients, however, as per the ADA recommendations, the nutrition prescriptions and recommendations should be determined only after considering the treatment goals and life style changes that the diabetic patient is willing or able to make, rather than prescribing a pre-determined energy levels or percentages of macronutrients -carbohydrates, proteins & fats. In other words, the goal of nutrition intervention is to assist individual lifestyle and behaviour changes that would lead to improved metabolic control (Franz *et al.*, 2002). MNT recommendations should also consider cultural and ethnic preferences, and the involvement of the diabetic patient in the final decision making process is crucial (Franz *et al.*, 2002).

1.4 Yogic management of type 2 diabetes

Yoga is a mind/body practice based on traditional Indian philosophy, depicting the ideal way of life, and is more than just a physical activity (Kumar et al., 2016). In terms of energy expenditure, it is similar to mild to moderate intensity exercise and unlike many 'traditional' therapies, yoga could be applied to a larger population with T2DM as it appears safe and inexpensive (McDermott et al., 2014). In addition to the physical movements *(asanas)*, yoga commonly involves multiple other components

such as controlled respiration *(pranayama)*, relaxation and meditation *(dhyana)*. Many studies are emerging on the benefits of yoga in various diseases (Hagins et al., 2013). Findings from extensive studies suggest yoga to have multiple benefits in the etiopathogenesis of T2DM and associated complications like improved glycaemic control, lipid profile, improved cognition, nerve conduction velocity, weight loss, reduced inflammation (Aljasir et al., 2010; Innes & Vincent, 2007), oxidative stress (Sinha et al., 2007; Gordon et al., 2008) and cardiovascular risk factors in T2DM patients (Siu et al., 2015; Schmidt et al., 1997). Comparative studies on yoga *vs.* exercise suggest that yoga is as effective, if not superior to physical exercise in health-related outcome measures like blood glucose, lipids, salivary cortisol and oxidative stress which are of greater significance in the management of T2DM, with additional benefits of improving subjective measures like fatigue, sleep, pain and Quality of Life (QoL) (Ross & Thomas, 2010).

Patients with T2DM have higher levels of oxidative stress and studies on yoga have showed a reduction in oxidative stress and increased anti-oxidant defence, by improving superoxide dismutase, glutathione, malondialdehyde, vitamin C and vitamin E profile (Hegde et al., 2011; Mahapure, Shete & Bera, 2008).

Glucose uptake into skeletal muscles could be stimulated via insulin independent mechanisms, that are activated by muscle contractions, hypoxia and nitric oxide, all of which are shown to increase membrane translocation of Glucose Transporter 4 (GLUT 4) (Henriksen, 2002; Zierath, Krook & Wallberg-Henriksson, 2000). In the insulin resistant state, as in metabolic syndrome and T2DM, the insulin-dependent glucose disposal in skeletal muscle is markedly impaired (Kahn, Hull & Utzschneider, 2006); however, the capacity for the insulin-independent Adenosine 5'-

monophosphate activated protein kinase (AMPK) -mediated glucose uptake is still intact in the muscle cells of patients with T2DM (Koistinen et al., 2003). Yoga-*asanas* and *pranayama* has shown to improve insulin sensitivity in T2DM (Singh et al., 2008). Insulin sensitivity is found to be significantly higher in regular practitioners of yoga (Chaya et al., 2008). The observed increase in glucose sensitivity could be attributed to the possible activation of AMPK through muscle contractions involved during yoga postures (Zhang, Zhou & Li, 2009). Increase in moderate physical activity is associated with multiple benefits like, improved insulin sensitivity, better glycaemic control, reduced BMI, improvement in lipid profile and other risk factors associated with diabetes such as obesity and hypertension (Pischke et al., 2006; Aune et al., 2015). However, physical exercise may need to be done with caution in patients with increased risk of cardiovascular events and co-morbidities associated with microvascular and macrovascular complications like diabetic neuropathy and proliferative retinopathy, which could worsen with intensive exercise programs (Zinman et al., 2004).

Reduction in the pro-inflammatory markers like TNF α, IL-6, CRP and hsCRP and increase in the anti-inflammatory markers like adiponectin are consistently reported through various studies on yoga (Kiecolt-Glaser et al., 2012; Sarvottam & Yadav, 2014; Vijayaraghava et al., 2015). Adiponectin activates AMP kinase of liver and thereby help reduce hepatic glucose production (HGP) (Combs et al., 2001). Role of adiponectin on improving endothelial Nitric Oxide synthatase (eNOS) and resultant increase in endothelial nitric oxide production is well established (Hattori et al., 2003; Chen et al., 2003), which is beneficial in the prevention of neuropathy, cardiovascular complications and delayed wound healing in diabetes. A systematic review on the effect of exercise on adiponectin states that moderate intensity exercise programs have significant impact on

the adiponectin levels (Simpson & Singh, 2008). This was ably supported by a study which found regular yoga practice to increase adiponectin levels (Kiecolt-Glaser et al., 2012).

Brain-Derived Neurotropic Factor (BDNF) prevents apoptosis and preserves insulin secreting capacity of β- cells (Bathina, Srinivas & Das, 2016). Similarly, serotonin is also reported to increase β-cell proliferation (Kim et al., 2010). Some yoga studies have reported improvement in the BDNF and serotonin levels following practise of yoga (Lee et al., 2014; Naveen et al., 2016). An improvement in cognitive brain functions of T2DM patients is also observed with regular yoga practise (Kyizom et al., 2010).