Chapter - 1

INTRODUCTION

1. Diabetes mellitus

Diabetes Mellitus is a metabolic disorder characterized by chronic hyperglycemia (American Diabetes Association, 2014). Deficiency in insulin production and its action is considered the main cause of Diabetes mellitus. Among all types of diabetes mellitus, type 2 diabetes mellitus (T2DM) contributes to more than 80%. It is all about long-term complications and its high prevalence, which has become a major concern for health care system across the globe. It is one among the major leading causes of morbidity and mortality across the global.

1.1. Increasing Burden of T2DM

Prevalence of T2DM is on the rise across the globe for past 2 decades. The global prevalence of T2DM in 2010 found to be 6.4%; this estimated to increase by 7.7% by 2030. In Asia, 1 in 7 (15%) adults reported to have either elevated fasting glucose or impaired glucose tolerance (pre-diabetes); every year 5 to 12% of these develop T2DM. A review by the Indian diabetes federation estimated an increase of T2DM from 415 million to 642 million people between 2015 and 2040. India is predicted to become the diabetes capital of the world (Joshi and Parikh, 2014; Mohan, Sandeep, Deepa, Shah B, 2007) by 2030 with a projected global increase by 48% (186 million).

1.2. Homeostasis

Homeostasis refers to the ability of the body or a cell to seek and maintain a condition of equilibrium or stability within it is internal environment when dealing with external changes to enable the entire system to function with maximum efficiency. It refers to the maintenance of a stable internal temperature and metabolic environment that involves all systems, specifically, the renal, cardiovascular, digestive and respiratory systems.

1.3. Metabolic homeostasis

Metabolic homeostasis refers to the amount of energy the body extracts, stores (anabolism) and uses to maintain itself (catabolism) (Rosen and Spiegelman, 2006). Hormonal regulation of glucose and lipid metabolism is pivotal for metabolic homeostasis and energy balance (Karpac *et al*., 2011).

1.4. Glucose homeostasis

The process of maintaining a stable glucose level with the blood levels within normal range is called “glucose homeostasis”. Pancreatic hormone production, peripheral glucose uptake, hepatic glucose production and renal excretion regulated by central and peripheral neural-

endocrinal mechanisms are the components involved in glucose homeostasis (Szablewski, 2011).

Table 1: Blood glucose ranges for normal, pre-diabetes and diabetes

Ranges of Glucose and Hba1C levels in the blood									
Status		**Serum**				**Capillary blood**			
		Mg/dl		**Mmols/dl**		**Mg/dl**		**Mmols/dl**	
Definition	**Time of blood draw**	Glucose	A1c	Glucose	HbA1c	Glucose	A1c	Glucose	A1c
Normal	**Fasting**	70 – 100	5.7	3.8 – 5.6	42	70 – 130	7.41	3.9 – 7.1	54.6
	2-hour - post meal	70 – 140		3.8 – 7.8		70 – 170		3.9 – 9.4	
Pre DM	**fasting glucose**	101 – 125	5.7 – 6.4	5.6 – 6.94	42-47	131 – 155	7.41 - 7.93	7.27 – 8.61	54.6 – 58.2
	2-hour post meal	149 – 200		8.27 – 11.1		170 – 230		9.44 – 12.7	
	After 75gms oral glucose	140 – 199		7.7 – 11.0		170 – 229		9.44 – 12.7	
Diabetes	**Fasting glucose**	>126	>6.5	>7.0	48	>156	>8.04	>8.66	59.3
	2hour-post meal	>200		>11.1		>230			
American diabetic Association, 2002									

Fasting hyperglycemia is blood glucose greater than 90 – 130 mg/dL (5–7.2 mmol/L) after fasting for at least 8 hours. Postprandial (after-meal) hyperglycemia is defined as blood glucose level usually greater than 180 mg/dL (10 mmol/L) (Fonseca, Kirkman y, Darsow, and Ratner, 2012).

Figure – 1. Blood glucose homeostasis

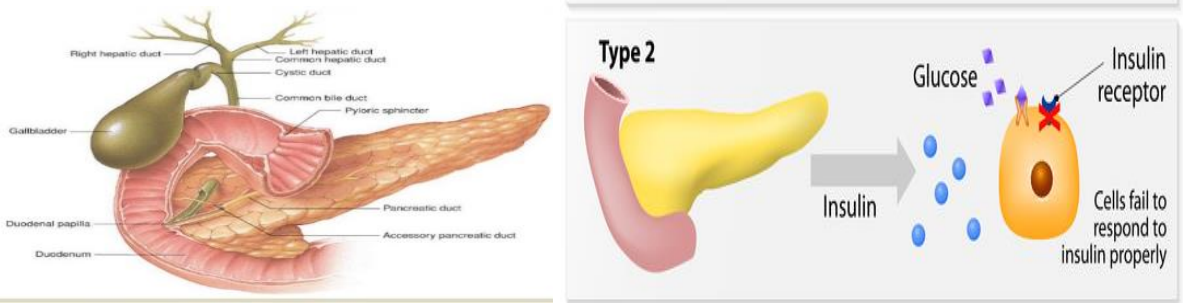


Figure 1 Shutter stock; Royalty-free stock illustration ID: 281113445; https://www.shutterstock.com/image-illustration/main-types-diabetes-mellitus-eitherpancreas-281113445, Figure 2: Genetic Home References; https://ghr.nlm.nih.gov/condition/type-2-diabetes

T2DM is characterized by disruption of glucose homeostasis resulting in chronic hyperglycemia due to insulin deficiency and/or inefficiency. Pre-diabetes occurs before T2DM sets in, wherein the fasting or post meal glucose and/or the HbA1C levels are in between the normal and hyperglycemic range.

Table– 2(Blood glucose level)

	Blood Glucose Level	What it means			
		Excellent	Good	Acceptable	Poor
Before meal	mmol / L	4.0 - 6.0	6.1 - 8.0	8.1 - 10.0	> 10
	mg/dl	72 - 109	110 - 144	145 - 180	> 180
2 hrs after meal	mmol / L	5.0 - 7.0	7.1 - 10.0	10.1 - 13.0	> 13
	mg/dl	90 - 126	127 - 180	181 - 234	> 235

1.5. Pre-diabetes

Pre-diabetes is diagnosed by: 1) Normal fasting blood glucose level is less than 7.0 mmol/L or 126 mg/dl). Pre-diabetes is characterized by Impaired Glucose Tolerance (IGT), a transition phase between normalcy and diabetes (Buysschaert and Bergman, 2011). IGT is a diagnosed by Oral Glucose Tolerance Test (OGTT): measuring plasma glucose, two hours after consuming 75 gms of glucose. The procedure typically involves testing glucose levels after an eight-hour fasting period and again two hours after having a drink with 75 gms of glucose. Generally, if the test after two hours shows blood glucose levels in the 140 and 199 mg/dL or 8 to 9 mmol/dl range, this could signify impaired glucose tolerance (Whiting *et al*., 2011). This indicates reduced glucose tolerance which may be due to insufficiency or inefficiency of insulin. Impaired glucose tolerance is often associated with several other related conditions

which are recognized as risk factors for T2DM. Each year, 1-5% of people whose test results show IGT actually develop diabetes (Yesudian *et al*., 2014).

1.6. Risk factors for Type 2 Diabetes

T2DM is caused by a combination of genetic and environmental factors. There are several risk factors identified which are contribute the cause of T2DM some of which are non-modifiable and some are modifiable risk factors (Yesudian *et al*., 2014).

1.6.1. Non-modifiable risk factors for T2DM

1.6.1.1. Family history

Individual having blood relative with diabetes, is at risk of developing T2DM.

1.6.1.2. Ethnicity

African-Americans, Asian-Americans, Latino/Hispanic-Americans, those with Native American or Pacific Islander descent have greater chances of developing diabetes.

1.6.1.3. Age

T2DM risk increases as the age advances. Generally, T2DM starts in the middle-aged adults, most frequently after 45 years and the incidence go on increasing as the age advances. However, health care providers are diagnosing more and more children and adolescents with T2DM (Chen *et al*., 2014).

1.6.1.4. History of gestational diabetes

Women with a history of delivering a baby over 9 lbs or diabetes during pregnancy have increased risk of T2DM (Khalsa *et al*., 2012).

1.6.1.5. Modifiable Risk Factors for Type 2 Diabetes

While some things that contribute to the development of diabetes are beyond a person's control, there are also a number of risk factors that are modifiable. By making healthy changes in these areas, these risks can be reduced and help in delaying the development of diabetes and improve their overall quality of life.

1.6.1.6. Overweight/obesity

About 50 percent of men and 70 percent of women who have diabetes are obese. Individuals with 20 % higher weight than their optimal body weight, have a higher risk of developing diabetes. Losing 5-7 percent of body weight can reduce the risk of developing pre-diabetes by

50%, which improves further on losing the excess weight and move towards optimal body weight (Klonoff *et al*., 2008). Excess fat accumulation is associated with increased insulin resistance and glycolysis. Thus, dysregulation off at metabolism is an important factor in the pathology of T2DM prominently.

1.6.1.7. Physical inactivity

Physical inactivity ranks among the top modifiable risk factors for pre-diabetes and T2DM. By achieving 150 minutes per week of moderate-intensity aerobic physical activity or 90 minutes per week of vigorous-intensity aerobic physical activity or a combination of the two, one can improve health and minimize risks of diabetes and cardiovascular disease. Physical inactivity disturbs the energy turn over. This contributes to increased gluconeogenesis, and decreased glucose uptake at the tissues. Physical inactivity also contributes to increased adiposity (Renaldi, 2006).

Figure – 2. Physical inactivity

(Fig-2. Livehealthyoc, 2018)

1.6.1.8. Abnormal cholesterol (lipid) levels

Low levels of high-density lipoprotein and / or high levels of triglycerides can increase the risk for T2DM. Both of these abnormalities can also increase the risk of cardiovascular disease. A healthy eating plan, sufficient aerobic physical activity, and a healthy weight can help to correct these lipid abnormalities (Chen *et al*., 2014).

1.6.1.9. High blood pressure (hypertension)

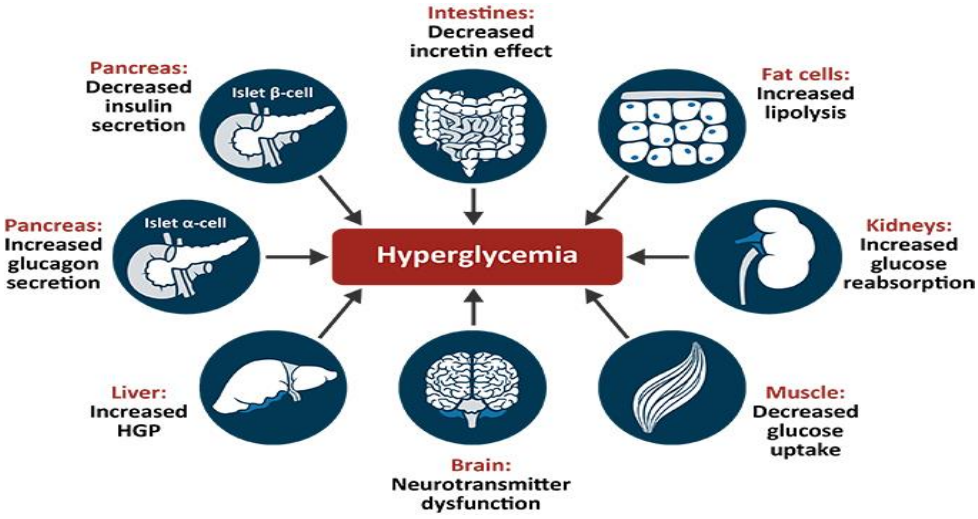
In addition to causing damage to the cardiovascular system, untreated high blood pressure has been linked to the development of diabetes (Barker *et al*., 1993).

1.7. Pathology in T2DM

1.7.1. Ominous octet

Recent evidences have found eight basic pathologies involved in T2DM called ominous octets. These are: 1). Decreased insulin production, 2) Decreased insulin action, 3) Increased lipolysis, 4). Increased glycogen production, 5) Increased glucose absorption from the kidneys, 6) Increased glucose production from the liver,7) Neurotransmitter dysfunction in the nervous system, 8) Decreased glucose uptake in tissues. These eight factors eventually lead to sustained hyperglycemia and T2DM (Bhansali *et al*., 2009).

Figure- 3. Ominous octet



(Eight organs involved in patho-physiology of T2DM : Medscape, 2019)

1.7.2. T2DM - a condition of disruption in glucose homeostasis in T2DM

T2DM is characterized by hyperglycemia which is the indicator of disruption in the glucose regulation i.e. glucose homeostasis. Many factors are involved in the glucose homeostasis such as insulin production, insulin action (sensitivity), hepatic glucose production etc.

1.7.3. Dysregulation of glucose homeostasis - Central nervous system

The nervous system is involved in the pathology of several chronic health problems including T2DM. Autonomic balance between sympathetic and parasympathetic nervous system maintains homeostasis of all visceral organs. Sympathetic nervous activation is responsible for "fight or flight" response which is characterized by excitation of several organs systems that results in increased blood pressure, heart rate, blood glucose etc. that help the individual to

adapt quickly to the demand and escape danger. The sympathetic activation is predominantly mediated through increased Hypothalamus-Pituitary-Adrenal axis (HPA axis) activity that increases the blood levels of stress hormones such as cortisol, adrenaline, nor-adrenaline etc. (Tsigos and Chrousos, 2002).

The parasympathetic nervous system is responsible for restoration after excitation for fight or flight reaction and also rejuvenation of the system through energy conservation i.e. "rest and digest". A balanced functioning of these two systems is mandatory for maintaining homeostasis which is effectively managed during acute stress. But the imbalance sets in when the stresses become chronic. Increased sympathetic activity is associated with decreased insulin production and increased glycolysis and production of stress hormones such as glucocorticoids which further contribute to disruption in glucose homeostasis. Evidence suggests that participants with T2DM exhibit increased sympathetic tone and decreased parasympathetic tone (Harni 2016).

Studies have demonstrated that there is increased low frequency and reduced high frequency bands of heart rate variability spectra and increased catecholamine in patients with T2DM (Boyda *et al.*, 2006). Pointing to heightened sympathetic tone, studies have shown that correction of autonomic deregulation is associated with improvement in glucose metabolism in patients with T2DM (Singh *et al.*, 2018).

1.7.4. Stress and autonomic deregulation

Autonomic dysfunction is attributed to psychological factors such as anxiety, stress, and depression. In addition, impaired sleep quality, and lack of physical activity are also involved in chronic autonomic imbalance. Increased chronic stress is associated with increased oxidative stress which is a major factor contributing to ß cell dysfunction and insulin resistance in T2DM. Studies have also shown that improvement in psychological factors like stress, anxiety, depression is associated with improved blood glucose level (Karasek, 2011).

1.7.5. Deregulation of glucose homeostasis due to Immune system variation in T2DM

Studies have established link between T2DM and increased systemic inflammation. Patients with T2DM exhibit elevated levels of C-reactive protein and pro-inflammatory cytokines (TNF alpha, IL1b, and IL-6) suggesting increased systemic inflammation (Nikolajczyk *et al.*, 2011). These pro-inflammatory cytokines are found to be key factors involved in insulin resistance

and ß cell dysfunction in T2DM. Increased adiposity has been a factor contributing to systemic inflammation in T2DM (Machado *et al*., 2013).

Conventional practice of *Yoga* recommends lifestyle modification in terms of increasing physical activity and diet modification in addition to anti-diabetic medication. However, a large number of patients with T2DM have poor compliance with medication, as these medications are less effective in controlling disease progression and normally associated with side effects. Conventional management of T2DM doesn't consider the management of psychological factors such as stress, anxiety, depression, which substantially contributes in T2DM development and progression. Further, as indicated earlier, T2DM is a condition characterized by deregulation in homeostasis. Any intervention which helps in correcting disruption in homeostasis in T2DM will have great significance in T2DM management.

1.8. Yoga

The goal of *Yoga* is to achieve tranquility and transcend the mind-body complex in order to achieve the higher goal of life i.e. self-realization. Health is a fundamental requirement to achieve the higher goals –

धर्मार्थ सुख साधनं आरोग्यम्मुलमुत्तमं ।

Dharmārtha Sukha sādhanam ārogyammulamuttamam।

(Vāgbhaṭṭa Saṁhitā)

The ancient holistic health care system such as *āyurveda and Yoga* have developed a lifestyle strategy to prevent disease and preserve health. *Yoga* is a science of holistic health emphasis on overall personality growth at different dimensions like physical, mental, intellectual, and spiritual. *Yoga* is a lifestyle promoting self-discipline that uses physical postures, breathing practices, meditation, to promote total health at all levels.

Recently, studies have shown that the health benefiting effects of different components of *Yoga* such as *āsana, prāṇāyāma* and meditation (Narasimhan, Nagarathna, and Nagendra, 2011) improves overall health and well-being of an individual. Evidences have reported tremendous usefulness of *Yoga* in different kinds of chronic disorders such as asthma, heart disease, obesity, neurological conditions and mood disorders (Nagarathna *et al*., 2012).

Several studies on *Yoga* have established significant role of *Yoga* in improving glycemic control, cardiac risk factors, reduction in the risk of developing complications in T2DM (Bijlani *et al*., 2005). However, no studies have clearly demarked the role of *Yoga* in improving homeostasis in T2DM. Hence, present study is intended to study the efficacy of *Yoga* in improving homeostasis in T2DM.