Risk Factors of Diabetes Mellitus; a Review

A Dissertation submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Master of Pharmacy.

Submitted by:
Nadia Afrin
2014-3-79-026

Department of Pharmacy
East West University

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Dissertation Supervisor:
Farhana Rizwan
Assistant Professor

Department of Pharmacy
East West University

This thesis paper
is dedicated
to my beloved Parents…

DECLARATION BY THE CANDIDATE

I, Nadia Afrin , hereby declare that this dissertation, entitled "**Risk Factors of Diabetes Mellitus; a Review"** East West University, in the partial fulfillment of the requirement for the degree of Master of Pharmacy, is a genuine & authentic research work carried out by me under the guidance of Farhana Rizwan, Assistant Professor, Department of Pharmacy, East West University, Dhaka. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute or University for the award of any Degree or Diploma of Fellowship.

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CERTIFICATION BY THE SUPERVISOR

This is to certify that the desertion, entitled "**Risk factors of Diabetes Mellitus; a Review**" is a benefice research work done, under our guidance and supervision by Nadia Afrin (ID: 2014-3-79-026), in partial fulfillment of the requirement for the degree of Master of Pharmacy.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the desertion "**Risk factors of Diabetes Mellitus; a Review**" submitted to the department of pharmacy, East West University in partial fulfillment of the requirements of the degree of M. Pharm in Clinical Pharmacy and Molecular Pharmacology was carried out by Nadia Afrin (ID: 2014-3-79-026) under our guidance and supervision and that no part of the desertion has been submitted for any other degree. We further certify that all the sources of information availed of in this connection is duly acknowledged.

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List of Content

List of Tables

List of Figure

Chapter One

Introduction

1.1 Background:

Diabetes comes from Greek, and it means a siphon. Aretus the Cappadocian, a Greek physician during the second century A.D., named the condition diabainein. He described patients who were passing too much water (polyuria) - like a siphon. The word became "diabetes" from the English adoption of the Medieval Latin diabetes.

In 1675 Thomas Willis added mellitus to the term, although it is commonly referred to simply as diabetes. Mel in Latin means honey; the urine and blood of people with diabetes has excess glucose, and glucose is sweet like honey. Diabetes mellitus could literally mean "siphoning of sweet water".

In ancient China people observed that ants would be attracted to some people's urine, because it was sweet. The term "Sweet Urine Disease" was coined.("Diabetes". World Health Organization. Retrieved 24 January 2011)

Diabetes (diabetes mellitus) is classed as a metabolism disorder. Metabolism refers to the way our bodies use digested food for energy and growth. Most of what we eat is broken down into glucose. Glucose is a form of sugar in the blood - it is the principal source of fuel for our bodies. When our food is digested the glucose makes its way into our bloodstream. Our cells use the glucose for energy and growth. However, glucose cannot enter our cells without insulin being present - insulin makes it possible for our cells to take in the glucose. (BC Endocrine Research Foundation) Insulin is a hormone that is produced by the pancreas. After eating, the pancreas automatically releases an adequate quantity of insulin to move the glucose present in our blood into the cells, and lowers the blood sugar level. A person with diabetes has a condition in which the quantity of glucose in the blood is too elevated (hyperglycemia). This is because the body does not produce enough insulin, produces no insulin, or has cells that do not respond properly to the insulin the pancreas produces. This results in too much glucose building up in the blood. This excess blood glucose eventually passes out of the body in urine. So, even though the blood has plenty of glucose, the cells are not getting it for their essential energy and growth requirements. [http://diabetes.webmd.com/diabetes-types-insulin (Accessed 20th March 2013) So, Diabetes is a metabolic disorder that is characterized by high blood glucose and either insufficient or ineffective insulin. 5.9% of the population in the United States has diabetes, and diabetes is the seventh leading cause of death in our country. Diabetes is a chronic disease without a cure, however, with proper management and treatment, diabetics can live a normal, healthy lives. Diabetes is a problem where our body makes but does not uses insulin or body can’t produce enough insulin. Insulin is needed to move blood sugar (glucose) into cells, where it is stored and later used for energy. When diabetes occurs fat, liver, and muscle cells do not respond correctly to insulin. This is called insulin resistance. As a result, blood sugar does not get into these cells to be stored for energy. When sugar cannot enter cells, high

levels of sugar build up in the blood. This is called hyperglycemia. (American Diabetes Association Clinical Guidelines, 2010)

In diabetes, there is an uncoupling of blood glucose levels and the concentration of insulin that prevents the proper regulation of glycemia (Figure 1). Instead of a narrow glycemic range, blood glucose deviations can extend from hypoglycemia (less than 60 mg/dl) into hyperglycemia (fasting blood glucose greater than 126 mg/dl, post- prandial blood glucose greater than 200 mg/dl). This can be the result of a complete insulin deficiency, which is classified as insulin- dependent diabetes mellitus (type1 diabetes). However, the predominant form of diabetes is non- insulin- dependent diabetes mellitus (type 2 diabetes). Those afflicted with type 2 diabetes are commonly overweight with a sedentary lifestyle. An abnormally high resistance to insulin causes sustained hyperglycemia, especially following meals. A third class of diabetes, gestational diabetes, presents itself during pregnancy and is a health concern for the mother and the developing fetus. ("Type 1 & Type 2 Diabetes Mellitus". Retrieved 2008-08-04.) . Diabetes is a serious chronic disease without a cure, and it is associated with significant morbidity and mortality, both acute and chronic. Acute complications are due to severe hyperglycemia. Chronic complications are characterized by damage, dysfunction, and eventual failure of various organs, especially the eyes, kidneys, nerves, heart, and brain. It was recognized by an asymptomatic phase between the real onset of diabetic hyperglycemia and clinical diagnosis which lasts at least for 4-7 years (Brown, Critchley, Bogowicz,Mayige, &Unwin, 2012). Late or lack of diabetes diagnosis causes the increase of various chronic vascular complications (Heydari, Radi, Razmjou, &Amiri, 2010). It is well known that about 30 to 80 percent of type 2 diabetic cases remain undiagnosed (Brown et al., 2012). Therefore, considering the prevention principle and in order to fight against the current widespread prevalence of diabetes, there is great emphasis on the significance of screening and recognition of those who might have diabetes or its higher probability without any symptoms. Timely diagnosis and prevention result in the decrease in mortality and prevention and decrease in the diabetes complications and improvement of quality of life (Gregget al., 2001)

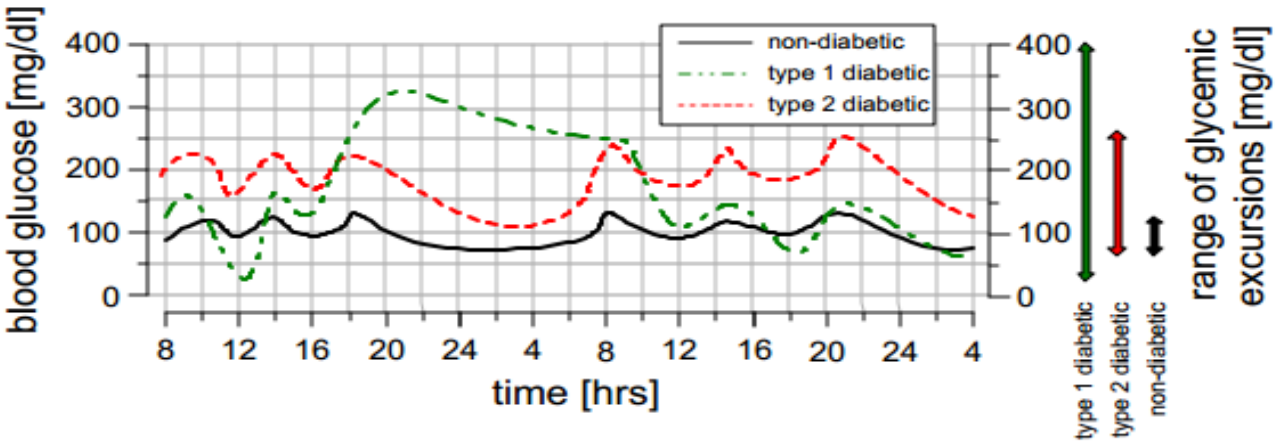

Figure 1: Typical variations in plasma glucose concentrations in patients with type 1 and type 2 diabetes versus non-diabetic individuals over a two day period [31].

1.2) Demography of Diabetes

In 2012 diabetes was the direct cause of 1.5 million deaths. More than 80% of diabetes deaths occur in low- and middle-income countries. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival.[Centers for Disease Control and Prevention (CDC)]

1.3) Prevalence of Diabetes

International Diabetes Federation (IDF) published a data of global league of diabetes where the data showed the prevalence of diabetes between different countries .The prevalence of diabetes is increasing rapidly, particularly in children and young adults. One third of cases of diabetes remain undiagnosed. The burden of death and disability from diabetes remains great despite broad advances in understanding and therapeutic techniques. Few patients with diabetes receive all the recommended annual screening evaluations for complications or preventive services. Organized systems of health care delivery can achieve better control of diabetes and its co morbidities..Diabetes was the seventh leading cause of death in the United States in 2010based on the 69,071 death certificates in which diabetes was listed as the underlying cause of death

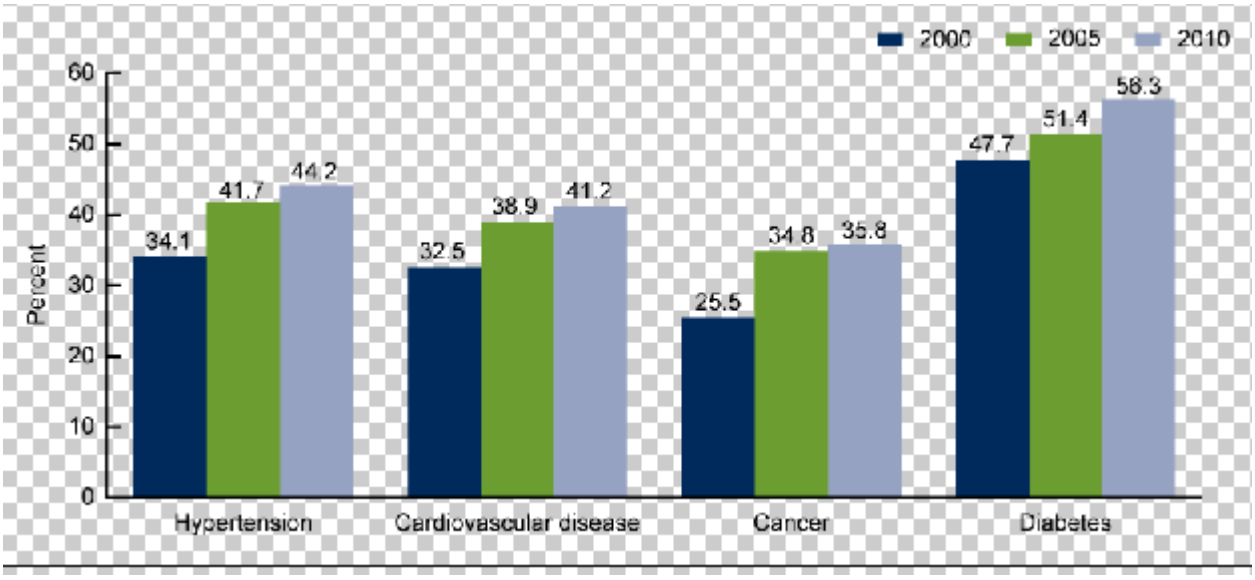

Fig 2: Percentage of diabetes occurring rates from other disease.(CDC/NCHS, National Health Interview Survey).

In Bangladesh Number of deaths in adults due to diabetes 111,371. Prevalence of diabetes in adults(20-79 years)

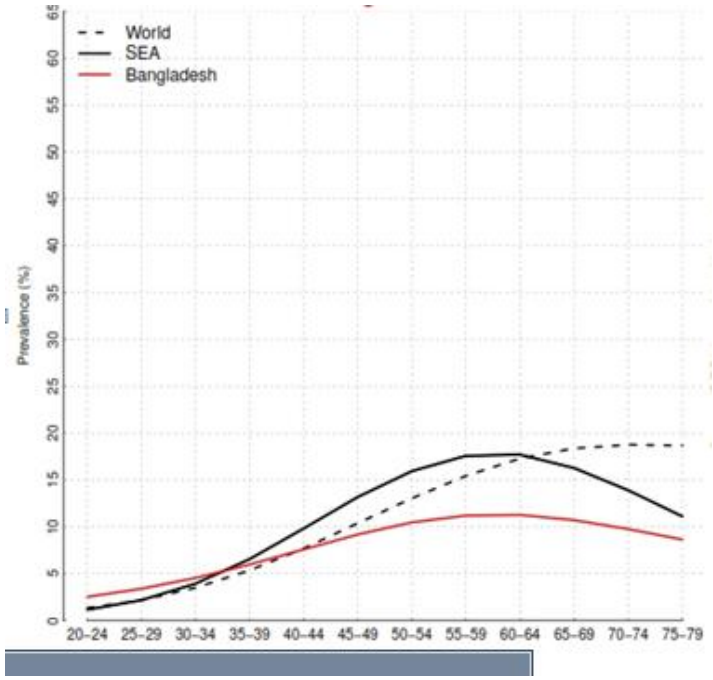

Fig:3 : Prevalence of diabetes in adults by age (IDF,2014)

In 2015, the International Diabetes Federation's (IDF) Diabetes Atlas estimates that: One in 11 adults has diabetes (415 million) .One in two (46.5%) adults with diabetes is undiagnosed 12% of global health expenditure is spent on diabetes (USD673 billion) .One in seven births is affected by gestational diabetes

Three-quarters (75%) of people with diabetes live in low- and middle-income countries 542,000 children have type 1 diabetes .Every six seconds a person dies from diabetes (5.0 million deaths) .By 2040, IDF estimates that: One adult in ten will have diabetes (642 million) Diabetes-related health expenditure will exceed USD 802 billion 37% of all adults with diabetes live in the Western Pacific region (which includes Australia);China with over 100 million people with diabetes (ranked highest number of people with diabetes),Indonesia with 10 million people with diabetes (7th highest), Japan with 7.2 million people with diabetes (9th highest).. People with pre-diabetes have a higher risk of developing type 2 diabetes and cardiovascular (heart and circulation) disease. There are two pre-diabetes conditions: Impaired glucose tolerance (IGT) is where blood glucose levels are higher than normal but not high enough to be classified as diabetes. Impaired fasting glucose (IFG) is where blood glucose levels are escalated in the fasting state but not high enough to be classified as diabetes. It is possible to have both Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) [IDF, 2015]

According to International Diabetes Federation global Atlas (2013)the top 10 countries with higher prevalence of diabetes are Tokelau (37.5%), Federated States of Micronesia (35%), Marshall Islands (34.9%), Kiribati (28.8%), Cook Islands (25.7%), Vanuatu (24%), Saudi Arabia (23.9%), Nauru (23.3%), Kuwait (23.1%) and Qatar (22.9%). It is interesting to highlight that 35 out of 219 countries (16% of the total) has very high prevalence of diabetes of 12% or higher. These countries are located mainly in Western Pacific, and Middle East and North Africa regions. Africa is the region with the lower prevalence of diabetes (4.9%), having Reunion (15.4%), Seychelles (12.1%) and Gabon (10.7%) as the top three countries with higher prevalence and 10 out of 48 countries with prevalence of diabetes higher than the upper quartile (6.3%) prevalence. Europe has 56 million people with diabetes (8.5%) having Turkey in the upper extreme of prevalence of diabetes with 14.9%, four percentage points higher that Montenegro (ranked #2) with 10.1% of prevalence. In North America and Caribbean, Belize (15.9%), Guyana (15.8%) and Curacao (14.5%) are the top three countries with the higher prevalence of diabetes. At the same time, this region presents the highest values of prevalence of IGT with a median of 12%. (Ref: IDF diabetes atlas, 2013).

International Diabetes Federation showed 2013 a data of diabetes prevalance among different countries.

Country	Prevalence
Polynesian Island	(24-37)%
Saudi Arabia	(23-24)%
UAR	19%

Egypt	17%
India	9.1%
USA	9.2%
Brazil	9.2%
China	9.0%
UK	4.9%

Table 1.1: Prevalance of diabetes among different countries. (IDF,2013)

1.4 Number of People with Diabetes: Top 10 Countries (According to IDF diabetes atlas, 5th Edition-2011):

2011		2030	
Country/territory	**Number of people with diabetes (millions)**	**Country/territory**	**Number of people with diabetes (millions)**
China	**90.0**	**China**	**129.7**
India	**61.3**	**India**	**101.2**
USA	**23.7**	**USA**	**29.6**
Russian Federation	**12.6**	**Brazil**	**19.6**

Brazil	**12.4**	**Bangladesh**	**16.8**
Japan	**10.7**	**Mexico**	**16.4**
Mexico	**10.3**	**Russian Federation**	**14.1**
Bangladesh	**8.4**	**Egypt**	**12.4**
Egypt	**7.3**	**Indonesia**	**11.8**
Indonesia	**7.3**	**Pakistan**	**11.4**

Table 1.2: Number of People with Diabetes: Top 10 Countries -2011

Number of People with Diabetes: Top 10 Countries (According to IDF diabetes atlas, 6th Edition, 2013):

2013		**2035**	
Country/territory	**Number of people with diabetes (millions)**	**Country/territory**	**Number of people with diabetes (millions)**
CHINA	**98.4**	**CHINA**	**142.7**
INDIA	**65.1**	**INDIA**	**109.0**
USA	**24.1**	**USA**	**29.7**
BRAZIL	**11.9**	**BRAZIL**	**19.2**

RUSSIA	**10.9**	**MEXICO**	**15.7**
MEXICO	**8.7**	**INDONESI**	**14.1**
INDONESI	**8.5**	**EGYPT**	**13.1**
GERMANY	**7.6**	**PAKISTAN**	**12.8**
EGYPT	**7.5**	**TURKEY**	**11.8**
JAPAN	**7.2**	**RUSSIA**	**11.2**

Table: 1.3: Number of People with Diabetes: Top 10 Countries-2013 , WHO, South-East Asia Region

Chapter Two

Overview of the Endocrine system

Overview of the Endocrinology:

2.1 Parts of the endocrine system

Endocrinology is a branch of medical science which deals with the study of different endocrine glands of the body. Endocrine glands are Hypothalmas (neuroendocrine gland),Pituitary(master gland)gland, Thyroid gland, Parathyroid glands, Adrenal glands, pancrease, Testis, Overies, Placenta(Guyton &Hall-11thed)

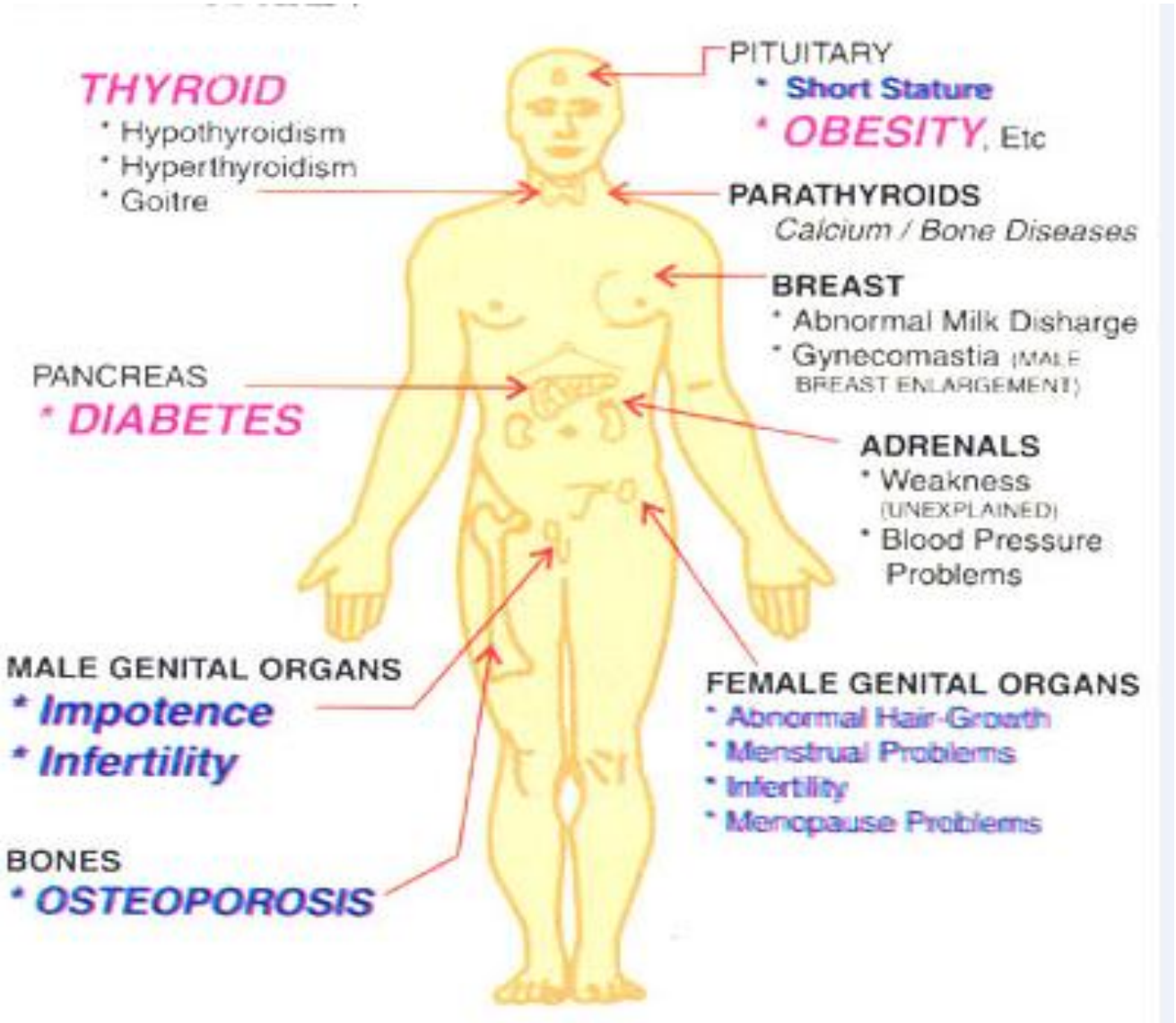

Fig 4: Endocrine system

2.2: Function of pancreas:

Pancreas act as both exocrine and endocrine gland. The exocrine secretion of the pancreas contains enzymes which promote the digestion of carbohydrate, proteins, and fats to small molecules to be absorbed by the intestinal mucosa. The two most important endocrine secretions of the pancreas are insulin and glucagon. These are enter the portal vein in relatively high concentrations and transported direct to the liver where they exert their effect. The exocrine and endocrine function of pancreas are closely interrelated. This view is strongly supported by embryological studies which show that the endocrine cells are formed by division of some of the acinar cells to form richly vascularized and innervated islets which have lost direct contact with the lumen of the smaller branches of the pancreatic duct. Before birth the Alpha cells secrete glucagon which prevents fetal hypoglycemia by means of insulin from the beta cells, and glucagon, comes into operation and remains active throughout life (Ref: Lefebvre and Unger 1972).

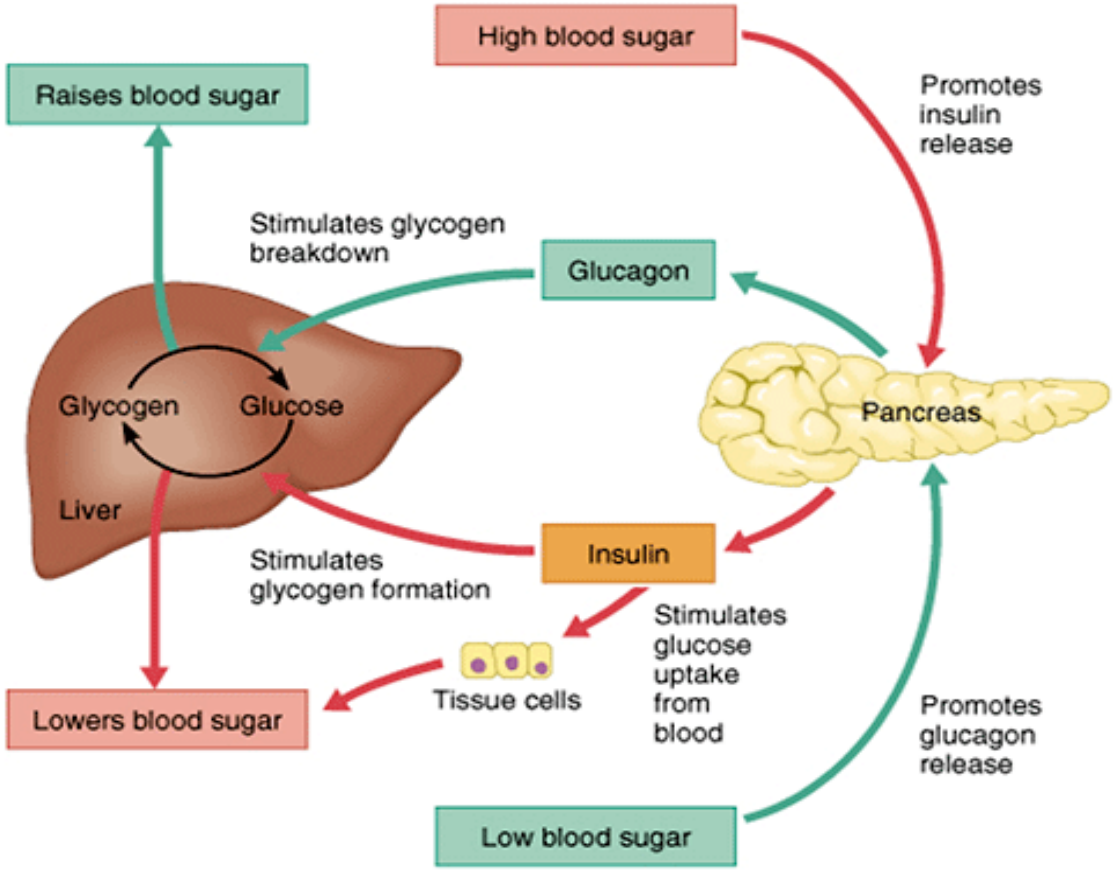

Fig 5: Function of pancreas

2.3 Insulin and its Chemistry

Insulin is a hormone made by the pancreas that allows our body to use sugar (glucose) from carbohydrates in the food that eat for energy or to store glucose for future use. Insulin helps keeps blood sugar level from getting too high (hyperglycemia) or too low (hypoglycemia). Insulin is composed of two different types of peptide chains. Chain A has 21 amino acids and Chain B has 30 amino acids. Both chains contain alpha helices but no beta strands. There are 3 conserved disulfide bridges which help keep the two chains together. Insulin can also form dimmers in solution due to the hydrogen bonding between the B chains . The dimers can further interact to form hexamers due to interaction between hydrophobic surfaces. This scene highlights the hydrophobic and polar parts of an insulin monomer at a pH of 7. (Lippincott William &wikkins)

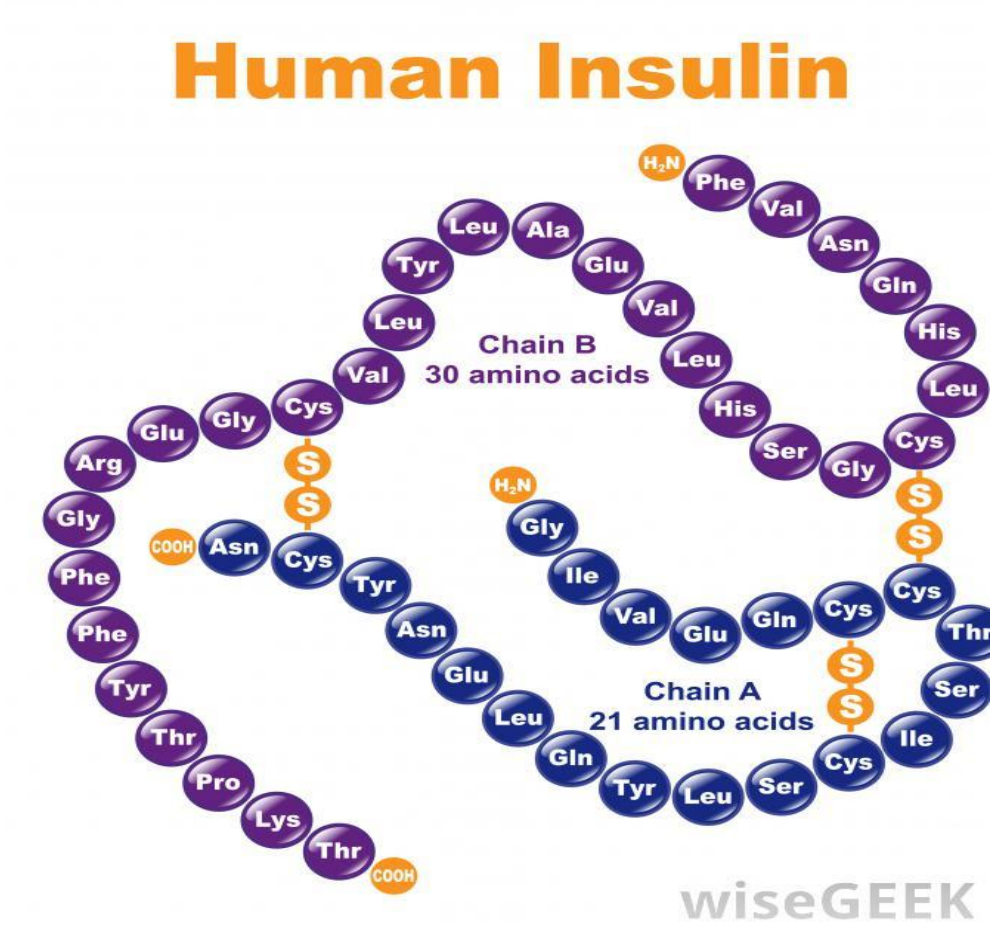

Fig 6: Insulin structure

2.4 Synthesis of insulin

Insulin is produced in the pancreas and released when any of several stimuli are detected. These stimuli include ingested protein and glucose in the blood produced from digested food. Carbohydrates can be polymers of simple sugars or the simple sugars themselves. If the carbohydrates include glucose, then that glucose will be absorbed into the bloodstream and blood glucose level will begin to rise. In target cells, insulin initiates a signal transduction, which has the effect of increasing glucose uptake and storage. Finally, insulin is degraded, terminating the steps.

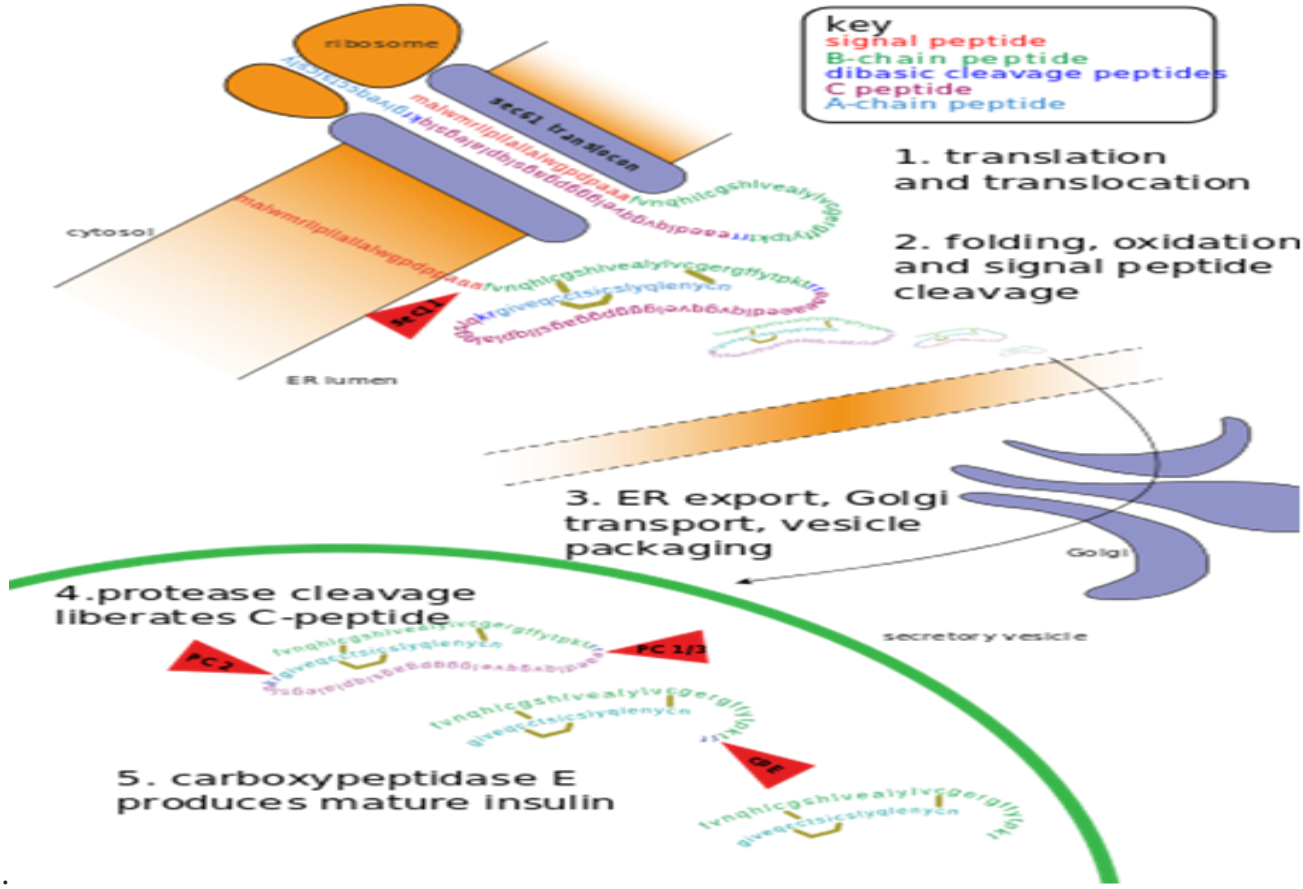

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Fig 7: Synthesis of insulin

Insulin undergoes extensive posttranslational modification along the production pathway. Production and secretion are largely independent; prepared insulin is stored awaiting secretion. Both C-peptide and mature insulin are biologically active. Cell components and proteins in this image are not to scale. In mammals, insulin is synthesized in the pancreas within the β-cells of the islets of Langerhans. One million to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. (Lippincott Williams& Wilkins) The endocrine portion accounts for only 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 65–80% of all the cells. Insulin consists of two polypeptide chains, the A- and B- chains, linked together by disulfide bonds. It is however first synthesized as a single polypeptide called pre proinsulin in pancreatic β-cells. Preproinsulin contains a 24-residue signal peptide which directs the nascent polypeptide chain to the rough endoplasmic reticulum (RER). The signal peptide is cleaved as the polypeptide is translocate into lumen of the RER, forming proinsulin.In the RER the proinsulin folds into the correct conformation and 3 disulfide bonds are formed. About 5–10 min after its assembly in the endoplasmic reticulum, proinsulin is transported to the trans-Golgi network (TGN) where immature granules are formed. Transport to the TGN may take about 30 min. Proinsulin undergoes maturation into active insulin through the action of cellular endopeptidases known as prohormon econvertase, (PC1 and PC2), as well as the exo protease carboxypeptidase. The endopeptidases cleave at 2 positions, releasing a fragment called the C-peptide, and leaving 2 peptide chains, the B- and A- chains, linked by 2 disulfide bonds. The cleavage sites are each located after a pair of basic residues (lysine-64 and arginine-65, and arginine-31 and -32).(Joslin's Diabetes Mellitus) After cleavage of the C-peptide, these 2 pairs of basic residues are removed by the carboxypeptidase. The C-peptide is the central portion of proinsulin, and the primary sequence of proinsulin goes in the order "B-C-A" (the B and A chains were identified on the basis of mass and the C-peptide was discovered later).The resulting mature insulin is packaged inside mature granules waiting for metabolic signals (such as leucine, arginine, glucose and mannose) and vagal nerve stimulation to be exocytosed from the cell into the circulation.

The endogenous production of insulin is regulated in several steps along the synthesis pathway:

- At the mRNA translation
- In the posttranslational modifications.

(Lippincott Williams& Wilkins, Goodman Gillman, Ronald Kahn; *et al* (2005) *Joslin's Diabetes Mellitus*)

2.5 Secretion and release of Insulin

2.5 (1) Insulin secretion: Insulin is secreted in primarily in response to elevated blood concentrations of glucose. This makes sense because insulin is "in charge" of facilitating glucose entry into cells. Some neural stimuli (e.g. sight and taste of food) and increased blood concentrations of other fuel molecules, including amino acids and fatty acids, also promote insulin secretion. The mechanisms behind insulin secretion remain somewhat fragmentary. Nonetheless, certain features of this process have been clearly

and repeatedly demonstrated, yielding the following model: Glucose is transported into the beta cell by facilitated diffusion through a glucose transporter; elevated concentrations of glucose in extracellular fluid lead to elevated concentrations of glucose within the beta cell. (Hall et al 1974) Elevated concentrations of glucose within the beta cell ultimately leads to membrane depolarization and an influx of extracellular calcium. The resulting increase in intracellular calcium is thought to be one of the primary triggers for exocytosis of insulin-containing secretory granules. The mechanisms by which elevated glucose levels within the beta cell cause depolarization is not clearly established, but seems to result from metabolism of glucose and other fuel molecules within the cell, perhaps sensed as an alteration of ATP:ADP ratio and transduced into alterations in membrane conductance. (Layden BT, Durai *etal*, 2010)Increased levels of glucose within beta cells also appears to activate calcium-independent pathways that participate in insulin secretion. Stimulation of insulin release is readily observed in whole animals or people. The normal fasting blood glucose concentration in humans and most mammals is 80 to 90 mg per 100 ml, associated with very low levels of insulin secretion. [("Tolerx, Inc. and GlaxoSmithKline (GSK) Announce Phase 3 Defend-1 Study of Otelixizumab in Type 1 Diabetes Did Not Meet Its Primary Endpoint"". Biospace. Retrieved 29 November 2

Secretion of Insulin:

Insulin is secreted from the B-cell of islets of Langerhans of pancreas.

↓

Increase glucose concentration of Blood

↓

Glucose enters in beta cells by glucose transporter

↓

Production of ATP

↓

Closure of ATP dependant K+ channel

↓

Depolarization

↓

Opening voltage gated Ca++ channel

↓

Increased intracellular ca++ level

↓

Insulin secretion

The figure to the right depicts the effects on insulin secretion when enough glucose is infused to maintain blood levels two to three times the fasting level for an hour. Almost immediately after the infusion begins, plasma insulin levels increase dramatically. This initial increase is due to secretion of preformed insulin, which is soon significantly depleted. The secondary rise in insulin reflects the considerable amount of newly synthesized insulin that is released immediately. Clearly, elevated glucose not only simulates insulin secretion, but also transcription of the insulin gene and translation of its mRNA.

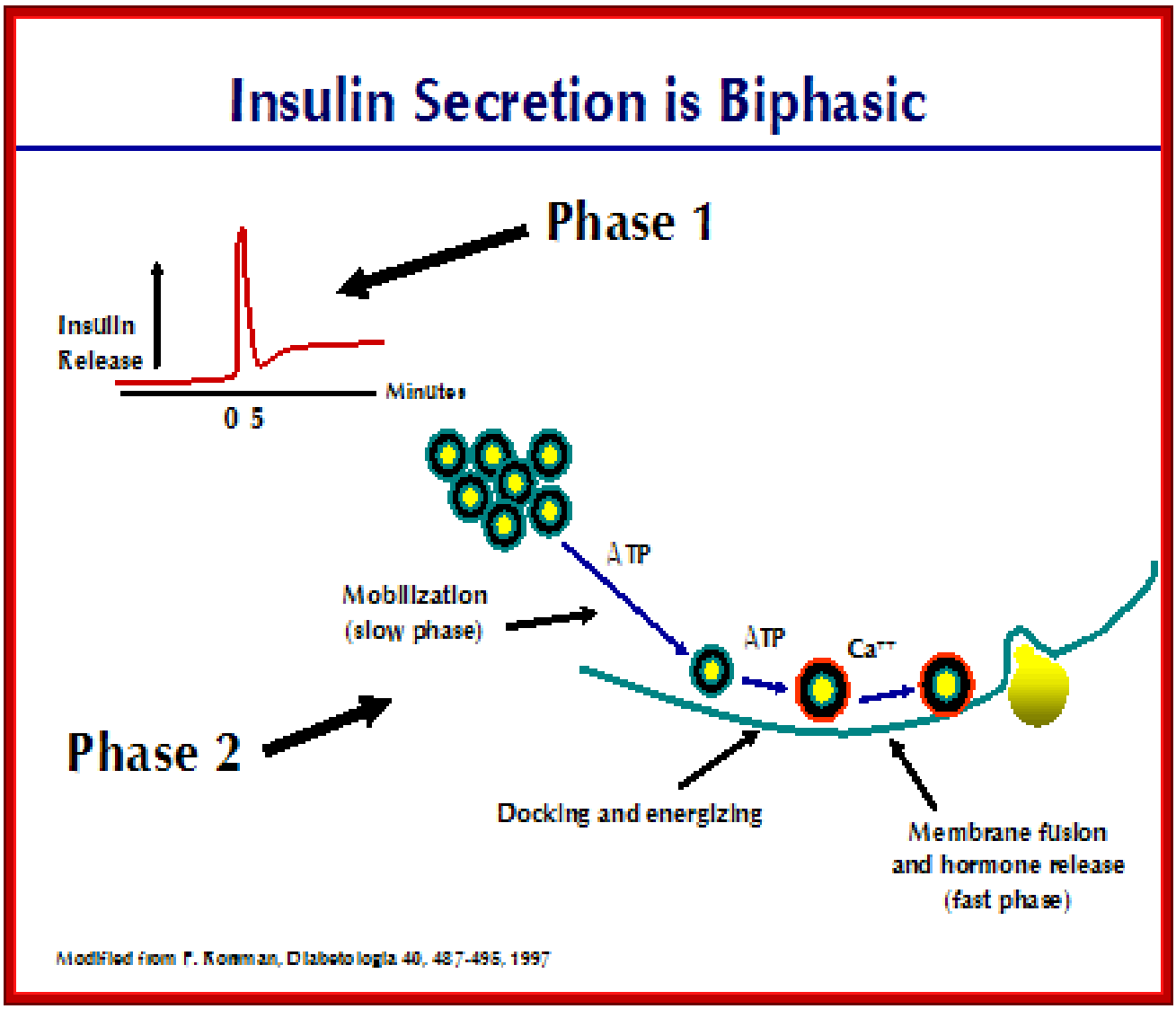


Fig 8: Insulin Secretion

2.5.1 (a) Ionic Control of insulin secretion

By controlling ion permeability, ion channels at the membrane play a major role in regulating both electrical activity and signal transduction in the β-cell. A proximal step in the cascade of events required for stimulus-secretion coupling is the closure of ATP-sensitive K^+ channels, resulting in cell depolarization. Of particular relevance is the finding that this channel is directly regulated by a metabolite of glucose, which is the primary insulin secretagogue. In addition, this channel, or a closely associated protein, contains the sulfonylurea-binding site. (American Diabetes Association ,1990) Another K^+ channel, the Ca^{2+}-activated K^+ channel, may be involved in cell repolarization to create homeostasis. Voltage-dependent Ca^{2+} channels are activated by cell depolarization and regulate Ca^{2+} influx into the cell. By controlling cytosolic free-Ca^{2+} levels ($[Ca^{2+}]_i$), these channels play an important role in transducing the initial stimulus to the effector systems that modulate insulin secretion. The link between a rise in [Ca^{2+}[(and the terminal event of exocytosis is the least-understood aspect of stimulus-secretion coupling. However, phosphorylation studies have identified substrate proteins that may correspond to those involved in smooth muscle contraction, suggesting an analogy in the processes of stimulus secretion and excitation contraction. The advent of new methodology, particulary the patch-clamp technique, has fostered a more detailed characterization of the β-cell ion channels. Furthermore, biochemical and molecular approaches developed for the structural analysis of ion channels in other tissues can now be applied to the isolation and characterization of the β-cell ion channels. This is of particular significance because there appear to be tissue-specific variations in the different types of ion channels. Given the importance of ion channels in cell physiology, a knowledge of the structure and properties of these channels in the β-cell is required for understanding the abnormalities of insulin secretion that occur in non-insulin-dependent diabetes mellitus. Ultimately, these studies should also provide new therapeutic approaches to the treatment of this disease. (doi: 10.2337/diacare.13.3.340 *Diabetes Care March 1990 vol. 13 no. 3 340-36)(*American Diabetes Association ,1990)

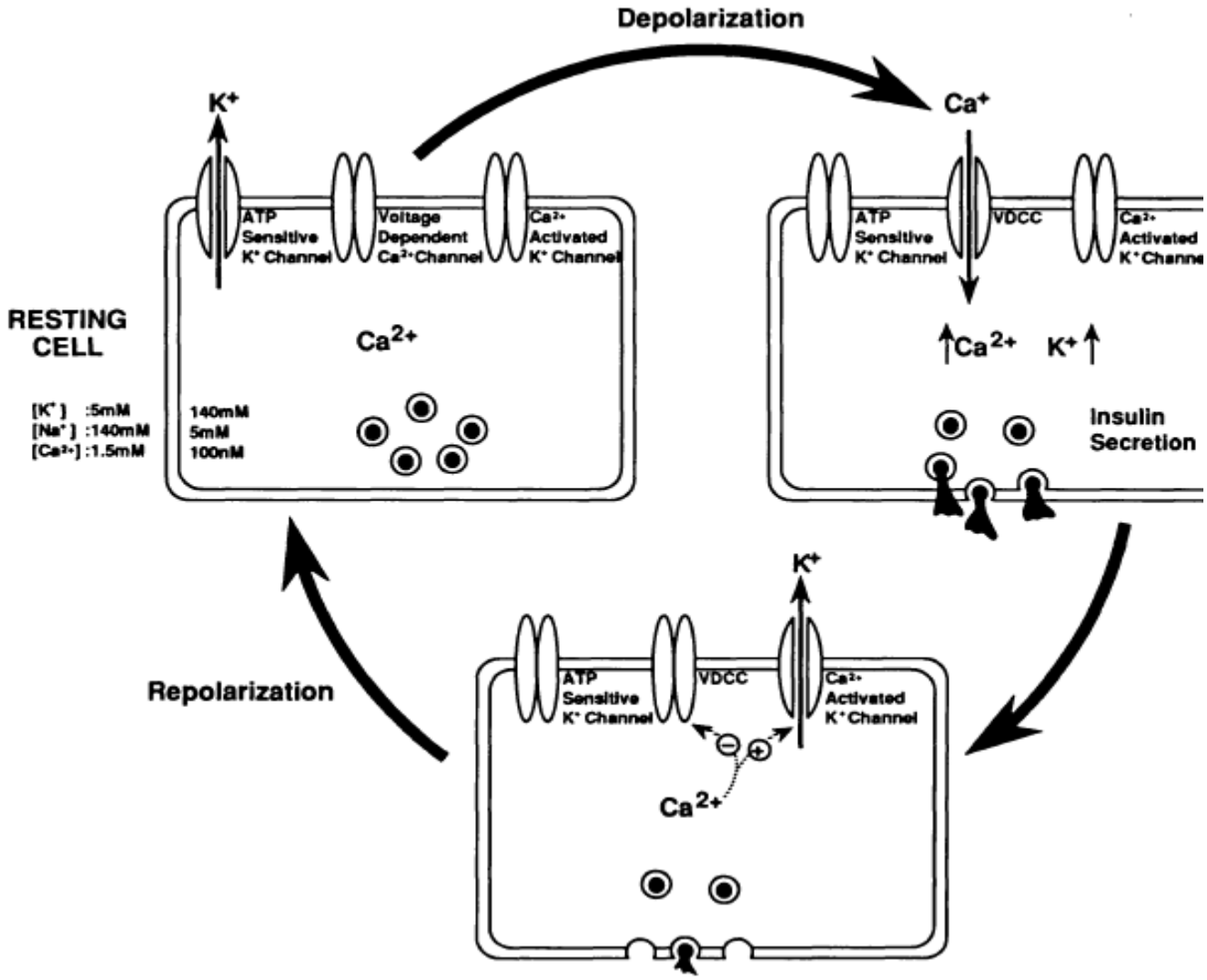


Fig 9: Ion Channel modulation of insulin secretion. Resting membrane potential in pancreatic β -cells is governed by K^+ conductance through ATP -sensitive K^+ channels. Closure of these channels leads to cell depolarization and ca $^+$ influx through voltage dependent ca $^{2+}$ influx through voltage dependent ca channels. Rise in free cystolic triggers insulin secretion. in addition, rise in cystolic Ca $^{2+}$ activates Ca ^{2} activates K^+ channels to enhance K^+ efflux and inactivate ca^{2+} channels. This result in depolarization and reversion of resting state. (Arun -S- Rajan, Daniel A, *et all*, 1990)

2.6 Release of Insulin

Beta cells in the islets of Langerhans release insulin in two phases. The first phase release is rapidly triggered in response to increased blood glucose levels. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar. The description of first phase release is as follows :(J Clin Invest. 1993 Mar; 91(3): 871–880)

Glucose enters the β-cells through the glucose transporters, GLUT2. Glucose goes into glycolysis and the Krebs cycle, where multiple, high-energy ATP molecules are produced by oxidation, leading to a rise in the ATP: ADP ratio within the cell. .(J Clin Invest. 1993 Mar; 91(3): 871–880) An increased intracellular ATP:ADP ratio closes the ATP-sensitive SUR1/Kir6.2 potassium channel (see sulfonylurea receptor). This prevents potassium ions (K^+) from leaving the cell by facilitated diffusion, leading to a buildup of potassium ions. As a result, the inside of the cell becomes more positive with respect to the outside, leading to the depolarization of the cell surface membrane. On depolarization, voltage-gated calcium ion (Ca^{2+}) channels open which allows calcium ions to move into the cells by facilitated diffusion.(J Clin Invest. 1993 Mar; 91(3): 871–880) An increased intracellular calcium ion concentration causes the activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate into inositol1,4,5.(J Clin Invest. 1993 Mar; 91(3): 871–880) trisphosphate and diacylglycerol. Inositol 1,4,5-trisphosphate (IP3) binds to receptor proteins in the plasma membrane of the endoplasmic reticulum (ER). This allows the release of Ca^{2+} ions from the ER via IP3-gated channels, and further raises the intracellular concentration of calcium ions. Significantly increased amounts of calcium ions in the cells cause the release of previously synthesized insulin, which has been stored in secretory vesicles. .(J Clin Invest. 1993 Mar; 91(3): 871–880) This is the primary mechanism for release of insulin. Other substances known to stimulate insulin release include the amino acids arginine and leucine, parasympathetic release of acetylcholine (via phospholipase C), sulfonylurea, cholecystokinin (CCK, via phospholipase C), and the gastrointestinally derived incritins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Release of insulin is strongly inhibited by the stress hormone nor epinephrine (noradrenaline), which leads to increased blood glucose levels during stress. It appears that release of catecholamines by the sympathetic nervous system has conflicting influences on insulin release by beta cells, because insulin release is inhibited by α_2-adrenergic receptors and stimulated by β_2-adrenergic receptors. The neither net effect of nor epinephrine from sympathetic nerves and epinephrine from adrenal glands on insulin release is inhibition due to dominance of the α-adrenergic receptors. When the glucose level comes down to the usual physiologic value, insulin release from the β-cells slows or stops. If blood glucose levels drop lower than this, especially to dangerously low levels, release of hyperglycemic hormones (most prominently glucagon from islet of Langerhans alpha cells) forces release of glucose into the blood from cellular stores, primarily liver cell stores of glycogen. By increasing blood glucose, the hyperglycemic hormones prevent or correct life-threatening hypoglycemia. (J Clin Invest. 1993 Mar; 91(3): 871–880)

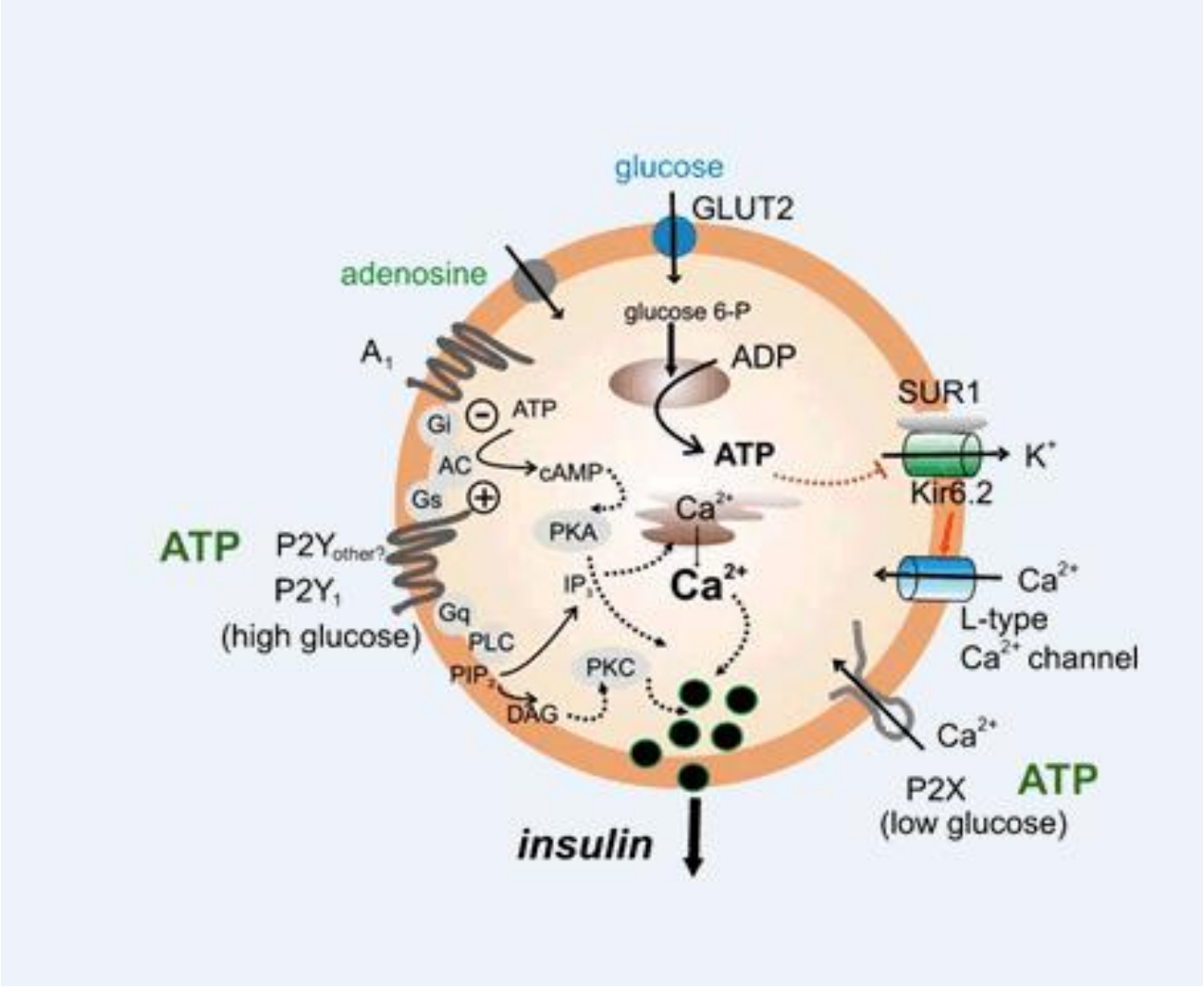


Fig 10: Release of insulin

2.7 Insulin degradation

The liver and kidney are the two main organs that remove insulin from circulation .The liver normally clears the blood of approximately 60% of the insulin released from the pancreas by virtue of its location as the terminal site of portal vein blood flow ,with the kidney removing 35-40% of the endogenous hormone. Insulin treated diabetes receiving subcutaneous insulin injection. 60% of exogenous insulin being cleared by the kidney and liver removing no more than 30-40% .The half life of circulating insulin is 3-5 min**.**

2.8 Measurement of circulating insulin

The radio immunoassay of insulin permits detection of insulin in picomolar quantities. The assay is based on antibodies developed in guinea pigs against bovine or pork insulin .Because of the similarities between these two insulins and human insulin,the assay successfully measures the human hormone as well. with this assay, basal insulin values of 5-15 micro U/ml (30-90 pmol/l) . **(**Text Book of Endocrinology)

2.9 Endocrine effects of insulin

Effect of insulin on liver

1)Reversible of catabolic features of insulin deficiency inhibits glycogenolysis.

2)Inhibit conversion of fatty acids and amino acids to keto acids

3)Inhibit conversion of amino acids to glucose

4)Promote glucose storage as glycogen

5)Increase triglycerides synthesis and very low density lipoprotein formation. (Text Book of Endocrinology)

Effect on muscle:

1) Increased protein synthesis

2) Increase amino acid transport

3) Increase ribosomal protein synthesis

4) Increased glycogen synthesis

5) Increase glucose transport

6) Increase glycogen synthesis and inhibit phosphorylase.

Effect on adipose tissue:

1)Increased triglycerides storage.

2)Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins.

3)Glucose transport into cell provides glycerol Phosphate to permit esterification of fatty acids supplied by lipoprotein transport .

4)Intracellular lipase is inhibited by insulin .(Ref: Aguilar-bryan L et al, 1995 (Text Book of Endocrinology)

2.10 Action of insulin on cell membrane:

Insulin acts upon the plasma membrane of muscle and adipose tissue cells to facilitate the transport of glucose ,amino acid ,K^+, and Mg, and inorgnic phosphate into the cell. The presence of glucose ,amino acids and ions into responsive cell.Insulin may reduce cAMP formation particularly in adipose tissue .This will reduce the lipolytic response to adrenalin or glucagon and favor anabolic process leading to synthesis of glycogen and deposition of triglyceride. The attachment of insulin into cell membrane surface may elicit a propagated disturbance through the membrane which may either inhibit the activity of adenylcyclase or enhance the phosphodiesterase, thus reducing cAMP concentration. The facilitated transport of ions into insulin-responsive cells may influence intracellular enzyme activities .Change in K^+ concentration may shift the balance between glycogen synthesis and glycogen breakdown. (Ref: Bloom, S.R.(1975).*Br.j.hosp.Med.*13, 150) (Ref: Krahl, M.E (1972). Insulin action at the molecular level.)

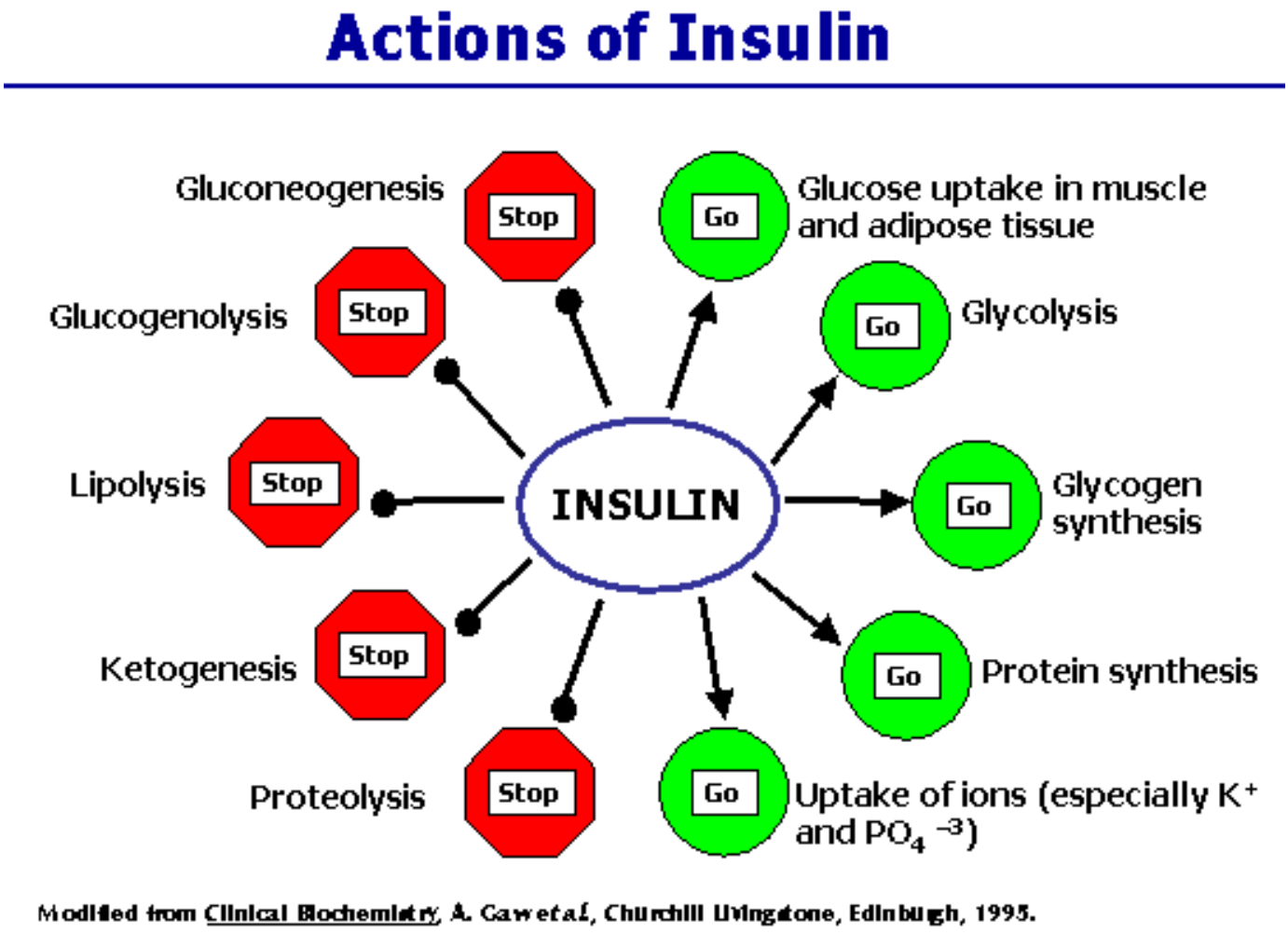


Fig 11: Action of insulin

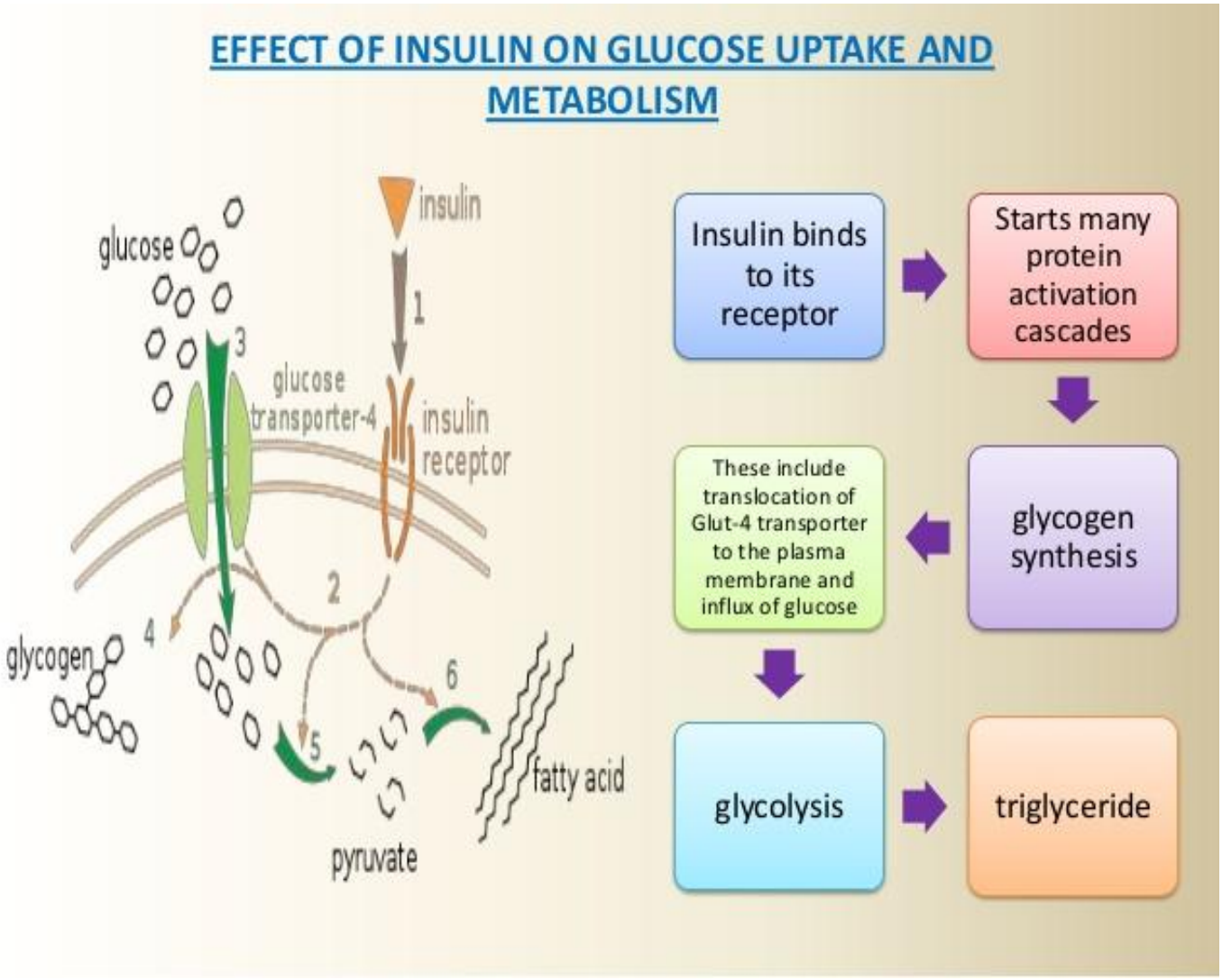


Fig 12: Effect of insulin

Chapter Three

Overview of Diabetes Mellitus

3.1 Features of Diabetes mellitus

Pre diabetes (potential diabetes):

These terms are applied to persons with a strong genetic predisposition to diabetes but who do not yet show any abnormality of carbohydrate metabolism .Hypertrophy of islets tissue may produce more insulin than normal and so delay the onset of diabetes. (Samson wrights applied physiology)

Latent diabetes:

It is the term applied to asymptomatic persons who develop glycosuria after stress or glucocorticoid administration .This occurs most commonly in obese subjects in whom plasma insulin concentration is higher than normal after a carbohydrate meal .Excess of fatty tissue creates resistance to the action of insulin and the normal state can be stored by restriction of carbohydrate intake which reduces body weight by reducing lipogenesis. (Samson wrights applied physiology)

Chemical diabetes mellitus: Chemical diabetes mellitus in which there is hyperglycemia, glycosuria and symptoms such as thirst, polyuria and weight loss or gain, which may go unrecognized for a time.

Overt diabetes mellitus

It's symptom takes two main forms with the following features (Samson wrights applied physiology)

Juvenile onset	Maturity onset
a) Under weight	a) Normal or overweight
b) Ketosis ,if untreated	b)Ketosis with severe infection; often absent.
c)Insulin secretion low or absent	c) Normal or increased insulin secretion .
d)Insulin treatment needed	d)Diet and oral hypoglycemic drugs effective
e)Patients are sensitive to insulin	e)Insulin resistant

3.2 Types of diabetes

There are three types of diabetes:

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Gestational diabetes mellitus

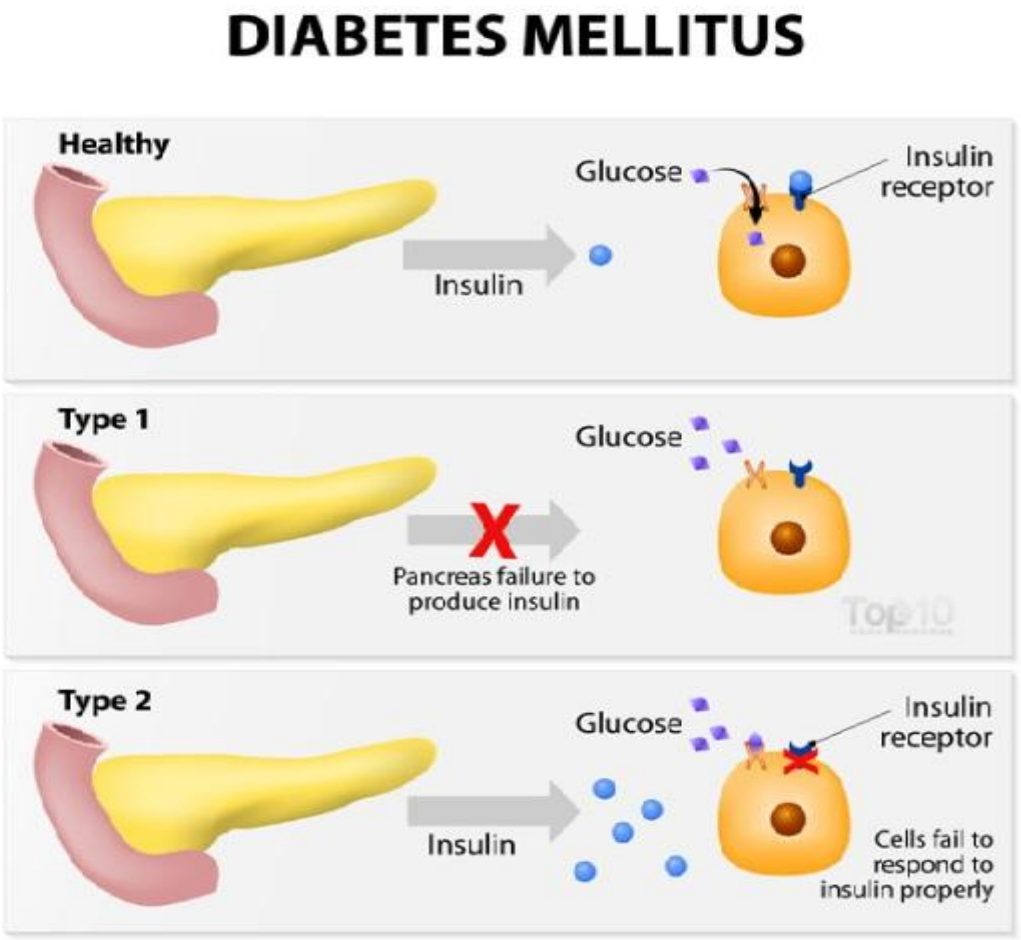


Fig 13: Types of diabetes mellitus

3.2 (a) Type 1 Diabetes Mellitus

Type 1 diabetes (DM-1) was previously known as IDDM (insulin dependent diabetes mellitus) or juvenile-onset diabetes. About 5-10% of patients with diabetes have DM-1. Type 1 diabetes affects 3 in 1000 children and its incidence is increasing worldwide both in low and high prevalence populations (Diabetes blue circle symbol, IDF)

3.2.1 Pathogenesis of Type 1 Diabetes

Type 1 diabetes is usually diagnosed in children and young adults, and was previously known as juvenile diabetes. Only 5% of people with diabetes have this form of the disease. .(American Diabetes Association Clinical Guidelines, 2010) In type 1 diabetes, the body does not produce insulin. Insulin is a hormone that the body needs to get glucose from the bloodstream into the cells of the body. In a genetically predisposed individual, (currently not well-defined) environmental factors trigger an autoimmune process (activation of T lymphocytes reactive to islet cell antigens) that leads to destruction of islet cells and insulin deficiency. .(American Diabetes Association Clinical Guidelines, 2010) Various factors may contribute to type 1 diabetes, including genetics and exposure to certain viruses. Although type 1 diabetes usually appears during childhood or adolescence . Genetics may play a role in this process, and exposure to certain environmental factors, such as viruses, may trigger the disease Type 1 diabetes has no cure. But it can be managed. With proper treatment, people with type 1 diabetes can expect to live longer, healthier lives than did people with type 1 diabetes in the past. Based on epidemiologic and genetic studies, it is well accepted that there is a strong genetic component for development of DM-1, although 90% of affected patients do not have a close relative with the disease. .(American Diabetes Association Clinical Guidelines, 2010) Multiple chromosomal loci associated with the disease have been identified: however, few true genes have been described. Loci associated with the development of DM-1 are found within the MHC-HLA class II region. These loci are known to harbor genes associated with presentation of antigens to T lymphocytes. (American Diabetes Association Clinical Guidelines, 2010)

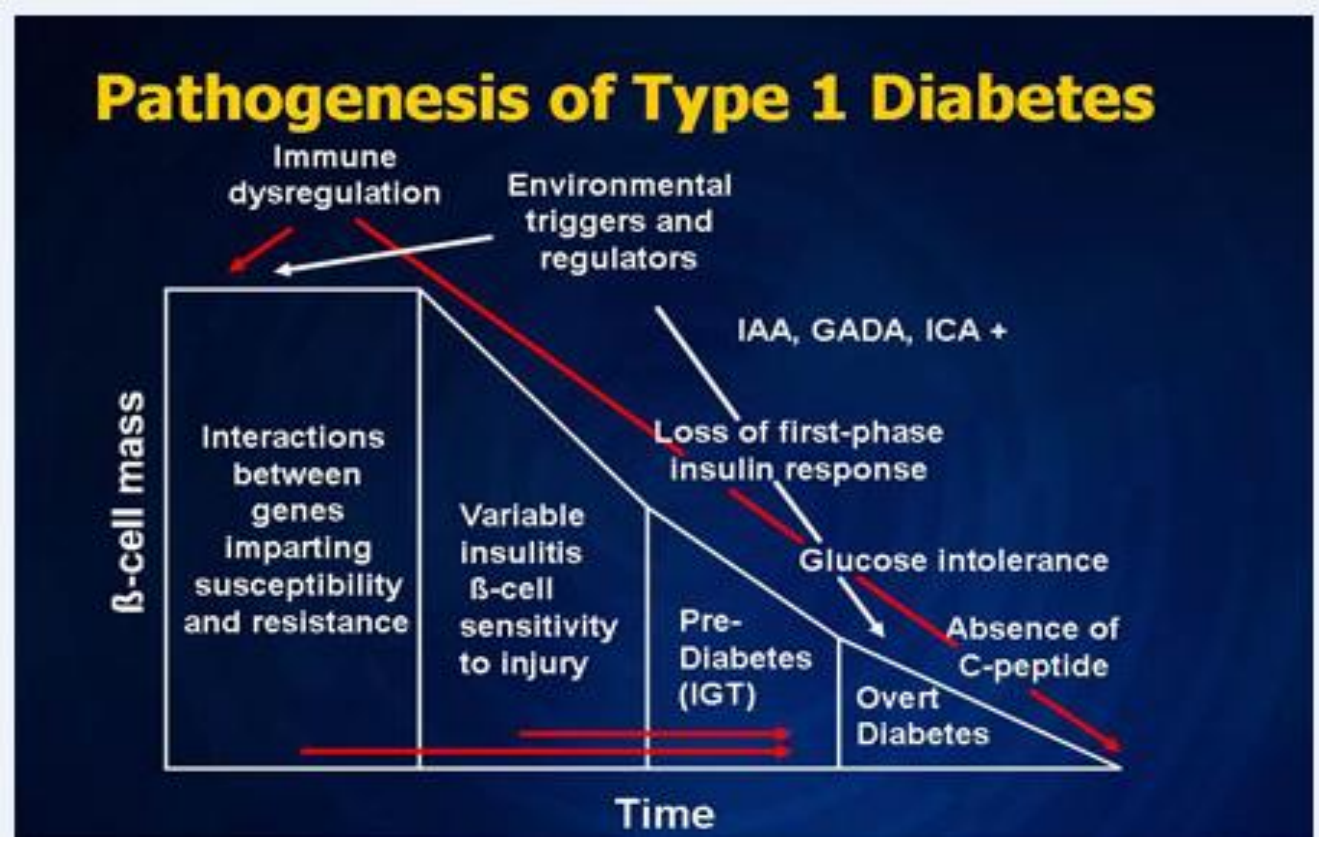


Fig 14: Pathogenesis of Type 1 diabetes

Immune dysregulation, caused by genetic susceptibility and environmental modifiers, leads to development of auto antibodies against various islet cell components, including glutamic acid

. Major islet-cell auto antigen-specific antibodies in type 1 diabetes

Autoantigen	Antibody	Sensitivity	Specificity
GAD-65	GAD-65 Ab	80%	99%
ICA512/IA-2	ICA512/IA-2 Ab	50%	99%
Insulin	IAA	50%	99%

Table 3.1: Specificity and sensitivity of antigen antibody in type 1 diabetes

decarboxylase antibodies (GAD-65), islet cell antibodies (ICA512/IA-2) and insulin antibodies (IAA). These antibodies serve as markers for DM-1 (Table 1). Indeed, the best predictor for future development of DM-1 is the expression of multiple auto antibodies. Beta cell destruction is thought to be primarily a T-cell mediated process, as evidence by the presence of intense insulitis in newly diagnosed patients. Beta

cell destruction is variable being more rapid in younger individuals and slower in older individuals. Type 1 diabetes is associated with other autoimmune disorders including Graves' disease, Addison's disease and autoimmune polyendocrine syndromes.(Atkinsn&Elsnbarth, Lancet.2001:358:221) (Pittas, AG and Greenberg AS. Contemporary Diagnosis and Management of Diabetes. *Handbooks in Health Care Co*, Newtown, PA. 2003.) (*Diabetes Care 24* (suppl. 1): 2003)

3.2.2 Causes:

The common causes of type 1 diabetes (90% cases) are autoimmune destruction of β-cells. Auto immune destruction of β-cell by environmental factors (virus and dietary component); Genetic factors (HLA) antigen; direct cytolytic effect (beta cell necrosis); expression of cytokinase ; immune response cross reacts with β cells. ("Type 1 & Type 2 Diabetes Mellitus". Retrieved 2008-08-04.)

3.2.3 Signs & Symptoms:

Symptoms linked to osmotic diuretics:- Polyuria, nocturia, Increased thirst & polydispepsia, Blurred vision, Drowsiness, dehydration, Etc.

Symptoms & signs linked to lack of insulin:- Hyperglycaemia with massive glucosuria, Extreme fatigue, Muscle wasting, Weight loss, Ketosis & ketoacidosis, Etc.

Symptoms of decreased resistance to Infections:-Skin infection, Genital pruritus, Etc.

Symptoms linked to Caloric depletion-Increased appetite, Weight loss, Etc. (*Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia:* report of a WHO/IDF consultation.)

3. 2.4 Type 2 Diabetes Mellitus:

Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2010 there were approximately 285 million people diagnosed with the disease compared to around 30 million in 1985.Type 2 diabetes (DM-2), previously known as NIDDM or adult-onset diabetes, is the most prevalent form of diabetes, accounting for over 90% of all cases of diabetes. With type 2 diabetes, body either resists the effects of insulin or doesn't produce enough insulin to maintain a normal glucose level. More common in adults, type 2 diabetes increasingly affects children as childhood obesity increases. There's no cure for type 2 diabetes, but may be able to manage the condition by eating well, exercising and maintaining a healthy weight. If diet and exercise aren't enough to manage blood sugar well, also may need diabetes medications or insulin therapy. The severity of diabetes can vary quite a bit: Some people only have to make minor changes to their lifestyle after they are diagnosed. Just losing a little weight and getting some more exercise may be enough for them to manage their diabetes. Other people who have type 2 diabetes need more permanent therapy that involves taking tablets or insulin. It is then especially important to have a good understanding of the disease and know what they can do to stay healthy. The

classic symptoms are excess thirst, frequent urination, and constant hunger. Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor blood flow in the limbs leading to amputations. The acute complication of ketoacidosis, a feature of type 1 diabetes, is uncommon, however hyperosmolar hyperglycemic state may occur. (Pittas, 2003)

3.2.5 Complication of Type 2 diabetes

This is partly due to a number of complications with which it is associated, including: two to four times the risk of **cardiovascular disease**, including **ischemic heart disease and stroke.**

Macro vascular complications

- Coronary and peripheral vascular disease,
- Hypertension,
- Diabetes may make it harder to control your blood pressure and cholesterol.
- This can lead to a heart attack, stroke, and other problems etc.[13]

Micro vascular complications

- Retinopathy with potential blindness

- Neuropathies with risk of foot ulcer (Nerves in your body can get damaged, causing pain, tingling, and a loss of feeling) ;(Because of nerve damage, could have problems digesting the food eat. could feel weakness or have trouble going to the bathroom. Nerve damage can make it harder for men to have an erection.) http://www.medicalnewstoday.com/info/diabetes)

- Nephropathy that may lead to renal failure (High blood sugar and other problems can lead to

kidney damage. Your kidneys may not work as well, and they may even stop working)

- Reduce resistance to infection (Infections of the skin, female genital tract, and urinary tract are also more common).

-amputation, Etc. (http://www.medicalnewstoday.com/info/diabetes)

Others complications

- Severe life threatening complications or emergencies including
- Hypoglycaemic coma, Diabetic ketoacidosis with or without coma, hyper osmolar non-ketotic coma, Lactic Acidosis, Etc.
- Mild complications including

-Insulin oedema, Blurred vision (presbyopia), insulin allergy, Acute neuro-pathy, Insulin abscess, Diabetic skin infections, Diabetic genital infection, impotence, etc

3.2.6 Risk factors for Type 2 diabetes:

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors. While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics. A lack of sleep has been linked to type 2 diabetes. This is believed to act through its effect on metabolism.

Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity and being overweight (defined by a body mass index of greater than 25), lack of physical activity, poor diet, stress, and urbanization. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of cases in Pima Indians and Pacific Islanders. Smoking also appears to increase the risk of type 2 DM. Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fats in the diet are also important, There are a number of medications and other health problems that can predispose to diabetes. Some of the medications include: Glucocorticoids, thiazides, beta blockers, atypical antipsychotics, and statins. Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes. Other health problems that are associated include: Cushing's syndrome, hyperthyroidism, pheocromocytoma, and certain cancers such as glucagonomas is also associated with type 2 diabetes. (Goodman & Gillman Pharmacological Basis of therapeutics)

Genetics

Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a type 2 diabetic. If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90%, while the rate for non identical siblings is 25–50%. As of 2011, more than 36 genes had been found that contribute to the risk of type 2 diabetes. All of these genes together still only account for 10% of the total heritable component of the disease. The TCF7L2 allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants. (http://www.medicalnewstoday.com/info/diabetes)

3.2.7 Pathophysiology of Type 2 diabetes

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance. Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue. In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion. Other potentially important

mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system. (Global status report, 2012)

3.2.8 Diagnosis criteria for Diabetes

A random blood sugar of greater than 11.1 mmol/l (200 mg/dL) in association with typical symptoms or a glycated hemoglobin (HbA_{1c}) of ≥ 48 mmol/mol (≥ 6.5 DCCT %) is another method of diagnosing diabetes. In 2009 an International Expert Committee that included representatives of the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the European Association for the Study of Diabetes (EASD) recommended that a threshold of ≥ 48 mmol/mol (≥ 6.5 DCCT %) should be used to diagnose diabetes. This recommendation was adopted by the American Diabetes Association in 2010. Positive tests should be repeated unless the person presents with typical symptoms and blood sugars >11.1 mmol/l (>200 mg/dl). Threshold for diagnosis of diabetes is based on the relationship between results of glucose tolerance tests, fasting glucose or HbA_{1c} and complications such as retinal problems. A fasting or random blood sugar is preferred over the glucose tolerance test, as they are more convenient for people. HbA_{1c} has the advantages that fasting is not required and results are more stable but has the disadvantage that the test is more costly than measurement of blood glucose. It is estimated that 20% of people with diabetes in the United States do not realize that they have the disease. .(""Diabetes Care" January 2010". American Diabetes Association. Retrieved 2010-01-247) Diabetes mellitus type 2 is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. This is in contrast to diabetes mellitus type 1 in which there is an absolute insulin deficiency due to destruction of [islet cells in the pancreas and gestational diabetes mellitus that is a new onset of high blood sugars associated with pregnancy. Type 1 and type 2 diabetes can typically be distinguished based on the presenting circumstances. If the diagnosis is in doubt antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes, with C-peptide levels normal or high in type 2 diabetes, but low in type 1 diabetes.(""*Diabetes Care*" January 2010". American Diabetes Association. Retrieved 2010-01-247)

Condition	**2 hour glucose**	**Fasting glucose**	**HbA_{1c}**	
Unit	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) &<7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

Table 3.2: Diabetes diagnosis criteria (According to WHO)

Glycated Hemoglobin (HbA1c)

The amount of glucose that is bound to hemoglobin (Of RBC) is called glycated hemoglobin (HbA1c). The level of HbA1c provides information on the average level of glucose in the body over a 90-120 day period of time.

HbA1c	**Comments**
7-8 %	Usually fine
8-10%	Not quite acceptable
>10%	Unacceptable

Table 3.3: Table for HbA1c Level

3.2.9 Clinical presentation and diagnosis of diabetes mellitus

The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin. Every few years, the diabetes community reevaluates the current recommendations for the classification, diagnosis, and screening of diabetes, reflecting new information from research and clinical practice. The body appears unable to sense glucose levels directly, but people with diabetes learn to appreciate when their blood glucose is outside the normal range by indirect cues, such as thirst when the glucose is too high and sweating and palpitations when it is too low. Diabetes may present acutely, with the three classic symptoms of thirst, polyuria and weight loss; even so, clinical recognition may be delayed until the patient is seriously ill. Many forms of diabetes, including type 2, present less dramatically. Increased thirst and polyuria may not be noticed because they develop slowly, and weight loss may be welcomed by those who are trying to diet. People at this stage of diabetes may call on their doctor with a range of non-specific symptoms such as tiredness and loss of energy; alternatively they may come to notice because of acute complications of diabetes, including hyperglycaemia emergencies and infections, or longer term complications including retinopathy, neuropathy, cataracts, cardiovascular or cerebrovascular disease. People with type 2 diabetes may have had the condition for several years before they come to clinical notice, and many countries now have screening policies to allow earlier detection and treatment**.** (ADA, 2010) The American Diabetes Association (ADA) issued diagnostic criteria for diabetes mellitus in 1997, with follow-up in 2003 and 2010 The diagnosis is based on one of four abnormalities: glycated hemoglobin (A1C), fasting plasma glucose (FPG), random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT) Patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are referred to as having increased risk for diabetes or pre diabetes.

Type 2 diabetes is by far the most common type of diabetes in adults (>90 percent) and is characterized by hyperglycemia and variable degrees of insulin deficiency and resistance. The majority of patients are asymptomatic and hyperglycemia is noted on routine laboratory evaluation, prompting further testing. The frequency of symptomatic diabetes has been decreasing in parallel with improved efforts to diagnose diabetes earlier through screening. Classic symptoms of hyperglycemia include polyuria, polydipsia, nocturia, blurred vision and, infrequently, weight loss. These symptoms are often noted only in retrospect, after a blood glucose value has been shown to be elevated. Polyuria occurs when the serum glucose concentration rises significantly above 180 mg/dL (10 mmol/L), exceeding the renal threshold for glucose, which leads to increased urinary glucose excretion. Glycosuria causes osmotic diuresis (ie, polyuria) and hypovolemia, which in turn can lead to polydipsia. Patients who replete their volume losses with concentrated sugar drink, such as non-diet sodas, exacerbate their hyperglycemia and osmotic diuresis.(ADA, 2010) Rarely adults with type 2 diabetes can present with a hyperosmolar hyperglycemic state, characterized by marked hyperglycemia without ketoacidosis, severe dehydration, and obtundation. Diabetic ketoacidosis (DKA) as the presenting symptom of type 2 diabetes is also uncommon in adults

but may occur under certain circumstances (usually severe infection or other illness) and in non-Caucasian ethnic groups. The classic symptoms of diabetes form the triad of thirst, polyuria and weight loss:

Thirst arises as a consequence of dehydration resulting from loss of fluid, salt and other electrolytes in the urine. The acute thirst of type 1 diabetes may be almost unquenchable. Some attempt to slake their thirst with sugar-containing fluids such as Coca-Cola, thus creating a spiral of hyperglycaemia, dehydration and increased craving for fluids.

Polyuria develops when the rate at which glucose enters the proximal tubules of the kidney exceeds the capacity of the tubules to pump glucose back into the circulation. This is achieved by an active transport system which (in most people) can extract almost all glucose below a concentration of ~10 mmol/l (180 mg/dl). Above this point, known as the renal threshold for glucose, glucose spills over into the urine. This exerts an osmotic effect, causing loss of water, salt and other electrolytes from the body, and resulting in dehydration and thirst.

Weight loss is a consequence of calories lost as glucose in the urine, amounting to hundreds of grams of glucose per day in severely uncontrolled diabetes. This is aggravated by insulin deficiency, which accelerates glucose production by the liver while promoting breakdown of fat and protein; the glucose loss and metabolic inefficiency of uncontrolled diabetes thus produces a state of accelerated catabolism.

Other Presentations

Although most people with clinical diabetes will have experienced the classic symptoms described above, these may not be mentioned spontaneously, especially when they have developed slowly and over a long period of time. When this is the case, diabetes may come to attention in many other ways.

Tiredness and lack of energy are common symptoms, but not at all specific for diabetes. Changing glucose levels can produce osmotic changes in the lens of the eye, causing changes in visual accommodation resulting in visual blurring, Another common presentation is with pruritus vulvae (genital itching) in women or balanitis (inflammation of the prepuce) in men. This is due to Candida albicans, a fungal infection which grows more readily in the presence of glucose.(lancet , 1998)

Other presentations represent early complications of diabetes, including characteristic retinal changes spotted by an optician, cataracts, or peripheral neuropathy presenting with numbness and tingling in the feet.

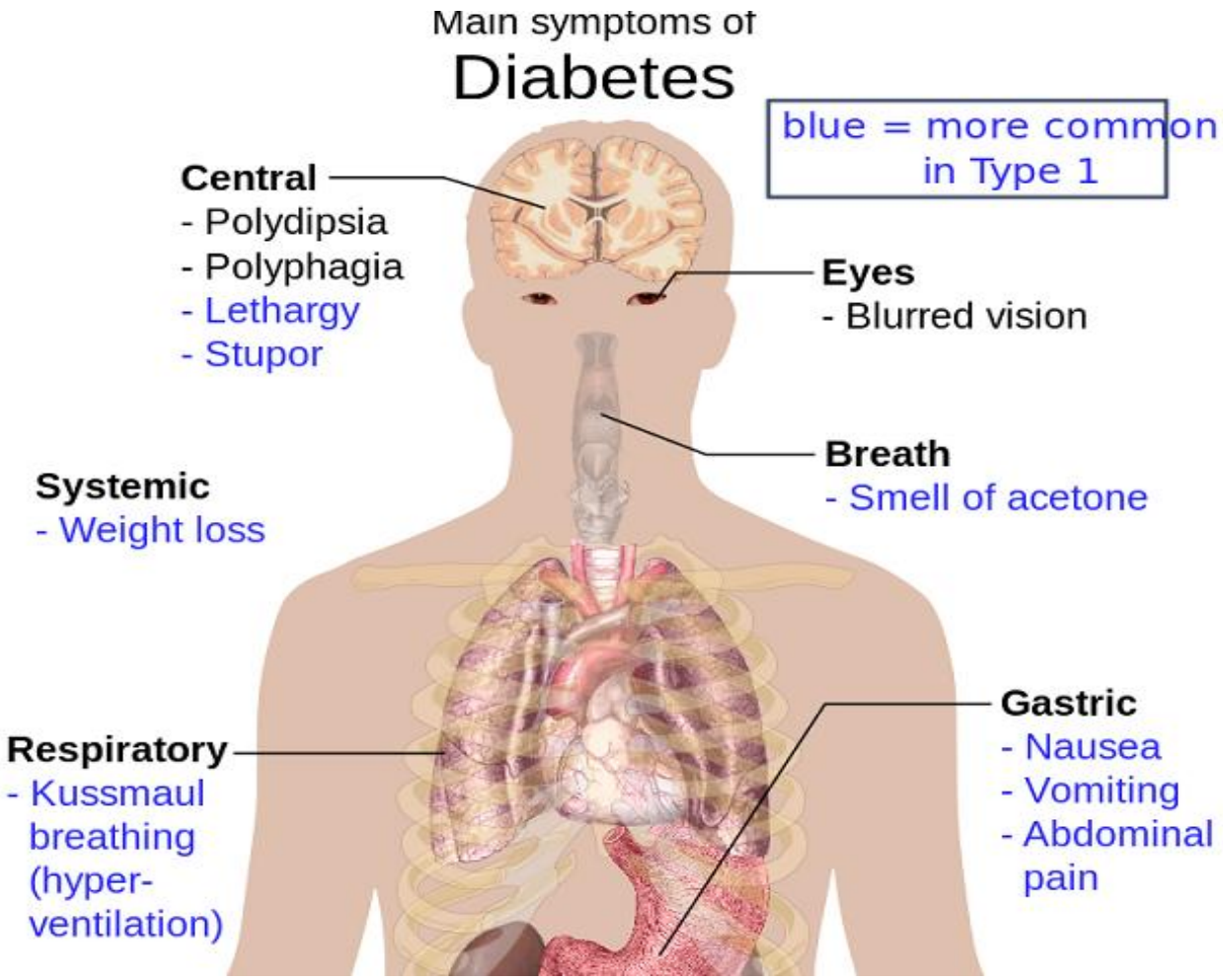


Fig 15: Overview of diabetes symptom

Finally, patients may present late with the metabolic emergencies of diabetic ketoacidosis, typical of type 1 diabetes, or the hyperosmolar non-ketotic state resulting from uncontrolled type 2 diabetes. Other associated emergencies are infections of the foot, skin infections (often staphylococcal), systemic infections (sometimes atypical) or abscesses.(Lancet, 1998)

3.2.10 Clinical Presentation of Diabetes in Children

Children with type 1 diabetes mellitus may have intermittent symptoms for many months before diabetes is recognized, with a typical interval of 4-6 weeks before diagnosis. In previous years a third or more of children presented in diabetic ketoacidosis, but this proportion has fallen markedly with greater awareness of the condition. The importance of early recognition is shown in the observation that children with an affected family member rarely present as an emergency. (Lancet, 1998)

Younger children present more of a diagnostic challenge because they are less able to articulate their symptoms, and may come to medical attention because of failure to thrive or bed-wetting; a higher proportion of young children will end in hospital because of later presentation. Children with classic type 1 diabetes require immediate treatment with insulin. In contrast, children with MODY or early onset type 2 diabetes may have few symptoms at diagnosis. MODY may be recognized because of a strong family history of diabetes, whereas children with type 2 diabetes are typically overweight. Physicians should note that overweight adolescents who appear to have type 2 diabetes may in fact have autoimmune diabetes and be at risk of developing ketoacidosis. Some people refer to this mixed form as "double diabetes".(Lancet, 1998)

3.2.11 Diabetes in Later Life

Hyperglycemia may cause fewer symptoms in older people. The likely reason for this is that the renal threshold for glucose rises with age and declining renal function, so that osmotic symptoms caused by glucose loss in the urine are less prominent. Old people may also have reduced appreciation of thirst. This, combined with renal insufficiency, leaves them at risk of dehydration, especially when the renal threshold is exceeded. Diabetes at every age has the potential to precipitate a metabolic emergency, and type 1 diabetes can and does present with ketoacidosis in very old people.

3.2.12 Symptom

Symptoms of diabetes can be either acute or chronic:

Acute Symptoms

Acute symptoms of diabetes are due to severe hyperglycemia and include polyuria, polydipsia, polyphagia, weight loss and blurred vision. Patients may exhibit impaired growth and increased susceptibility to infections (e.g. recurrent vaginal candidiasis or urinary tract infections). Acute marked hyperglycemia may lead to diabetic ketoacidosis (DKA) in type 1 diabetes or to the hyperglycemic hyper osmolarnonketotic syndrome (HHNS) in type 2 diabetes. These conditions are covered further in the lecture on diabetic complications and discussed during the small group sessions.

Chronic Symptoms

Chronic symptoms of diabetes are due to vascular damage from persistent hyperglycemia. Vascular damage leads to end-organ damage. Other conditions associated with diabetes, such as hypertension, dyslipidemia (as well as smoking) accelerate the development of vascular damage and the chronic complications of diabetes.

IDDM Vs NIDDM

Points	**IDDM**	**NIDDM**
Type	Type 1	Type 2
Age of onset	Juvenile onset usually <30	Adult onset usually >40
Body weight	Normal or low	Obese (50-90)%
Ketonuria	Common	No
Endogenous insulin	Severe deficiency	Moderate deficiency
Insulin resistant	Occasional	Almost always
Islets cell antibodies	Present	Absent
Family history of diabetes	No	Present
Treatment with insulin	Always necessary	Usually not required

Table 3.4: Difference between IDDM and NIDDM

3.2.13 Impact of diabetes:

Over time, diabetes can lead to blindness, kidney failure, and nerve damage. These types of damage are the result of damage to small vessels, referred to as micro vascular disease. Diabetes is also an important factor in accelerating the hardening and narrowing of the arteries (atherosclerosis), leading to strokes, coronary heart disease, and other large blood vessel diseases. This is referred to as macro vascular disease. **.**

3.2.14 Hypoglycemia in diabetes

Intensive glucose control can increase the risk of severe hypoglycemia by three fold .Insulin therapy can influence risks of hypoglycemia in all diabetic patients. Oral medications carry less risk but can contribute to hypoglycemia in type 2 diabetes. Hypoglycemia-associated autonomic failure can occur in all diabetic patients, and it contributes to increased severity and frequency of hypoglycemia. Exercise, gender, sleep, ethanol consumption, and age can influence frequency of hypoglycemia. Patient education, matching medications to patients' lifestyle and frequent glucose monitoring are critical for preventing and treating hypoglycemia. (UK Prospective Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have both clearly demonstrated that intensive control of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) delays the onset and slows the

progression of long-term micro vascular complications such as neuropathy, nephropathy, and retinopathy.1 However, in both T1DM and T2DM, intensive versus conventional glucose control also contributes to a significant increase in severe hypoglycemia. In fact, the DCCT found a three-fold increase in severe hypoglycemia (blood sugar less than 50mg/dL where the patient needed external resuscitative assistance) when hemoglobin A1c (HbA1c) was 7.2% as compared to 9.0%.The rates of severe hypoglycemia in T2DM are much less than those in T1DM.In addition, hypoglycemia contributes to increased morbidity and mortality of diabetes.(Lancet ,1998). The type of insulin treatment can contribute to the incidence of hypoglycemia in T1DM, and although it is less commonly reported, insulin therapy may also contribute to hypoglycemia in T2DM.Oral agents have lower reported rates of hypoglycemia compared with multiple doses of traditional insulin. A patient's gender may also influence the ability to counter regulate in the face of hypoglycemia. It has been clearly demonstrated that healthy young women55-57 and young women with T1DM58 have reduced counter regulatory responses to hypoglycemia compared to men.mia, which supports this hypothesis.65 However, the normal physiologic changes in insulin sensitivity that occur at night, the insulin regimen, and the potential lack of symptomatic and counterregulatory responses during sleep all contribute to the prevalence of nocturnal hypoglycemia. (The Diabetes Control and Complications Trial Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial.) Lancet (1998). (The Diabetes Control and Complications Trial Research Group: Hypoglycaemia in the diabetes control and complication trial ,1997.)

3.2.15 Treatment

Drugs used in diabetes

It should be remembered that control of modifiable cardiovascular risk factors such as lipids and blood pressure are the most important interventions to be made in patients with type II diabetes. Drugs used for the treatment of diabetes are called anti-diabetic drugs. As these types of drugs lower blood glucose level, they are called hypoglycemic agents. [Center for diabetes control and prevention (CDC)] Healthy eating should be tried first, and drug therapy added if glycemic control is unsatisfactory after a 3 month trial of dietary restrictions and an increase in physical activity. (Standards of medical care in diabetes , 2011)

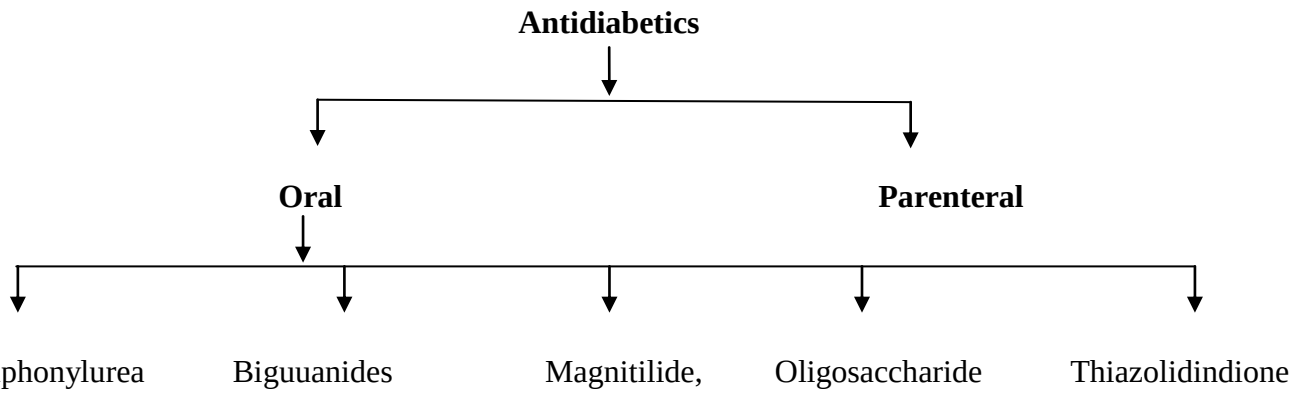
Dual Therapy

For patients who have not reached HbA_{1c} <6.5% (or their agreed target) on metformin monotherapy, add in a sulphonylurea as the standard second line agent. Consider a gliptin (or a glitazone) to metformin if hypoglycaemia on a sulfonylurea is a potential problem, or if a sulphonylurea is not tolerated or contraindicated. A gliptin may be preferable to a glitazone in patients where further weight gain would be problematic, or where a glitazone is contraindicated (e.g. heart failure), not tolerated/effective. Continue either only if 0.7% reduction in HbA1c in 6 months.(.(Standards of medical care in diabetes , 2011)

Triple Therapy

For patients who have not reached HbA_{1c} <7.5% (or their agreed target) on metformin and a sulphonylurea, consider adding a gliptin (or a glitazone). If human insulin likely to be unacceptable or ineffective (because of employment (e.g. HGV drivers), social, recreational or other personal issues, or obesity/metabolic syndrome) consider use of GLP-1 receptor agonist. Continue only if 0.7% reduction in HbA1c in 6 months. Sitagliptin is the only gliptin licensed for use in a triple combination

3.2.16 Different Types of Anti-diabetic Drugs:



Biguanides:

Biguanides reduce absorption of the carbohydrede from the gut and increase the utilization of glucose in peripheral tissue provided insulin in present.

Oral Anti diabetic:

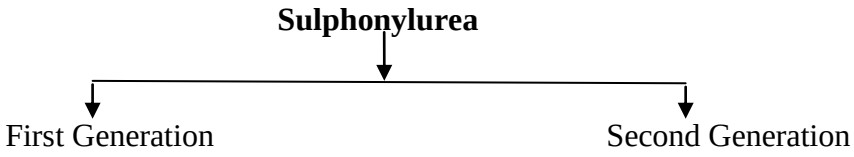
These agents are useful in the treatment of patients who have non-insulin dependent mellitus (NIDDM) but cannot be managed by diet alone. Oral hypoglycemic agents should not be given to patients with type-I diabetes. [http://www.medicalnewstoday.com/info/diabetes, 25.05.14]

Sulphonylurea

The main effect of sulphonylurea is to stimulate the release of insulin from the pancreatic beta cells (Insulin secretagogues), but they also exert extrapancreatic effects. Particularly in reducing the hepatic release of glucose. .[Masharani U. Diabetes mellitus & hypoglycemia. In: McPhee SJ, et al. Current Medical Diagnosis & Treatment 2010. New York, N.Y.:

Examples: Phenformin, Metformin, Buformin Sulphonylureas have two generation. 1st generation drugs are Acetohexamide Carbutamide Chlorpropamide Metahexamide Tolbutamide and Glibenclamide

(Glyburide) Glibornuride Glipizide Gliquidone Glisoxepide Glyclopyramide Glimepiride Gliclazide are second generation of drug.



Example:

First Generation : Tolbutamide, Chlorpamide, Carbutamide, Tolazamide

Second Generation: Gliclazide, Glibenclamide, Glipizide, Glyburide, Glimepiride

Acetohexamide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body use insulin efficiently. The pancreas must produce insulin for this medication to work. For this reason, acetohexamide is not used to treat diabetes mellitus type 1. Acetohexamide should not used in diabetic ketoacidosis. It's FDA pregnancy category is C.Chlorpropamide is a drug in the sulfonylurea class used to treat type 2 diabetes mellitus. It is a long-acting 1st generation sulfonylurea. It has more side effects than other sulfonylureas and its use is no longer recommended. Like other sulfonylureas, chlorpropamide acts to increase the secretion of insulin, so it is only effective in patients who have some pancreatic beta cell function. It can cause relatively long episodes of hypoglycemia; this is one reason why shorter-acting sulfonylureas such as gliclazid or tolbutamide are used instead. (Ref : Zhang, Yifan; Si, (2007). The risk of hypoglycemia makes this drug a poor choice for the elderly and patients with mild to moderate hepatic and renal impairment. Chlorpropamide is also used in partial central diabetes insipidus. Maximal plasma concentrations are reached 3 to 5 hours after quick and nearly complete (>90%) resorption from the gut. Plasma half life is 36 hours; the drug is effective for about 24 hours, longer than other sulfonylureas. More than 99% of chlorpropamide are excreted unchanged via the kidneys. It is first filtrated in the glomeruli , then reabsorbed, and finally secreted into the tubular lumen. Some medical conditions like pregnancy, liver ,heart ,kidney problems may interact with chlorpropamide. This medication will only help lower blood sugar in people whose bodies produce insulin naturally. Chlorpropamide is not used to treat type 1 diabetes (condition in which the body does not produce insulin and, therefore, cannot control the amount of sugar in the blood) or diabetic ketoacidosis (a serious condition that may occur if high blood sugar) is not treated. Tolbutamide is a 1st generation potassium channel blocker. sulfonylurea oral hypoglycemic drug. Mechanism of this drug also same as acetohexamide, or chlorpopamide. Gliclazide was shown to protect human pancreatic beta-cells from hyperglycemia-induced apoptosis. (British Journal of Clinical Pharmacology) .It was also shown to have an antiatherogenic effect. Gliclazide is used for control of hyperglycemia in gliclazide-responsive diabetes mellitus of stable, mild, non-ketosis prone, type 2 diabetes. It is used when diabetes cannot be controlled by proper dietary management and exercise

or when insulin therapy is not appropriate. Gliclazide selectively binds to sulfonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonylurea receptors (SUR-2A) in the heart.(This binding effectively closes the K+ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release. ("Type 1 & Type 2 Diabetes Mellitus". Retrieved 2008-08-04). (British Journal of Clinical Pharmacology)

Biguanides

Biguanides have been used in treatment of diabetes mellitus for over 30 years now**.** The main biguanides, metformin and phenformin, were introduced in 1957 as oral glucose-lowering agents to treat non-insulin-dependent diabetes mellitus (NIDDM). (Bailey CJ *et al* ,1992) Phenformin was withdrawn in many countries because of an association with lactic acidosis, but metformin does not have the same risk if appropriately prescribed. Metformin is now widely used as a monotherapy and in combination with a sulfonylurea. Unlike sulfonylureas, metformin is not bound to plasma proteins, is not metabolized, and is eliminated rapidly by the kidney. The glucose-lowering effect occurs without stimulation of insulin secretion and results mainly from increased glucose utilization. The presence of insulin is required, and enhancement of insulin action at the post receptor level occurs in peripheral tissues such as muscle. In peripheral tissues metformin increases insulin-mediated glucose uptake and oxidative metabolism. Metformin also increases glucose utilization by the intestine, primarily via non oxidative metabolism. (Bailey CJ *et al* ,1992) The extra lactate produced is largely extracted by the liver and serves as a substrate to sustain gluconeogenesis. This limits the extent to which metformin reduces hepatic glucose production but provides a safeguard against excessive glucose lowering. Because metformin does not cause clinical hypoglycemia, it is actually an antihyperglycemic drug. It does not cause weight gain, it helps combat hypertriglyceridemia, and Metformin offers a useful treatment for insulin-resistant overweight NIDDM patients. Biguanides lower blood sugar by: Decreasing the amount of sugar produced by the liver, increasing the amount of sugar absorbed by muscle cells, decreasing the body's need for insulin. Biguanides do not increase pancreatic insulin secretion, they are referred to as antihyperglycemic agents, as opposed to hypoglycemic agents. Biguanides reduce hyperglycemia by increasing, insulin sensitivity, decreasing glucose absorption, and inhibiting hepatic gluconeogenesis. Advantages of metformin include achieving glycemic control without exacerbating weight gain or hyperinsulinemia and beneficially affecting serum cholesterol concentrations. Metformin should be avoided in those with severely compromised renal function (creatinine cl (Bailey CJ etal ,1992)earance < 30 ml/min), acute/decompensated heart failure, severe liver disease and for 48 hours after the use of iodinated contrast dyes due to the risk of lactic acidosis. Lower doses should be used in the elderly and those with decreased renal function. Metformin decreases fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels, which are reflective of the last 8-10 weeks of glucose control. Metformin may also have a positive effect on lipid levels. (Bailey CJ *et al*, 1992)

Magnitilide Derivatives:

These drugs are oral prandial glucose regulators. Repaglinide directly stimulates endogenous insulin secretion and is taken immediately before food.

Example: Repaglinid

Thiazolidinedione:

These level drugs (Also called TZD drugs, glitazone') work by enhancing the action of endogenouse insulin. Insulin sensitivity (mainly in adipose tissue) is improved only in patients with insulin resistance; plasma insulin concentrations are increased and hypoglycemia is not a problems. [Masharani U. Diabetes mellitus & hypoglycemia. In: McPhee SJ, et al. Current Medical Diagnosis & Treatment 2010. New York, N.Y]

Example: Troglitazone, Pioglitazone, Rosiglitazone.

Oligosaccharide

In the class of oligosaccharide, acarbose or maglitol is available and is taken with each meal. Both lower and post-prandial blood glucose and modestly improve overall glycemic condition. They can be combined with a sulphonylurea. The main side effects are flatulence, abdominal bloating and diarrhea.[Masharani U. Diabetes mellitus & hypoglycemia. In: McPhee SJ, et al. Current Medical Diagnosis & Treatment 2010. New York, N.Y]

Example: Acarbose

Clinical Use of Oral Antidiabetic Drugs

Oral anti diabetic drugs are used to control hyperglycemia in the following ways-

1. As monotherapy, as an adjunct to died or exercise to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactory managed on diet or exercise alone.
2. Insulin resistance case. [Kasper,2005]

Insulin Therapy

Insulin therapy is a critical part of treatment for those with type 1 diabetes and also for many with type 2 diabetes. The goal of insulin therapy is to maintain blood sugar levels within your target range. Insulin is usually administered in the fat under your skin using a syringe, insulin pen or insulin pump. There are different types of insulin depending on how quickly they work, when they peak, and how long they last.

Insulin cannot be taken as a pill because it would be broken down during digestion just like the protein in food. It must be injected into the fat under skin for it to get into your blood.

Characteristics of Insulin

Insulin has 3 characteristics:

- Onset is the length of time before insulin reaches the bloodstream and begins lowering blood glucose.
- Peak time is the time during which insulin is at maximum strength in terms of lowering blood glucose.
- Duration is how long insulin continues to lower blood glucose

Insulin Type	**Onset**	**Peak**	**Duration**
Rapid Acting	15 Min	30-90 Min	3 to 5 hours
Short Acting	30 to 60 minutes	2 to 4 hours	5 to 8 hours
Intermediate Acting	1 to 3 hours	8 hours	12 to 16 hours
Long Acting	1 hour	No clear peak	20 to 26 hours

In some cases, pre-mixed insulin a combination of specific proportions of intermediate-acting and short- or rapid-acting insulin in one bottle or insulin pen may be an option. Insulin therapy is recommended for patients with type 2 diabetes mellitus and an initial A1C level greater than 9 percent, or if diabetes is uncontrolled despite optimal oral glycemic therapy. Insulin therapy may be initiated as augmentation, starting at 0.3 unit per kg, or as replacement, starting at 0.6 to 1.0 unit per kg. When using replacement therapy, 50 percent of the total daily insulin dose is given as basal, and 50 percent as bolus, divided up before breakfast, lunch, and dinner. Augmentation therapy can include basal or bolus insulin. Replacement therapy includes basal-bolus insulin and correction or premixed insulin. Glucose control, adverse effects, cost, adherence, and quality of life need to be considered when choosing therapy. Metformin should be continued if possible because it is proven to reduce all-cause mortality and cardiovascular events in overweight patients with diabetes. In a study comparing premixed, bolus, and basal insulin, hypoglycemia was more common with premixed and bolus insulin, and weight gain was

more common with bolus insulin. Titration of insulin over time is critical to improving glycemic control and preventing diabetes-related complications. Insulin is available in different strengths; the most common is U-100 .Rapid acting and short acting insulins are dispensed as clear solution at neural pH and contain small amount of zinc to improve their stability and shelflife. All other commercial insulin have been modified to provide prolonged action and are with the exception of insulin glargine, dispensed as turbid suspension at neutral pH with either protamine in phosphate buffer or varying concentration of zinc in acetate buffer. Insulin glargine is only soluble long acting insulin. The goal of subcutaneous insulin therapy is to replace the normal basal (overnight, fasting, and between meal) as well as prandial (mealtime) insulin. Current regimens generally use intermediate or long acting or short acting insulin to meet the mealtime requirement .An exact reproduction of the normal glycemic profile is technically not possible because of the limitation inherent in subcutaneous administration of insulin. The most sophisticated insulin regimens delivers rapid –acting insulin through a continuous subcutaneous insulin infusion device; alternative intensive regimen referred as multiple daily injection (MDI) use long acting ,short acting insulin. Rapid insulins, which are a type of insulin known as analogue insulins, can either be injected or delivered via an insulin pump.

Rapid acting insulins are usually taken just before or with a meal. They act very quickly to minimise the rise in blood sugar which follows eating. Rapid acting insulins are commonly prescribed to people with type 1 diabetes, however, there may be times when they can be prescribed for type 2 diabetes as well. begins to work about 15 minutes after injection, peaks in about 1 hour, and continues to work for 2 to 4 hours. Two rapid acting insulin analogs are commercially available :Insulinlispro and insulin aspart The rapid acting insulin permit more physiologic prandial insulin replacement because their rapid onset and early peak action more closely mimics normal endogenous prandial insulin secretion than does regular insulin. Their duration of action is 3 to 5 hours which decreases the risk of late post meal hypoglycemia. They have the lowest variability of absorption of all available insulin preparation. Insulin lispro is example of rapid acting insulin. Insulin lispro is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli. Insulin lispro differs from human insulin in that the amino acidprolineat position B28 is replaced by lysine and the lysine in position B29 is replaced by prolineIt is faster-acting than soluble insulin, and is therefore extremely useful around mealtimes. It may be combined with intermediate or longer-acting insulin for a longer period of blood glucose maintenance. Insulin aspart. is extremely fast-acting, and works rapidly to normalize blood sugar levels. It typically begins working after 10-20 minutes, and will last for between 3 and 5 hours. It may be injected before a meal, and sometimes immediately after, to ensure strict control of post-prandial levels. Insulin lispro is used to treat type 1 diabetes (condition in which the body does not produce insulin and therefore cannot control the amount of sugar in the blood). It is also used to treat people with type 2 diabetes (condition in which the body does not use insulin normally and therefore cannot control the amount of sugar in the blood) who need insulin to control their diabetes. In patients with type 1 diabetes, insulin lispro is always used with another type of insulin, unless it is used in an external insulin pump. In patients with type 2 diabetes, insulin lispro may be used with another type of insulin or with oral medication(s) for diabetes. Insulin lispro is a short-acting, man-made version of human insulin. Insulin lispro works by replacing the insulin that is normally produced by the body and by helping move sugar from the blood into other body

tissues where it is used for energy. It also stops the liver from producing more sugar. (The Basis and clinical pharmacology, Lippintcott)

Chapter Four

Literature Review

Obesity, Fat Distribution, and Weight Gain as Risk Factors for Clinical Diabetes in Men

Diabetes Care, 17(9): 961-969, 1994

A study Performed by June M Chan, Eric B Rimm *et al* on Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men and their objective is to investigate the relation between obesity, fat distribution, and weight gain through adulthood and the risk of non-insulin-dependent diabetes mellitus (NIDDM). They analyzed data from a cohort of 51,529 U.S. male health professionals, 40-75 years of age in 1986, who completed biennial questionnaires sent out in 1986, 1988, 1990, and 1992. During 5 years of follow-up (1987-1992), 272 cases of NIDDM were diagnosed among men without a history of diabetes, heart disease, and cancer in 1986 and who provided complete health information. Relative risks (RRs) associated with different anthropometries measures were calculated controlling for age, and multivariate RRs were calculated controlling for smoking, family history of diabetes, and age and finally they found a strong positive association between overall obesity as measured by body mass index (BMI) and risk of diabetes. Men with a BMI of ≥35 kg/m^2 had a multivariate RR of 42.1 (95% confidence interval [CI] 22.0-80.6) compared with men with a BMI <23.0 kg/m^2. BMI at age 21 and absolute weight gain throughout adulthood were also significant independent risk factors for diabetes. Fat distribution, measured by waist-to-hip ratio (WHR), was a good predictor of diabetes only among the top 5%, while waist circumference was positively associated with the risk of diabetes among the top 20% of the cohort. These data suggest that waist circumference may be a better indicator than WHR of the relationship between abdominal adiposity and risk of diabetes. Although early obesity, absolute weight gain throughout adulthood, and waist circumference were good predictors of diabetes, attained BMI was the dominant risk factor for NIDDM; even men of average relative weight had significantly elevated RRs. (June M Chan, 1994)

Lower educational level is a predictor of incident type 2 diabetes in European countries

International Journal of Epidemiology ;41:1162–1173,2012

Carlotta Sacerdote, Fulvio Ricceri *et al* studied on Lower educational level is a predictor of incident type 2 diabetes in European countries: The EPIC-InterAct study .They performed a case-cohort study in eight Western European countries nested in the EPIC study (n¼340 234, 3.99 million person years of follow-up). A random sub-cohort of 16 835 individuals and a total of 12 403 incident cases of T2DM were identified. Crude and multivariate-adjusted hazard ratios (HR) were estimated for each country and pooled across countries using meta-analytical methods. Age-, gender- and country-specific relative indices of inequality (RII) were used as the measure of educational level and RII tertiles were analysed. They compared with participants with a high educational level (RII tertile 1), participants with a low educational level (RII tertil3) had a higher risk of T2DM [HR: 1.77, 95% confidence interval (CI): 1.69–1.85; P-trend<0.01]. The HRs adjusted for physical activity, smoking status and propensity score according to macronutrient intake were very similar to the crude HR (adjusted HR: 1.67, 95% CI: 1.52–1.83 in men; HR: 1.88, 95% CI: 1.73–2.05 in women). The HRs was attenuated only when they were

further adjusted for BMI. (BMI-adjusted HR: 1.36, 95% CI: 1.23–1.51 in men; HR: 1.32, 95% CI: 1.20–1.45 in women). Their study demonstrates the inequalities in the risk of T2DM in Western European countries, with an inverse relationship between educational level and risk of T2DM that is only partially explained by variations in BMI. (Carlotta Sacerdote, 2012)

Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C.

Journal Of Hepatology, Volume 35, Issue 2, Pages 279–283,2001

Jean- Michel Petit, Jean Baptiste *et al* Bour work on Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. Their aim was to investigate the host and viral specific factors associated with diabetes mellitus (DM) and insulin resistance in chronic hepatitis C patients. One hundred and three hepatitis C virus (HCV)-infected were studied to assess the effects of HCV genotype, hepatic iron content, steatosis, hepatic fibrosis, body mass index (BMI) and family history of DM on the occurrence of DM. Insulin resistance (HOMA IR) was studied in 81 non-diabetic patients to determine the mechanism associated with insulin resistance in this subgroup. Sixteen of the 123 were diabetic (13.0%). The variables predictive of DM were METAVIR fibrosis score 4 (OR, 13.16; *P*=0.012), family history of diabetes (OR, 16.2; *P*=0.0023), BMI (OR, 1.37; *P*=0.017) and age (OR, 1.09; *P*=0.002). In non-diabetic HCV-infected patients, HOMA-IR of METAVIR fibrosis score 0 and 1 patients were significantly different than score 2 and score 3/4 patients. Their findings indicate that older age, obesity, severe liver fibrosis and family history of diabetes help identify those HCV patients who might have potential risk factors for development of DM. They observed that insulin resistance in non-diabetic HCV-infected patients was related to grading of liver fibrosis, and occurs already at an early stage in the course of HCV infection. (Jean- Michel Petit, 2001)

Perinatal Risk Factors for Diabetes in Later Life

Diabetes vol. 58 no. 3- 523-526, 2009

Magnus Kaijser *et al* studied on Perinatal Risk Factors for Diabetes in Later Life and they studied that Low birth weight is consistently associated with an increased risk of type 2 diabetes in adulthood, but the individual contributions from poor fet al growth and preterm birth are not known and investigated the significance of these two factors separately. They identified a cohort of subjects born preterm or with low birth weight at term at four major delivery units in Sweden from 1925 through 1949. A comparison cohort of subjects was identified from the same source population. Of 6,425 subjects in all, 2,931 were born at <37 weeks of gestation and 2,176 had a birth weight <2,500 g. Disease occurrences among participants were assessed through nationwide hospital registers from 1987 through 2006. During follow-up, there were 508 cases of diabetes. Low birth weight was strongly negatively associated with risk of diabetes (*P* for trend <0.0001). Both short gestational duration and poor fet al growth were associated with later diabetes (*P* for trend <0.0001 and <0.0004, respectively). Very preterm birth (≤32 weeks of gestation at birth) was associated with a hazard ratio (HR) of 1.67 (95% CI 1.33–2.11) compared with term birth. Birth weights below 2 SDs of mean birth weight for gestational age were associated with an HR of 1.76 (1.30–2.38) compared with birth weights between the mean weight and the weight at 1 SD above the

mean. Their results suggest that the association between low birth weight and diabetes is due to factors associated with both poor fet al growth and short gestational age. (Magnus Kaijser, 2009)

Prevalence of Diabetes and Its Risk Factors in Chinese population

Diabetes Care, 20(11), 1997

Xiao-Ren Pan, Wen-Ying Yang, *et al* works on Prevalence of Diabetes and Its Risk Factors in Chinese population. This study as a population-based cross-sectional study of 224,251 residents aged 25–64 years in 19 provinces and areas, including cities and rural areas of the north, south, east, and middle part of China. Using the 1985 World Health Organization criteria, the prevalence of diabetes and IGT was 2.5 and 3.2%, respectively, in 213,515 subjects aged 25–64 years. Two thirds (70.3%) of the cases had newly recognized diabetes. The prevalence of diabetes in China is about three times higher than it was 10 years ago. On average, subjects with diabetes are older, have higher personal annual incomes, and more often have a family history of diabetes. They also have higher mean BMI, waist-to-hip ratio (WHR), systolic blood pressure, diastolic blood pressure, and a greater prevalence of hypertension. They perform less physical activity and have less education than people with normal oral glucose tolerance test results. Multiple logistic stepwise regression analysis shows that age, BMI (or WHR), family history of diabetes, hypertension, less physical activity, and higher annual income are independent risk factors of NIDDM, and that low education is also an independent risk factor of NIDDM in people with higher personal annual income. The prevalence of diabetes in China is increasing with economic development and changes from traditional to modernized lifestyle, especially where people had lower level of education and socioeconomic development. Therefore, Chinese people should attempt to retain certain features of their traditional lifestyle (physical activity, healthy food, moderate body weight). Increased knowledge of risk factors for diabetes may help to prevent a further rapid increase in the prevalence of diabetes in China.(Xiao-Ren Pan, 1969)

Risk factors for Type 2 (non-insulin-dependent) diabetes mellitus

Dibetologia, Volume 31, Issue 11, pp798-805,1988)

L. -O. Ohlson *et al* studied on Risk factors for Type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913 and they report that antecedents of Type 2 (non-insulin-dependent) diabetes mellitus in a homogeneous sample of randomly selected 54-year-old men from an urban Swedish population with a diabetes incidence of 6.1% during 13.5 years of follow-up. The increased risk leading to diabetes for those in the top quintile compared to the lowest quintile of the distribution of statistically significant risk factors were: body mass index = 21.7, triglycerides = 13.5, waist-to-hip circumference ratio = 9.6, diastolic blood pressure = 6.7, uric acid = 5.8, glutamic pyruvic transaminase = 3.9, bilirubin = 3.2, blood glucose = 2.7, lactate = 2.4 and glutamic oxaloacetic transaminase = 2.0. Those with a positive family history of diabetes had 2.4-fold higher risk for developing diabetes than those without such a history. In a multivariate analysis glutamic pyruvic transaminase, blood glucose, body mass index, bilirubin, systolic blood pressure, uric acid and a family history of diabetes were all significantly associated with the development of diabetes. Their study demonstrates the great importance of adiposity and body fat distribution for the risk of diabetes. A number of established risk factors for coronary heart disease are risk factors for diabetes as well.

Disturbed liver function and increased levels of lactate are early risk factors for diabetes presumably indicators of the presence of impaired glucose tolerance and/or hyper insulinaemia. (L. -O. Ohlson ,1988)

Risk factors for diabetes in three Pacific populations

Am J Epidemiol 119: 396–409, 1994

Hilary King *et al* surveyed on Risk factors for diabetes in three Pacific populations and investigate the association between the prevalence of diabetes and three suspected risk factors—overweight, physical inactivity, and urbanization—has been studied in 5519 subjects from three Pacific populations: Melanesians and migrant Asian indians in Fiji in 1980, and Micronesians in the Republic of Kiribati (formerly the Gilbert Islands). In 1981, associations were found to be inconsistent between populations, and between the sexes within populations. In some cases, overweight was strongly associated with prevalence in others, the principal variable associated with diabetes appeared to be physical inactivity. More than one factor was associated with increased risk in Micronesians, and some evidence of interaction between factors also emerged. Although longitudinal studies will be required for the complete elucidation of risk factors for diabetes, these findings suggest that risk factors may be heterogeneous in their effect upon different populations, and that an assessment of risk variables operating in a given target community may be of value in the initial phase of a diabetes prevention or control program. (King, 1984;)

Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey

Dibetologia October 2001, Volume 44, Issue 10, pp 1221-1231

B.C.K choi and F. Shi studied on Risk factors for diabetes mellitus by age and sex and their study was based on the Canadian 1996–1997 National Population Health Survey which comprised 69,494 participants aged 12 years and over. The prevalence of diabetes mellitus was analyzed in relation to age, sex, body mass index, overweight status, energy expenditure, physical activity, smoking, drinking, income, marital status, education and rural or urban residence. The prevalence of diabetes increased with age and body mass index and increased inversely with energy expenditure in both males and females. Current and former smokers were associated with a higher prevalence of diabetes. No effect was observed in regular or former drinkers. Prevalence of diabetes increased inversely with income, especially among women. Women who were single and 35 to 64 years old had a higher prevalence of diabetes than women of the same age who were married. The prevalence of diabetes was not found to be related to the level of education. Urban or rural residence was not found to have an effect on the prevalence of diabetes. Women and men of all ages should avoid becoming overweight, by maintaining their body mass index below 25 kg/m^2 and 27 kg/m^2, respectively. They should maintain a moderate level of physical activity. Patients with diabetes should give up smoking completely. Diabetes prevention and control strategies should be targeted for women in low income groups (B.C.K choi, 2001)

Studied on Olive oil consumption and risk of type 2 diabetes in US women

Guasch-Ferré M *et al* studied on Olive oil consumption and risk of type 2 diabetes in US women. He suggested that olive oil has been shown to improve various cardio metabolic risk factors and association

between olive oil intake and type 2 diabetes (T2D) has never been evaluated in the US population. He followed 59,930 women aged (37-65) years from the Nurses' Health Study (NHS) and(85,157)years women aged 26-45 years from the NHS II who were free of diabetes, cardiovascular disease, and cancer at baseline. They assessed diet by validated food-frequency questionnaires, and data were updated every 4years. Incident cases of T2D were identified through self-report and confirmed by supplementary questionnaires. After 22 y of follow-up, he documented 5738 and 3914 incident cases of T2D in the NHS and NHS II, respectively. With the use of Cox regression models with repeated measurements of diet and multivariate adjustment for major lifestyle and dietary factors, the pooled HR (95% CI) of T2D in those who consumed >1 tablespoon (>8 g) of total olive oil per day compared with those who never consumed olive oil was 0.90 (0.82, 0.99). The corresponding HRs (95% CIs) were 0.95 (0.87, 1.04) for salad dressing olive oil and 0.85 (0.74, 0.98) for olive oil added to food or bread. They estimated that substituting olive oil (8 g/d) for stick margarine, butter, or mayonnaise was associated with 5%, 8%, and 15% lower risk of T2D, respectively, in the pooled analysis of both cohorts.

Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study

Clinical Endocrinology 71, 679–685, 2009

Nam H. Cho *et al* studied on Cigarette smoking is an independent risk factor for type 2 diabetes and investigate that there is an association between smoking and its additive effects with insulin resistance and b-cell function on the incidence of type 2 diabetes in a prospective population-based cohort study. 10 038 subjects were recruited from rural and urban areas for this study. All subjects underwent 75 g oral glucose tolerance tests and full biochemical assessments at baseline
and during 4-year follow-up period. The final analysis was limited to 4041 men due to the low smoking rates in women. The ex- and heavy current smokers had the highest incidence of diabetes of 12Æ5% and 11Æ1% respectively, compared with never-smokers (7Æ9%) during 4 years. After multivariate adjustment by Cox-proportional hazard model, ex- and current smokers reveal a relative risk of 1Æ60 (95% CI: 1Æ07–2Æ39), 2Æ06 (1Æ35–3Æ16, for <20 cigarettes/day) and 2Æ41 (1Æ48–3Æ93, for ‡20 cigarettes/day) respectively compared with never smokers. The risk of new onset diabetes was the highest in those with low homeostasis model assessment for beta cell function (HOMA-b) and high homeostasis model assessment for insulin resistance (HOMA-IR) group in both smokers and never smokers. They concluded that Smoking is an independent risk factor for type 2 diabetes mellitus and showed synergistic interaction with the status of low insulin secretion and high insulin resistance for developing Diabetes. (Nam H. Cho*, Juliana C. N. Chan†, Hak Chul Jang Soo Lim: Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study, *Clinical Endocrinology* (2009) 71, 679–685)

Risk Factor for Type 2 Diabetes: Results from a Long-Term Prospective Study

Diabetes 61:2369–2374, 2012

Alessandra Gambineri *et al* examined that Polycystic ovary syndrome (PCOS) recently has been identified as a risk factor associated with type 2 diabetes. However, the evidence derives from cross-sectional observational studies, retrospective studies, or short-term prospective studies. This long-term prospective study of a large cohort of women with PCOS, followed from youth to middle age, aimed at

estimating, for the first time, the incidence and potential predictors of type 2 diabetes in this population. A total of 255 women with PCOS were followed for at least 10 years (mean follow-up 16.9 years). Six women were patients with diabetes at baseline, and another 42 women developed type 2 diabetes during the follow-up. The incidence rate of type 2 diabetes in the study population was 1.05 per 100 person-years. The age standardized prevalence of diabetes at the end of follow-up was 39.3%, which is significantly higher with respect to that of the general Italian female population of a similar age (5.8%). The likelihood of developing type 2 diabetes significantly increased as BMI, fasting glucose, and glucose area under the curve at baseline increased and significantly decreased as sex hormone–binding globulin (SHBG) levels at follow-up increased. This study demonstrates that the risk of type 2 diabetes is markedly elevated in middle-aged women with PCOS and suggests including BMI, glucose, and SHBG-circulating levels in the risk stratification. (Alessandra Gambineri, 2012)

Population-Based Incidence Rates and Risk Factors for Type 2 Diabetes in White Individuals

Diabetes 53:1782–1789, 2004

Enzo Bonora Stefan Kiechl *et al* studied on Population-based incidence rates and risk factors for Type 2 Diabetes in White Individuals, they found that incidence rates and risk factors for type 2 diabetes in low-risk populations are not well documented. They investigated these in white individuals who were aged 40–79 years and from the population of Bruneck, Italy. Of an age- and -stratified random sample of 1,000 individuals who were identified in 1990, 919 underwent an oral glucose tolerance test (OGTT) and an assessment of physiological risk factors for diabetes, including insulin resistance (homeostasis model assessment, HOMA-IR), and post challenge insulin response (Sluiter's Index). Diabetes at baseline by fasting or 2-h OGTT plasma glucose (World Health Organization criteria, 82) was excluded, leaving 837 individuals who were followed for 10 years. Incident cases of diabetes were ascertained by confirmed diabetes treatment or a fasting glucose >7.0 mmol/l. At follow-up, 64 individuals had developed diabetes, corresponding to a population-standardized incidence rate of 7.6 per 1,000 person-years. Sex and age-adjusted incidence rates were elevated 11-fold in individuals with impaired fasting glucose at baseline, 4-fold in those with impaired glucose tolerance, 3-fold in overweight individuals, 10-fold in obese individuals, and 2-fold in individuals with dyslipidemia or hypertension. Incidence rates increased with increasing HOMA-IR and decreasing Sluiter's Index. As compared with normal insulin sensitivity and normal insulin response, individuals low insulin sensitivity and low insulin response had a seven fold higher risk of diabetes. Baseline impaired fasting glucose, BMI, HOMA-IR, and Sluiter's Index were the independent predictors of incident diabetes in multivariate analyses. They conclude that 1% of European white individuals aged 40–79 years develop type 2 diabetes annually and that "sub diabetic" hyperglycemia, obesity, insulin resistance, and impaired insulin response to glucose are independent predictors of diabetes. (Enzo Bonora, 2004)

Dairy Consumption, Type 2 Diabetes, and Changes in Cardio metabolic Traits: A Prospective Cohort Study of Middle-Aged and Older Chinese in Beijing and Shanghai

Diabetes Care 2014; 37:56–63

Geng Zong, Qi Sun, *et al* works on Risk of type 2 diabetes after diary consumption. 2,091middle-aged and older Chinese men and women were recruited and followed for 6 years. Baseline dairy consumption was assessed by a 74-item food frequency questionnaire. Erythrocyte fatty acids were analyzed by gas chromatography coupled with flame ion detector. Cardio metabolic traits were measured at both baseline and follow-up visits. Only 1,202 (57.5%) participants reported any dairy consumption, with a median intake of 0.89 (interquartile range 0.19–1.03) serving/day. Compared with non-consumers, the relative risks (RRs) of type 2 diabetes among those having 0.5–1 serving/day and >1 serving/day were 0.70 (95% CI 0.55–0.88) and 0.65 (0.49–0.85), respectively, after multivariate adjustment (Ptrend < 0.001), which were attenuated by further adjusting for changes in glucose during follow-up (Ptrend = 0.07). Total dairy consumption was associated with favorable changes in glucose, waist circumference, BMI, diastolic blood pressure (all Ptrend < 0.05), and systolic blood pressure (Ptrend = 0.05) after multivariate adjustment, including baseline values of dependent variables. Erythrocyte trans-18:1 isomers were significantly correlated with total dairy consumption (rs = 0.37, Ptrend < 0.001), and these dairy food biomarkers were associated with a lower risk of type 2 diabetes. The RR of type 2 diabetes comparing extreme quartiles of trans-18:1 isomers was 0.82 (0.65–1.04, Ptrend = 0.02), which was attenuated after adjustment for dairy consumption (Ptrend = 0.15). They concluded that dairy consumption was associated with a significantly lower risk of type 2 diabetes and favorable changes of cardio metabolic traits in Chinese.(Geng Zong, 2014)

Diet Soda Intake and Risk of Incident Metabolic Syndrome and Type 2 Diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA)

Diabetes Care 32:688–694, 2009

Jenifer A. Youfa Wang *et al studied on* diet soda consumption and risk of incident metabolic syndrome, its components, and type 2 diabetes in the ulti-ethnic study of atherosclerosis. Diet soda consumption was assessed by food frequency questionnaire at baseline (2000–2002). Incident type 2 diabetes was identified at three follow-up examinations (2002–2003, 2004–2005, and 2005–2007) as fasting glucose _126 mg/dl, self-reported type 2 diabetes, or use of diabetes medication. Metabolic syndrome (and components) was defined by National Cholesterol Education Program Adult Treatment Panel III criteria. Hazard ratios (HRs) with 95% CI for type 2 diabetes, metabolic syndrome, and metabolic syndrome components were estimated, adjusting for demographic, lifestyle, and dietary confounders. At least daily consumption of diet soda was associated with a 36% greater relative risk of incident metabolic syndrome and a 67% greater relative risk of incident type 2 diabetes compared with non consumption (HR 1.36 [95% CI 1.11–1.66] for metabolic syndrome and 1.67 [1.27–2.20] for type 2 diabetes). Of metabolic syndrome components, only high waist circumference (men_102 cm and women_88 cm) and high fasting glucose (_100 mg/dl) were prospectively associated with diet soda consumption. Associations between diet soda consumption and type 2 diabetes were independent of baseline measures of adiposity or change. Although these observational data cannot establish causality, consumption of diet soda at least daily was associated with significantly greater risks of select incident metabolic syndrome components and type 2

diabetes in these measures, whereas associations between diet soda and metabolic syndrome were not independent of these factors. (Jennifer A, 2009)

Sitting Time and Waist Circumference Are Associated With Glycemia in U.K. South Asians

Diabetes Care 34:1214–1218, 2011

Jason M.R gill, PHD Raj bhopal, MB, CHB *et al* investigate the independent contributions of waist circumference, physical activity, and sedentary behavior on glycaemia in South Asians living in Scotland. Participants of this study were 1,228 (523 men and 705 women) adults of Indian or Pakistani origin screened for the Prevention of Type 2 Diabetes and Obesity in South Asians (PODOSA) trial. All undertook an oral glucose tolerance test, had physical activity and sitting time assessed by International Physical Activity Questionnaire, and had waist circumference measured. Mean 6SD age and waist circumference were 49.8610.1 years and 99.2610.2cm, respectively. One hundred ninety-one participants had impaired fasting glycaemia or impaired glucose tolerance, and 97 had possible type 2 diabetes. In multivariate regression analysis, age (0.012 mmol z L21 z year21 [95%CI 0.006–0.017]) and waist circumference (0.018mmol z L21 z cm21 [0.012–0.024]) were significantly independently associated with fasting glucose concentration, and age (0.032 mmol z L21 z year21 [0.016–0.049]), waist (0.057 mmol 0.040–0.074]), and sitting time (0.097 mmol z L21 z h21 z day21 [0.036–0.158]) were significantly independently associated with 2-h glucose concentration. Vigorous activity time had a borderline significant association with 2-h glucose concentration (20.819 mmol [21.672 to 0.034]) in the multivariate model .These data highlight an important relationship between sitting time and 2-h glucose levels in U.K. South Asians, independent of physical activity and waist circumference. Although the data are cross-sectional and thus do not permit firm conclusions about causality to be drawn, the results suggest that further study investigating the effects of sitting time on glycemia and other aspects of metabolic risk in South Asian populations is warranted. (Jason M.,2011)

Low Sex-Hormone-Binding Globulin Concentration as Independent Risk Factor for Development of NIDDM 12-Yr Follow-Up of Population Study of Women in Gothenburg, Sweden

Diabetes 40:123-28, 1991

In 1991 Goran Lindsted, Perarne Lundberg *et al* Goran Lindsted, Perarne Lundberg *et al* published a report that contain risk factors of non insulin dependent diabetes mellitus (NIDDM) due to Low Sex-Hormone-Binding Globulin Concentration. myocardial infarction, stroke, and premature death in a prospective study of 1462 randomly selected women, aged 38-60 yr, over 12 yr of observation. In multivariate analysis, taking only age into consideration as a confounding factor, low initial concentration of SHBG was significantly correlated to the incidence of NIDDM and stroke, and high initial concentration of CBG was correlated to the incidence of NIDDM. There were also significant correlations between SHBG and CBG concentrations on one hand and possible risk factors for the end points studied, such as serum triglycerides, serum cholesterol, fasting blood glucose, body mass, body mass index,

waist/hip ratio, smoking habits, and systolic blood pressure, on the other. When these possible confounders, in addition to age, were taken into consideration in multivariate analyses, only the inverse significant correlation between SHBG and NIDDM remained. The increased incidence of diabetes was confined to the lowest quintile of SHBG values, where it was 5-fold higher than in the remaining group. This incidence was further increased to 8- and 11-fold in the lowest 10 and 5% of the values, respectively. They conclude that SHBG is a uniquely strong independent risk factor for the development of NIDDM in women (Goran Lindsted, 1991)

Population-Based Incidence Rates and Risk Factors for Type 2 Diabetes in White Individuals

Diabetes 53:1782–1789, 2004

Enzo Bonora, Stefan *et al* in 2004 works on a topic which is identifying the risk factors of white individuals. They investigated these in white individuals who were aged 40–79 years and from the population of Bruneck, Italy. Of an age- and sex-stratified random sample of 1,000 individuals who were identified in 1990, 919 underwent an oral glucose tolerance test (OGTT) and an assessment of physiological risk factors for diabetes, including insulin resistance (homeostasis model assessment, HOMA-IR), and post challenge insulin response (Sluiter's Index). Diabetes at baseline by fasting or 2-h OGTT plasma glucose (World Health Organization criteria, *n* _ 82) was excluded, leaving 837 individuals who were followed for 10 years. Incident cases of diabetes were ascertained by confirmed diabetes treatment or a fasting glucose >7.0 mmol/l. At follow-up, 64 individuals had developed diabetes, corresponding to a population-standardized incidence rate of 7.6 per 1,000 person-years. Sex and age-adjusted incidence rates were elevated 11-fold in individuals with impaired fasting glucose at baseline, 4-fold in those with impaired glucose tolerance, 3-fold in overweight individuals, 10-fold in obese individuals, and _2-fold in individuals with dyslipidemia or hypertension. Incidence rates increased with increasing HOMA-IR and decreasing Sluiter's Index. As compared with normal insulin sensitivity and normal insulin response, individuals with low insulin sensitivity and low insulin response had a sevenfold higher risk of diabetes. Baseline impaired fasting glucose, BMI, HOMA-IR, and Sluiter's Index were the only independent predictors of incident diabetes in multivariate analyses. They conclude that _1% of European white individuals aged 40–79 years develop type 2 diabetes annually and that "sub diabetic" hyperglycemia, obesity, insulin resistance, and impaired insulin response to glucose are independent predictors of diabetes.(Enzo Bonora, 2004)

High Risk of Progression to NIDDM in South-African Indians With Impaired Glucose Tolerance

Diabetes 42:556-63, 1993

Ayeshaa, Motala, *et al* works on High risk of progression to NIDDM in South-African Indians with impaired glucose tolerance. A four-yr prospective study was undertaken to examine the natural history of IGT in 128 South-African Indians classified as such at year 0 of the study, based on WHO criteria. Subjects were reexamined at year 1 and year 4. Of the 113 subjects who completed the study, 50.4% progressed to NIDDM (rate of progression 12.6%/yr), 24.8% persisted with IGT, and 24.8% reverted to NGT. The majority (72%) who progressed to NIDDM did so in year 1. At year 1, 47 subjects were still

classified as IGT; of the 40 subjects completing the study, 16 subjects (40%) progressed to NIDDM, 17 subjects (42.5%) persisted with IGT, and 7 subjects (17.5%) reverted to NGT. Examination of risk factors predictive of subsequent progression to NIDDM was undertaken by analysis of baseline variables in two ways: When year 0 was used as baseline (in 113 IGT0 subjects), significant predictive risk factors were the FPG and 2-h plasma glucose concentrations. All subjects who at year 0 had 2-h plasma glucose >10.2 and <11.1 mM or FPG >7.3 but <7.8 mM, subsequently progressed to NIDDM. When year 1 was used as baseline (40 IGT., subjects), 90-min plasma glucose concentration (midtest level) was found to be a significant risk factor for development of NIDDM. In conclusion, this study has demonstrated that in South-African Indians with IGT, the majority (50.4%) progress to NIDDM within 4 yr; significant predictors of subsequent diabetes are the baseline fasting and 2-h plasma glucose concentration. The mid test plasma glucose also may be a useful predictor of clinical outcome. Moreover, the study highlighted the rapid decompensating to NIDDM in the first year and the demonstration of cut-off levels of plasma glucose above which the risk of development of NIDDM (Ayeshaa, Motala Mahomed, 1993)

Genetic Variation in the Gene Encoding Adiponectin Is Associated With an Increased Risk of Type 2 Diabetes in the Japanese Population

Diabetes 51:536–540, 2002

Kazuo hara , Philippe, Yasmichi mori *et al* published a data which contain Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. genome- wide scans have mapped a diabetes susceptibility locus to chromosome *3q27*, where the adiponectin gene (*APM1*) is located. Herein, we present evidence of an association between frequent single nucleotide polymorphisms at positions 45 and 276 in the adiponectin gene and type 2 diabetes (*P* 0.003 and *P* _ 0.002, respectively). Subjects with the G/G genotype at position 45 or the G/G genotype at position 276 had a significantly increased risk of type 2 diabetes (odds ratio 1.70 [95% CI 1.09–2.65] and 2.16 [1.22–3.95], respectively) compared with those having the T/T genotype at positions 45 and 276, respectively. In addition, the subjects with the G/G genotype at position 276 had a higher insulin resistance index than those with the T/T genotype (1.61 _ 0.05 vs. 1.19 _ 0.12, *P* _ 0.001). The G allele at position 276 was linearly associated with lower plasma adiponectin levels (G/G: 10.4 _ 0.85 _g/ml, G/T: 13.7 _ 0.87 _g/ml, T/T: 16.6 _ 2.24 _g/ml, *P* _ 0.01) in subjects with higher BMIs. Based on these findings together with the observation that adiponectin improves insulin sensitivity in animal models, They conclude that the adiponectin gene may be a susceptibility gene for type 2 diabetes (Kazuo Hara,2002)

Prevalence and risk factors for diabetes and impaired glucose tolerance in Asian Indians: A community survey from urban Eastern India

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 6 (2012) 96–101

D.S. Prasad , Zubair Kabir *et al* works on Prevalence and risk factors for diabetes and impaired glucose tolerance in Asian Indians. Their Objectives is to determine the prevalence of diabetes and impaired glucose tolerance (IGT) and to identify risk factors for the same specific to an underdeveloped urban locale of Eastern India. Urban city-dwellers in Orissa one of the poorest states of Eastern India bordering

a prosperous state of Andhra Pradesh of Southern India was selected for this study. and 1178 adults of 20–80 years age randomly selected from 37 electoral wards of urban populace. The crude rates of diabetes and IGT in the study population were 15.7% and 8.8%, respectively. Similarly age-standardized rates of diabetes and IGT were 11.1% and 6.7%, respectively. Both diabetes and IGT had shown a male preponderance. Diabetes and IGT were very highly prevalent in this urban populace. Cardiometabolic risk factors like older age, central obesity, inadequate fruit intake, hypertension, hypertriglyceridemia and socio economic status were found to be significant predictors of diabetes in this study. They also found that the aged 65 years and above are at five-fold increased risk of diabetes; individuals with inadequate fruit intake had three-fold increased risk of diabetes, centrally obese individuals were two-and half times more likely to have diabetes compared with those having normal waist and individuals with hypertension were almost twice as likely to be at risk of diabetes. Likewise individuals of middle socioeconomic status or with hypertriglyceridemia have a similar magnitude of diabetes risk. Similarly older age, central obesity, inadequate fruit intake and hypertriglyceridemia significantly contributed to an increased risk for IGT amongst this urban population.(D.S. Prasad, 2012)

Risk of diabetes in combined metabolic abnormalities and body mass index categories

Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 51:536–540, 2002

Mohsen Janghorbani, Norredin Soltanian *et al* et al were studied on Risk of diabetes in combined metabolic abnormalities and body mass index categories and their aim was to estimate the progression rates from combination of normal weight, overweight, obesity, and number of metabolic abnormalities (MA) to type 2 diabetes (T2D) in a non-diabetic high risk population in Isfahan, Iran. total of 1869 non-diabetic first-degree relatives (FDR) of patients with T2D 30–70 years old were examined and followed for a mean (SD) of 7.3 (2.2) years for T2D incidence. At baseline and through follow-up, participants underwent a standard 75-g 2-h oral glucose tolerance test. Results: The metabolically healthy overweight and obese at baseline were associated with incidence of T2D, independently of age and gender. Any one MA increased the risk of developing T2D among normal weight, overweight and obese individuals. Those with normal weight and _3 MA were over 20 times (odds ratios (OR) 20.21; 95% confidence intervals (CI) 2.4, 170.4) and those with overweight and _3 MA 22.5 times (OR 22.5; 95% CI 3.0, 167.0) and obese with _3 MA were 25.4 times (OR 25.4; 95% CI 3.4, 187) more likely to develop T2D than those with normal weight and without MA. Compared with participants without MA, obese individuals with concomitant MA were not significantly more likely to progress to T2D, and provide further evidence that normal weight, overweight and obese individuals with MA had a higher risk of incident T2D than normal weight individuals without MA. Their data shown that in normal weight, overweight, and obese, participants with higher number of MA had increased yearly probability of T2D, which was significantly different compared with participants with normal weight, overweight and obese but without MA ($P < 0.05$). Number of MA is a strong predictor of incident T2D independent of BMI status and overweight and obesity is a predictor of incident T2D independent of MA in a cohort of FDR of patients with T2D in Iran. The highest risk estimate was seen in obese and normal weight .This observation was also confirmed by the results from Kaplan–Meier method of survival analysis. These associations suggest that in participants without T2D, number of MA may be more contribute to the development of T2D than BMI status. Several cohort studies have investigated the combined effect of an elevated BMI and the presence of MA in the development of T2D ght participants with _3 MA. Individuals, who had _3 MA,

even in normal weight subjects, were substantially at higher risk of future T2D. (Mohsen Janghorbani, 2002)

Evaluation of prevalence and risk factors of gestational diabetes in a tertiary care hospital in Kerala

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 51:536–540, 2002

Manju A. Mohan, Abin Chandrakumar performed a study which was conducted with the aim to evaluate the prevalence and risk factors of gestational diabetes mellitus in a tertiary care referral hospital in Kerala. prospective observational study was conducted with the aim to study the prevalence, risk factors, complications, treatment pattern and cost analysis of GDM. The study was carried out in the Obstetrics & Gynecology Department of Al Shifa Hospital located in northern Kerala. Results: Over an eight-month period, 201 patients who met the inclusion criteria were enrolled for study from which prevalence of GDM was estimated at 15.9%. The study revealed higher prevalence of risk factors and complications such as age >25 years, BMI >26 kg/m2, family history of DM, past history GDM, history of big baby, gestational hypertension, vaginal candidiasis, premature rupture of membranes and hyper bilirubinemia in GDM group as compared to non-GDM group. The study also demonstrated that modern life-style was a major influencing factor for development of diabetes in the study population. The study reveals the necessity of proper screening diagnosis and management of GDM in pregnant women by the clinicians so as to prevent the future burden of type 2 diabetes, Obesity was another major risk factor identified in the current study and can be attributed to increased demands on maternal metabolism during pregnancy from excess weight, resulting in imbalances in hormonal carbohydrate regulation mechanisms and insulin sensitivity. Study by Nilofer et al. also demonstrated obesity as a risk factor in 88.89% of GDM patients. (Manju A. 2002)

Risk of diabetes in combined metabolic abnormalities and body mass index categories

Diabetes Care 39:43–49 , 2016

Norredin Soltanian, Mohsen Janghorbani *et al* study which was designed to estimate the progression rates from combination of normal weight, overweight, obesity, and number of metabolic abnormalities (MA) to type 2 diabetes (T2D) in a non-diabetic high risk population in Isfahan, Iran. A total of 1869 non-diabetic first-degree relatives (FDR) of patients with T2D 30–70 years old were examined and followed for a mean (SD) of 7.3 (2.2) years for T2D incidence. At baseline and through follow-up, participants underwent a standard 75-g 2-h oral glucose tolerance test. The metabolically healthy overweight and obese at baseline were associated with incidence of T2D, independently of age and gender. Any one MA increased the risk of developing T2D among normal weight, overweight and obese individuals. Those with normal weight and _3 MA were over 20 times (odds ratios (OR) 20.21; 95% confidence intervals (CI) 2.4, 170.4) and those with overweight and _3 MA 22.5 times (OR 22.5; 95% CI 3.0, 167.0) and obese with _3 MA were 25.4 times (OR 25.4; 95% CI 3.4, 187) more likely to develop T2D than those with normal weight and without MA. Compared with participants without MA, obese individuals with concomitant MA were not significantly more likely to progress to T2D. Their data provide further

evidence that normal weight, overweight and obese individuals with MA had a higher risk of incident T2D than normal weight individuals without MA. (Mohsen Janghorbani , 2016)

Prevalence, awareness and risk factors of diabetes in Ahvaz

Diabetes and Metabolic Syndrome: Clinical Research and Reviews
http://dx.doi.org/10.1016/j.dsx.2016.03.007

Azdanpanah L, Shahbazian HB conducted a study was designed to assess the prevalence of diabetes in people aged over 20 years in Ahvaz, Iran. The study population was chosen by cluster sampling. A checklist included: age, sex, weight, height, blood pressure, waist circumference, educational level, smoking status and previous history of diabetes was completed for each patient. Fasting Plasma Glucose (FPG) ≥126mg/dl and/or oral hypoglycemic treatment and/or insulin consumption was defined as diabetes, FPG =100-125 mg/dl as Impaired Fasting Glucose(IFG) and FPG <100mg/dl as normal. Study population was 944 persons. Mean age of population was 42.2±14 years. Diabetes was detected in 15.1 % of population. Only 40.4% of cases were aware of their disease. Diabetes was detected in 14.7% of female and 15.7% of male participants. Diabetes was related to age, waist circumference, family history of diabetes, hypertension, waist to hip ratio, educational level, marital status, serum triglyceride, cholesterol and body mass index (BMI) in both genders. But by using logistic regression analysis, age, family history of diabetes, hypertension, hypertriglyceridemia, and marital status had significant effect on diabetes. This study showed that using FPG criteria or current medication 15.1% of this population had diabetes and about 60% of patients were unaware of their disease. Age, hypertension, family history of diabetes, hypertriglyceridemia and marital status are the risk actors of diabetes in Ahvaz population. IFG have high prevalence and diabetes screening should be intensified in this population. (Yazdanpanah, Shahbazian, ,2016)

Low Carbohydrate–Diet Scores and Long-term Risk of Type 2 Diabetes Among Women With a History of Gestational Diabetes Mellitus: A Prospective Cohort Study

Diabetes Care 39:43–49, 2016

Wei Bao, Shanshan Li, have shown in 2016 of low carbohydrate–diet scores and long-term risk of type 2 diabetes among women with a history of gestational diabetes mellitus. Low carbohydrate diets (LCDs) may improve short-term glycemic control in patients with gestational diabetes mellitus (GDM), but the long-term effect on progression from GDM to type 2 diabetes mellitus (T2DM) is unknown. So their aimed to examine the long-term risk of T2DM in association with a low-carbohydrate dietary pattern among women with a history of GDM. Overall, 4,502 women with a history of GDM from the Nurses' Health Study II(NHSII) cohort, as part of the Diabetes & Women's Health (DWH) study, were followed up from 1991 to 2011. Overall, animal, or vegetable LCD scores, which represent adherence to different low-carbohydrate dietary patterns, were calculated using diet intake information assessed every 4 years since 1991 by validated food-frequency questionnaires. They used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs

They documented 722 incident cases of T2DM during 68,897 person-years of observation. The multivariable-adjusted HRs (95% CIs) of T2DM, comparing the highest with lowest quintiles, were 1.36 (1.04–1.78) for overall LCD score (P = 0.003 for trend), 1.40 (1.06–1.84) for animal LCD score (P = 0.004 for trend), and 1.19 (0.91– 1.55) for vegetable LCD score (P = 0.50 for trend). In this prospective cohort study with up to 20 years of follow-up, they observed that a dietary score representing a low-

carbohydrate, high–animal protein, and high–animal fat dietary pattern was significantly and positively associated with T2DM risk among women with a history of GDM. These associations were partly explained by BMI. By contrast, a dietary score representing a low-carbohydrate, high–vegetable protein, and high–vegetable fat dietary pattern was not associated with the risk of developing T2DM. The observed associations were not significantly modified by age, family history of diabetes, smoking, obesity status, or time since the first GDM pregnancy. (Wei Bao, 2016)

potato consumption and risk of type 2 diabetes: results from three prospective cohort studies

Diabetes Care 39: 376–384, 2016

Isao Muraki, Eric B. Rimm *et al* Potato Consumption and Risk of Type 2 Diabetes. They aimed to elucidate whether potato consumption is associated with a higher risk of type 2 diabetes (T2D). They analyzed data in three cohorts consisting of U.S. male and female health professionals without diabetes, cardiovascular disease, and cancer at baseline: 70,773 women from the Nurses' Health Study (1984–2010), 87,739 women from Nurses' Health Study II (1991–2011), and 40,669 men from the Health Professionals Follow-up Study (1986–2010). Potato consumption was assessed quadrennials using validated food frequency questionnaires (FFQs), and they calculated 4-year change in potato consumption from consecutive FFQs. Self-reported T2D diagnosis was confirmed using a validated supplementary questionnaire. During 3,988,007 person-years of follow-up, 15,362 new cases of T2D were identified. Higher consumption of total potatoes (including baked, boiled, or mashed potatoes and French fries) was significantly associated with an elevated risk for T2D the pooled hazard ratio (HR) of T2D compared with <1 serving/week was 1.07 (95% CI 0.97–1.18) for 2–4 servings/week and 1.33 (95% CI 1.17–1.52) for ‡7 servings/ week after adjustment for demographic, lifestyle, and dietary factors. In addition, the pooled HRs of T2D for every 3 servings/week were 1.04 (95% CI 1.01–1.08) for baked, boiled, or mashed potatoes, and 1.19 (95% CI 1.13–1.25) for french fries. They further estimated that the HR of T2D was 0.88 (95% CI 0.84–0.91) for replacing 3 servings/ week of total potatoes with the same amount of whole grains. Last, in comparison with stable potato consumption, every 3-servings/week increment of potato consumption in 4 years was associated with a 4% (95% CI 0–8%) higher T2D risk. In three cross-sectional and case-control studies, intake of potatoes or french fries was positively associated with insulin resistance
and prevalent T2D (12–14). In a Finnish cohort comprising 4,303 men and women, participants who consumed .283 g/day of total potatoes had 42% higher incident diabetes medication use than those consuming ,132 g/day of potatoes (15). In the Women's Health Study, which comprised 39,876 female health professionals, total potato consumption was not associated with diabetes risk after multivariable adjustment . (Isao Muraki, 2016)

Risk of Developing Type 2 Diabetes in Adolescents and Young Adults With Autism Spectrum Disorder : A Nationwide Longitudinal Study

Diabetes Care 39:788–793, 2016

In 2006 Mu-Hong Chen, Wen-Hsuan Lan *et al* published a data that suggested the association between autism spectrum disorder (ASD) and type 2 diabetes mellitus (DM)–related risk factors, such as obesity

and dyslipidemia. Used the Taiwan National Health Insurance Research Database for enrolling 6,122 adolescents and young adults with ASD and 24,488 age- and sex-matched control subjects between 2002 and 2009 and monitored them until the end of 2011. Participants who developed type 2 DM during the follow-up period were identified. Adolescents (hazard ratio [HR] 2.71 [95% CI 1.64–4.48]) and young adults (HR 5.31[95% CI 2.85–9.90]) with ASD had a higher risk of developing type 2 DM than those without ASD, after adjustment for demographic data, atypical antipsychotics use, and medical comorbidities. Sensitivity analyses after excluding first year (HR 3.03 [95% CI 2.03–4.51]) and first 3-year (HR 2.62 [95% CI 1.62–4.23]) observation periods were consistent. Short-term (HR 1.97 [95% CI 1.20–3.23]) and long-term (HR 1.64 [95% CI 1.02–2.63]) use of atypical antipsychotics were associated with a higher likelihood of subsequent type 2 DM. Adolescents and young adults with ASD were more likely to be diagnosed with type 2 DM during the follow-up after adjustment for demographic data, atypical antipsychotics use, and medical comorbidities. found that dyslipidemia and obesity were associated with the risk of developing type 2 DM among males with ASD and that hypertension and dyslipidemia increased the likelihood of subsequent type 2 DM among females with ASD. This result may imply the sex effect in the pathophysiology between ASD and type 2 DM and type 2 DM–related metabolic disorders. genes between ASD and type 2 DM may increase the risk of type 2 DM in patients with AS GLO1, an enzyme involved in the detoxification of methylglyoxal and in limiting the advanced glycation end products formation, is crucial in autism susceptibility and type 2 DM disease progression. Reported that a patient with a de novo duplication on chromosome 17p13.1 involving neuroligin 2, ephrin B3, and GLUT type 4 genes manifested obesity, type 2 DM, intelligence disability, and autistic traits. Additional genome-wide association studies are necessary to identify more susceptible candidate genes for the risk of type 2 DM in patients with ASD. Moreover, immune dysregulation and pro inflammatory cytokine over secretion may explain the temporal association between ASD and subsequent type 2 DM. (Mu-Hong Chen, 2016)

Review of Risk Factors for Insulin-Dependent Diabetes

Diabetes Care 13:1062-68, 1990)

Janice S. Dorman, PhD; Bridget J.*et al* works on risk factors for insulin-dependent diabetes . The etiology of this disorder remains unclear. Epidemiologic patterns, including the higher IDDM incidence rates in Caucasians compared with African Americans or Hispanics, the increase in risk at puberty, and the more frequent occurrence of the disease during the winter months, suggest that viruses, nutrition, and socioeconomic factors may be involved. The genes that confer susceptibility to IDDM are located in the HLA region of chromosome 6. Individuals who carry alleles containing DNA sequences coding for arginine in position 52 of the DQ a chain (DQA1*Arg-52) and an amino acid other than aspartic acid in position 57 of the DQ b chain (DQB1*non-Asp-57) are known to be at high risk for IDDM. Genetically susceptible individuals who also have autoantibodies to islet cell antigens or to glutamic acid decarboxylase are at greatest risk for developing IDDM. Seasonal variation in the onset of IDDM has been observed worldwide, suggesting that infectious agents are potential risk factors. They have been shown that More than 80% of cases of IDDM occur in individuals with no family history of the disease. However, in the remaining 20%, IDDM aggregates in families. The overall risk before age 30 years for North American Caucasian siblings, parents, and offspring of individuals with IDDM ranges from 1% to 15%.compared with rates of <1% for individuals without IDDM relatives. Most data on risk of IDDM in family members are from Caucasian populations that have similar incidence rates. For children with

IDDM who have an IDDM parent, the father is more likely to have the disease than the mother Prospective studies that ascertained IDDM in the offspring of parents with IDDM have also revealed a higher risk of IDDM in children of affected fathers than mothers. Various nutrients and nutritional practices have been associated with the development of IDDM. Animal studies have consistently shown that diets containing intact protein, in contrast to diets with protein hydrolysates or an amino acid mixture, contribute to high rates of diabetes in susceptible animals,. In addition, the intake of foods containing high amounts of nitrosamines appears to be related to the etiology of the disease. The most widely studied nutritional risk factor for IDDM is breast-feeding and exposure to cow's milk Protein. Antibody levels were especially high in IDDM children age <3 years, suggesting that cow's milk proteins may have a particularly significant effect on the development of IDDM in young children. The whey protein, bovine serum albumin (BSA), is the suspected milk protein trigger of an autoimmune response in genetically susceptible individuals. Antibodies to a 17-amino acid section of the BSA molecule (ABBOS), which react with a b-cell surface protein109, have been found in children with IDDM. (Janice S. Dorman, 1990

Risk factors for Type 2 Diabetes Mellitus in college students: association with socio demographic variables

Adman Câmara Soares Lima Márcio Flávio Moura Araújo *et al* in 2014 have been shown that Risk factors for Type 2 Diabetes Mellitus in college students. They identify the modifiable risk factors for type 2 diabetes mellitus in college students and associate these factors with their sociodemographic variables and they cross-sectional study, involving 702 college students from Fortaleza-CE, Brazil. Sociodemographic, anthropometric, physical exercise data and blood pressure and fasting plasma glucose levels were collected. The most prevalent risk factor was sedentariness, followed by overweight, central obesity, high fasting plasma glucose and arterial hypertension. A statistically significant association was found between overweight and sex (p=0.000), age (p=0.004) and marital status (p=0.012), as well as between central obesity and age (p=0.018) and marital status (p=0.007) and between high fasting plasma glucose and sex (p=0.033). and finally they found distinct risk factors were present in the study population, particularly sedentariness and overweight.

Assessment of the Common Risk Factors Associated with Type 2 Diabetes Mellitus in Jeddah, International Journal of Endocrinology

International Journal of Endocrinology, http://dx.doi.org/10.1155/2014/616145, 2014

Manal A.Murad, Samia S. Abdulmageed *et al* performed a study of Assessment of the Common Risk Factors Associated with Type 2 Diabetes Mellitus in Jeddah. Performed a case-control study in 2013 at ten primary health care centers in Jeddah, Saudi Arabia to determine the common risk factors of diabetes mellitus type 2 (DM2) and the demographic background of adult Saudi patients with DM2. Known diabetic patients were recruited as cases, while non diabetic attendants were selected as controls. A pretested designed questionnaire was used to collect data from 159 cases and 128 controls. Cases were more likely than controls to be men ($P < 0.0001$), less educated ($P < 0.0001$), natives of eastern Saudi Arabia ($P < 0.0001$), retired ($P < 0.0001$), lower-salaried ($P < 0.0001$), o married or divorced ($P < 0.0001$). By univariate analysis cases were likely to be current smokers ($P < 0.0001$), hypertensive ($P < 0.0001$), or overweight/obese ($P < 0.0001$). Cases were also more likely to have a history of D Mina first-degree relative ($P = 0.020$). By multivariate analysis, cases were more likely to be older than 40 years (*P*

< 0.0001), less educated (P = 0.05), married or divorced (P = 0.04), jobless/housewives (P < 0.0001), or current smokers (P = 0.002).They were also more likely to have salaries <7000 Saudi riyals (P = 0.01). Overall, pre diabetic and high risk groups should be identified and counseled early before the occurrence of diabetes. They found that Patients who were physically active, those who did not perform household chores, and those who had a servant were more likely to have DM2; however, these results were not statistically significant. Similarly, there was also no significant association between diabetes and the patients' self-perception of being physically active. They found that male gender, age > 40 years, low educational attainment (illiterate or having completed primary school), salaries <7000 Saudi riyals, marital status (married or divorced), and smoking status (current smoker) were risk factors associated with DM2 in adult Saudi patients. It is probable that these individuals have the least information about dietary factors and the importance of self-care. Smoking status is an independent modifiable risk factor for DM2 since it is associated with glucose showed that high BMI was significantly associated with diabetes, which might be because obesity enhances insulin resistance intolerance, impaired fasting glucose, and, consequently, DM2. The increasing incidence of DM in the Saudi population has been linked to obesity, which is a consequence of major sociocultural and lifestyle changes. The promotion of fast foods, change in the traditional Saudi diet, both in quantity and quality, and physical inactivity are as a result of urbanization.(Manal A.Murad, 2014)

Diabetes Risk Factors in Middle Income Pakistani School Children Pakistan Journal of Nutrition

Journal of Nutrition 3 (1): 43-49, 2004

M. Zafar Iqbal Hydrie, Abdul Basit, Naeema Badruddin *et al* studied on Diabetes risk factors in middle income Pakistani school children. To assess the risk factors for diabetes such as dietary habits, physical fitness score, physical activity, body mass index (BMI) and family history of diabetes amongst school children. A cross-sectional study was conducted on 103 children (ages 8-12 years), from middle-income families from two schools of Karachi. Data of physical fitness score was taken by a physical fitness test and BMI was calculated by measuring weight and height. Dietary records were taken by 24 hours self reported diet recall charts of two weekdays. Health knowledge was obtained by a questionnaire given to children and a separate questionnaire was given to mothers to get this information. Majority of the children took less healthy food from the choice given to them; according to the self reported dietary intakes, 88% had poor intake of vegetables, 84% had poor intake of milk while 80% had poor intake of fruits. More than 40% of the children consumed soft drinks and fast foods daily. A child on the average watched 2.9 hours of TV/per day on weekdays and 3.5 hours of TV of weekends. Physical fitness score of 45% of the children was unsatisfactory while 29% of children had BMI > 20 Kg/m2. Eighty four percent of the children had first or second degree relative with diabetes. Majority of the children had high risk factors for diabetes with unhealthy diet and low physical activity patterns augmented by strong family history of diabetes. This shows that these children are at increased risk of developing diabetes in later years and preventive measures are required early in life, including lifestyle and behavioral changes to save our future generations from developing diabetes. This information will help in designing interventions for better lifestyle and eating habits which may reduce the later incidence of diabetes in children at adulthood.(M. Zafar Iqbal Hydrie, 2004

Risk Factors for Diabetes and Cardiovascular Disease in Young Australian Aborigines.

Diabetes care, volume 19,number 5,1996

Barry braun et al have been worked on the risk factors of diabetes in young Australian aborigines and investigated the hypothesis that hyperinsulinemia and glucose tolerance are present at an early stage of Australian aborigines. Baseline anthropometric, pubertal stage and blood pressure data were collected for 100 Australian aboriginal children and adolescents in 1989. Plasma concentrations of glucose, insulin, C-peptide, triglycerides, and LDL, HDL, and total cholesterol were measured before and during an oral glucose tolerance test. All measurements were repeated in 74 individuals from the original study population in 1994. Results were compared among hyperinsulinemic and normoinsulinemic subjects and subjects with normal or abnormal glucose tolerance. Diabetes and IGT were diagnosed according to the criteria of the World Health Organization (WHO) (28). A positive family history of diabetes was defined as the presence of diabetes in at least one biological parent, grandparent, or sibling. To define overweight using BMI (29), we used the following age- and sex-specific criteria (85th percentile; derived from the U.S. National Health and Nutrition Examination Surveys). Central-type obesity, which is associated with increased risk for NIDDM and CVD (30),was defined as a WHR >0.8 for female subjects and >0.9 for male subjects. The prevalence of cigarette smoking was 45% (53% in male and 38% in female subjects). Alcohol use was reported by 54% of subjects (75% in male and 34% in female subjects). Of the subjects, ~37% had a family history positive for diabetes. The major finding of this study is the high prevalence of these risk factors for NIDDM and CVD in a population of aboriginal children and adolescents (Table 4). At a mean age of 18.5 years, 17.6% of the subjects were overweight, 8.1% of the population had IGT, and 2.7% had diabetes. Several cross-sectional studies have suggested (8,17-19) and one longitudinal study has shown (23) that hyperinsulinemia in youth may be predictive of later glucose intolerance in populations that develop NIDDM at high rates. The major finding of this study is the high prevalence of risk factors for NIDDM and cardiovascular disease in this population of aboriginal children and adolescents. Abnormalities of carbohydrate and lipid metabolism were well established by late in the second decade of life. Although many subjects had high insulin levels and there was evidence of insulin resistance in the population, hyperinsulinemia did not predict the development of abnormal glucose tolerance 5 years later. (Barry braun Ahlbom,1996)

Work Stress and Low Sense of Coherence Is Associated With Type 2 Diabetes in Middle-Aged Swedish Women

Diabetes Care 26:719–724, 2003

Emile E. Agradh *et al* , 2003 studied on Work Stress and Low Sense of Coherence Is Associated With Type 2 Diabetes in Middle-Aged Swedish Women. The risk of type 2 diabetes is suggested to be increased for individuals exposed to stress. They analyzed the association of work stress by high demands, low decision latitude, and job strain (combination of high demands and low decision latitude) with type 2 diabetes. They also studied low sense of coherence (SOC) (a factor for successful coping with stressors) in association with type 2 diabetes. Finally, they investigated the combination of SOC and demands or SOC and decision latitude in association with the disease. This cross-sectional study recruited 4,821 healthy Swedish women (aged 35–56 years) residing in five municipalities in the Stockholm area.

An oral glucose tolerance test identified 52 women with type 2 diabetes. Relative risks (RRs) with 95% CIs were estimated in a logistic multiple regression analysis. No association was found between high demands and type 2 diabetes (RR 1.1 [CI 0.5–2.2]). Low decision latitude was associated with type 2 diabetes with a RR of 2.2 (1.0 – 4.8). The RR of type 2 diabetes with low SOC was 3.7 (1.2–11.2). The combination of low SOC and low decision latitude was associated with type 2 diabetes with a RR of 2.6 (1.2–5.7). Homeostasis model assessment revealed an association of 4.2 (1.2–15.0) between low SOC and insulin resistance. Exposure to long-term stress affects the entire neuroendocrine system, activating the HPA axis and/or the central sympathetic nervous system (17). Increased cortisol levels following activation of the HPA axis could play a role in the development of decreased glucose tolerance. Thus, cortisol has been shown to induce insulin resistance by increasing hepatic glucose production, suppressing glucose usage, and inhibiting insulin secretion . The RRs related to low decision latitude and low SOC were preserved even after controlling for other risk factors such as FHD, BMI, WHR, smoking, and physical inactivity. A low SOC, interpreted as a low ability to cope with stressors, was associated with type 2 diabetes. It could be suggested that people with low SOC are more likely to have unhealthy lifestyle patterns, which lead to disease. (Emile E. Agardh, 2003)

Obesity, Fat Distribution , and Weight Gain as Risk Factors for Clinical Diabetes in Men.

Diabetes care, volume 17, number 9, 1994

June M Chan et al investigate the relation between obesity, fat distribution, and weight gain through adulthood and the risk of non-insulin-dependent diabetes mellitus (NIDDM). They analyzed data from a cohort of 51,529 U.S. male health professionals, 40-75 years of age in 1986, who completed biennial questionnaires sent out in 1986, 1988, 1990, and 1992. During 5 years of follow-up (1987-1992), 272 cases of NIDDM were diagnosed among men without a history of diabetes, heart disease, and cancer in 1986 and who provided complete health information. Relative risks (RRs) associated with different anthropometric measures were calculated controlling for age, and multivariate RRs were calculated controlling for smoking, family history of diabetes, and age. found a strong positive association between overall obesity as measured by body mass index (BMI) and risk of diabetes. Men with a BMI of ^35 kg/m2 had a multivariate RR of 42.1 (95% confidence interval [CI] 22.0-80.6) compared with men with a BMI <23.0 kg/m2. BMI at age 21 and absolute weight gain throughout adulthood were also significant independent risk factors for diabetes. Fat distribution, measured by waist-to-hip ratio (WHR), was a good predictor of diabetes only among the top 5%, while waist circumference was positively associated with the risk of diabetes among the top 20% of the cohort. These data suggest that waist circumference may be a better indicator than WHR of the relationship between abdominal adiposity and risk of diabetes. Although early obesity, absolute weight gain throughout adulthood, and waist circumference were good predictors of diabetes, attained BMI was the dominant risk factor for NIDDM; even men of average relative weight had significantly elevated RRs. Risk of diabetes increased continuously with increasing levels of BMI. Men with a BMI of 25.0-26.9 kg/m2 had a risk 2.2 times (95% confidence interval (CI) 1.3-3.8) greater than men with a BMI <23.0 kg/m2 after adjusting for age, family history, and smoking habits. Risk rose markedly for men with a BMI 2:29 kg/m2. As expected, the men in the highest category, BMI >35.0 kg/m2, had the highest RR (multivariate RR = 42.1, 95% CI 22.0-80.6). To examine the relation between early adult obesity and diabetes risk, BMI at age 21 was calculated. Recent weight gain was strongly associated with the risk of diabetes. Information was available on weight gained in the 5 years before 1986 for 259 of the 272 NIDDM cases. After controlling for BMI in 1981, family history,

age, and smoking habits, men who had gained >13.6 kg (the equivalent of ^30 lbs) had a risk 4.5 times that of men who were within 4.5 kg of their 1981 weight (95% CI 2.4-8.2). found an extremely strong association between BMl and risk of NIDDM. Increased risks were seen for all BMl levels ^24.0 kg/m2, well below the standard criteria for obesity. Thus, even men of average weight are substantially more likely to develop diabetes than men with a BMl <23.0 kg/m2. The extremely strong RR for men with a BMl >29.0 kg/m2 combined with metabolic data and the effect of weight loss on glucose tolerance warrant the conclusion that the relationship between obesity and risk of diabetes is causal. (June M Chan, 1994)

Type 2 diabetes mellitus and obesity in sub-Saharan Africa

Diabetes Metab Res Rev 26: 433–445, 2010

Vivian C. *et al* studied on Type 2 diabetes mellitus (T2DM) is the most common form of diabetes (90–95%), exhibiting an alarming prevalence among peoples of this region. Its main risk factors include obesity, rapid urbanization, physical inactivity, ageing, nutrition transitions, and socioeconomic changes. Patients in sub-Saharan Africa also show manifestations of β-cell dysfunction and insulin resistance. However, because of strained economic resources and a poor health care system, most of the patients are diagnosed only after they have overt symptoms and complications. Micro vascular complications are the most prevalent, but metabolic disorders and acute infections cause significant mortality. The high cost of treatment of T2DM and its comorbidities, the increasing prevalence of its risk factors, and the gaps in health care system necessitate that solutions be planned and implemented urgently. Aggressive actions and positive responses from well-informed governments appear to be needed for the conducive interplay of all forces required to curb the threat of T2DM in sub-Saharan Africa. Despite the varied ethnic and transitional factors and the limited population data on T2DM in sub-Saharan Africa, this review provides an extensive discussion of the literature on the epidemiology, risk factors, pathogen. Obesity is a fast-growing problem that is reaching epidemic proportions worldwide. It occurs as a result of an imbalance between energy intake and expenditure and is characterized by increased body fat stores. Persistent obesity disrupts metabolic processes controlling blood glucose, blood pressure, and lipids. A body mass index (BMI) of ≥30 kg/m2 is the most common lysis, complications, treatment, and care challenges of T2DM in this region. Used measure of obesity, although other anthropometric parameters, such as waist circumference and waist-to-hip ratio, are also used. The increasing prevalence of T2DM in SSA will negatively impact the health care system and socioeconomic development in the region. The burdens of T2DM are multiple, since its comorbidities, e.g. vascular diseases, complicate the management of this disease. Health care systems in SSA are inadequate and more structured towards the management of the communicable diseases, which are still a major problem in this resource-poor
region. It is therefore important to initiate cost-effective intervention programs geared at reducing the prevalence of the modifiable risk factors, such as obesity and physical inactivity, which can be ascribed to rapid urbanization and socioeconomic transitions. At the same time, improvement/and or expansion of health care systems should be targeted to achieve optimal care of patients with T2DM and its related chronic disorders along with the communicable diseases.

Prevalence, risk factors and complications associated with type 2 diabetes in migrant South Asians.

Diabetes Metab Res Rev,28: 6–24. 2012

Sara D *et al* estimated that type 2 diabetes (T2D) currently affects about 246 million people worldwide, with South Asians, especially Indians, having both the largest number of cases and the fastest growing prevalence. South Asian ethnicity has been identified as a major risk factor for the development of T2D with central adiposity, insulin resistance and an unfavorable lipid profile being identified as predominant signals of alarm. Leading databases, including *Web of Science, Medline, Pub Med* and *Science Direct*, were consulted and manual searches were conducted for cited references in leading diabetes-related journals. In all, 152 articles were included for the final assessment reported in this review. Genetic predisposition, central adiposity and unfavorable lifestyle, including physical inactivity and an unhealthy diet, were associated with the prevalence of T2D in migrant South Asians. 'Westernization', acculturation, socio-economic factors and lack of knowledge about the disease have also been identified as contributors to the development of T2D in this population. Higher prevalence of T2D in migrant
South Asians may not be entirely attributed to genetic predisposition; hence, ethnicity and associated modifiable risk factors need further investigation. Preventive measures and appropriate interventions are currently limited by the lack of ethnic-specific cut-off points for anthropometric and biological markers, as well as by the absence of reliable methods for dietary and physical activity assessment. The majority of the studies reported an unhealthy diet to be a strong risk factor for T2D in migrant South Asians, in particular the consumption of energy-dense foods that are rich in total fat, saturated fat and refined sugar and low in fibre. Such foods have also been found to cause unfavorable lipid profiles including high triglyceride and low HDL levels. The main sources of trans and saturated fatty acid were reported to be *ghee* and milk fat, whereas inadequate intake of fish and fruits and vegetables accounted for deficiencies in *n*–3 fatty acids and fibre, respectively. However, in the absence of reliable food composition data and validated dietary assessment tools such information may be incomplete. This population might benefit from a reduction in total and refined carbohydrate intake to guidance levels found to favour insulin metabolism. Compared to subjects living in their homeland, migrant South Asians have limited physical activity that might predispose them to T2D. Physical inactivity has been attributed to religious believes, time constraints, ill health, poor socio-economic status and lack of public health education. Culturally acceptable interventions are urgently needed to encourage a physically active lifestyle. While various genes have been linked to T2D, TCF7L2 appears to be a strong predictor of T2D in various ethnic groups, including South Asians. Some genetic polymorphisms have been found to have a positive effect on the prevention of T2D in certain population groups but these might not offer similar protection to all populations. For example, for peroxisome proliferator activated receptor-γ 2 Pro 12Ala polymorphism, the protection was only found to be present in Caucasians but not in South Asians. However, G53C single nucleotide polymorphism appears to be protective against T2D, as well as against obesity, in Asian Indians. Further studies are required to better understand the role of genetic factors in a representative sample using case–control studies. Modifiable factors including diet, exercise and socio-economic indicators attributed to the onset and prevalence of T2D in migrant South Asians (Sara D. Gardu 2012)

Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg Cohort Study.

Am J Clin Nutr 84:483–9, 2006

Christa Meisinger *et al* have been studied o*n body* fat distribution and risk of type 2 diabetes in the general population. The objective was to examine the sex-specific relevance of WC, WHR, and BMI to the development of type 2 diabetes. The prospective population-based cohort study was based on 3055 men and 2957 women aged 35–74 y who participated in the second (1989 –1990) or third (1994 –1995) MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) Augsburg survey. The subjects were free of diabetes at baseline. Hazard ratios (HRs) were estimated from Cox proportional hazards models. Both overall and abdominal adiposity were strongly related to the development of type 2 diabetes. Because there was an additive effect of overall and abdominal obesity on risk prediction, WC should be measured in addition to BMI to assess the risk of type 2 diabetes in both sexes. Although BMI, WC, and WHR were almost equally good predictors of diabetes in men, WC and BMI displayed the greatest relative risks in women. In joint analyses there was an additive effect of BMI and WC and of BMI and WHR on risk prediction. Because WC is easy to interpret, it should be measured in addition to BMI to assess the risk of type 2 diabetes in men and women. This would entail an improvement in risk stratification, particularly in women, and may help to prevent type 2 diabetes. It has been postulated that expanded intra abdominal fat stores affects insulin metabolism by releasing free fatty acids (26). Free fatty acids reduce the hepatic clearance of insulin, which may lead to insulin resistance and hyperinsulinemia. In contrast, a larger hip circumference. is associated with high lipoprotein lipase activity and relatively low rates of basal and stimulated lipolysis (29). This fat distribution pattern may protect the liver from high exposure to free fatty acids through uptake and storage. Furthermore, adrenal and sex steroid concentrations and growth hormone concentrations may play a role in visceral fat accumulation and in the development of insulin resistance. (Christa Meisinger,2006)

Weight Change and Diabetes Incidence: Findings from a National Cohort of US Adults

Am J Epidemiol Vol. 146, No. 3, 1997

Earl S. Ford *et al* examine how long-term patterns of weight change affect the risk for diabetes, especially non-insulindependent diabetes mellitus, the authors examined the relation of weight change over a period of about 10years (from the baseline examination in 1971-1975 until the first follow-up examination in 1982-1984) to the 9-year incidence of diabetes mellitus (1984-1992) in a national cohort of 8,545 US adults from the National Health and Nutrition Examination Survey Epidemiologic Followup Study. Diabetes incidence was identified from death certificates, hospitalization and nursing home records, and self-report. In this cohort, 487 participants developed diabetes. The hazard ratios were 2.11 (95% confidence interval (Cl) 1.40-3.18) for participants who gained 5-<8 kg , 1.19 (95% Cl 0.75-1.89) for participants who gained 8-<11 kg, 2.57 (95% Cl 1.84-3.85) for participants who gained 11-<20 kg, and 3.85 (95% Cl 2.04-7.22) for participants who gained 20 kg or more compared with participants whose weights remained relatively stable. The authors found no evidence that the results differed by age, sex, or

race. They estimated that the population attributable risk was 27% for weight increases of 5 kg or more. Results from this study and other recent studies suggest that the increase in body mass index in the United States that occurred during the 1980s may portend an increase in the incidence of non-insulin-dependent diabetes mellitus with important public health consequences in future. In addition, obesity is often associated with increased insulin production by pancreatic cells. Perhaps as a function of the duration and magnitude of obesity, further deterioration in glucose homeostatic mechanisms occurs when /3-cells become glucose incompetent and clinical diabetes develops. If weight gain occurred after the onset of diabetes, hazard ratios were likely overestimated. If weight loss occurred after the onset of diabetes, hazard ratios were likely underestimated. Finally, we were unable to separate persons with insulin dependent diabetes mellitus from those with NIDDM. However, because insulin-dependent diabete data suggest that, for every kilogram of increase in weight, the risk for diabetes increases by 4.5 percent. Consequently, the average weight gain of 3.6 kg recorded from NHANES *U* to NHANES m could theoretically result in an approximately 16 percent increase in the incidence of diabetes by the year 2000 compared with that in 1990. This estimate is consistent with an 18 percent increase in risk for diabetes for each unit increment in body mass index reported by Helmrich et al. s mellitus usually has an early onset. (Earl S. Ford, David F.1997)

Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study.

Am J Epidemiol 158:416–423, 2003

Mercedes R. *et al* has been studied on Symptoms of depression may predict incident diabetes independently or through established risk factors for diabetes. US men and women aged 25–74 years who were free of diabetes at baseline (n = 6,190) were followed from 1971 to 1992 (mean, 15.6 years; standard deviation, 6) for incident diabetes. Depressive symptoms were measured by using the General Well-Being Depression subscale and were categorized to compare persons with high (9%), intermediate (32%), and low (59%) numbers of symptoms. The incidence of diabetes was highest among participants reporting high numbers of depressive symptoms (7.3 per 1,000 person-years) and did not differ between persons reporting intermediate and low numbers of symptoms (3.4 and 3.6 per 1,000 person years, respectively) ($p < 0.01$ for high vs. low). In the subset of participants with less than a high school education (a marker of low socioeconomic status), the risk of developing diabetes was three times higher (95% confidence interval: 2.0, 4.7) for persons reporting high versus low numbers of depressive symptoms. These results persisted following adjustment for established diabetes risk factors. Depressive symptoms had no impact on diabetes incidence among persons with at least a high school education. Results suggest an independent role for depressive symptoms in the development of diabetes in populations with low educational attainment. In this population-based sample, men and women with less than a high school education who reported the highest numbers of symptoms of depression were at increased risk of developing diabetes. This relation appears to act independently of established risk factors for the development of diabetes and a related psychological construct, anxiety. Biologic mechanisms that may explain the association between depressive symptoms and diabetes include inflammation, activation of the hypothalamic-pituitary-adrenal axis, or an interaction between genetic predisposition and depression or stress. In cross-sectional studies, inflammatory markers including the cytokines interleukin-1β, and tumor necrosis factor-and C-reactive protein were found to be elevated in depressed persons. Two population studies reported that inflammatory markers are associated with the development of diabetes. One suggested mechanism is that obesity or atherosclerosis is associated with the expression of low-grade

inflammation that can be detected prior to the development of diabetes alternatively, inflammation may be associated with oxidative damage and the release of free radicals that damage pancreatic cells, thus limiting the release of insulin. The inflammatory process also may inhibit insulin uptake, a critical process in glucose regulation. Further research is needed into a possible role for inflammation regarding the relation between depressive symptoms and incident diabetes. A dysregulation of the hypothalamic-pituitary-adrenal axis in depressed persons may result in elevated cortisol levels. Cortisol may antagonize the actions of insulin mediated glucose disposal or cause preferential deposition of fat in the abdomen (visceral adiposity), which is a risk factor for developing diabetes. It has also been shown that insulin sensitivity, an important mechanism in the development of type 2 diabetes, can be manipulated by treatment for depression. In an experimental study, depressed patients had lower. insulin sensitivity, but, when treated with heterocyclic antidepressants, depressive symptoms im Depression is highly correlated with physiologic and psychological stress; therefore, it is possible that the reported relation between stress and hyperglycemia may also mediate the relation between depression and diabetes. Stressful situations have been shown to induce hyperglycemia in glycemic animals and in humans with a genetic predisposition toward developing diabetes proved concurrently with insulin sensitivity. Persons of lower socioeconomic status may be more likely to consume diets high in fats, carbohydrates, and alcohol; to smoke cigarettes more frequently; and to engage in a sedentary lifestyle, all of which are predisposing factors for developing diabetes. Persons of depressed mood and fewer economic and education resources may be especially vulnerable to these maladaptive behaviors; thus, depressed mood and low socioeconomic status may act synergistically to increase the risk of diabetes.

Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta analysis.

Diabetologia (2006) 49: 837–845)

M. J. Knol *et al* hasbeen *reported in their studies that* Depression may occur as a consequence of having diabetes, but may also be a risk factor for the onset of type 2 diabetes. This study examined the latter association by reviewing the literature and conducting a meta-analysis of longitudinal studies on this topic. Pooled relative risks were calculated using fixed and random effects models. To explore sources of heterogeneity between studies, subgroup analyses and meta-regression analyses were performed. Nine studies met our inclusion criteria for this meta-analysis. Depressed adults have a 37% increased risk of developing type 2 diabetes mellitus. The pathophysiological mechanisms underlying this relationship are still unclear and warrant further research. A randomised controlled study is needed to test whether effective prevention or treatment of depression can reduce the incidence of type 2 diabetes and its health consequences. Results of this meta-analysis of nine longitudinal studies suggest that adults with depression or high-depressive symptoms have a 37% increased risk of developing type 2 diabetes compared with those who are not depressed or have low-depressive symptoms. (M. J. Knol 2006) ,

Twelve-year trends in the prevalence and risk factors of diabetes and pre diabetes in Turkish adults

Eur J Epidemiol 28:169–180, 2013

Ilhan Satman *et al* aimed to determine the prevalence of diagnosed and undiagnosed diabetes, prediabetes and their 12-year trends and to identify risk factors for diabetes in the adult Turkish population. A cross-sectional, population- based survey, TURDEP-II' included 26,499 randomly sampled adults aged C 20 years. The prevalence of isolated-IFG and impaired glucose tolerance (IGT), and combined prediabetes was 14.7, 7.9, and 8.2 %, respectively; and that of obesity 36 % and hypertension 31.4 %. Compared to TURDEP-I; the rate of increase for diabetes: 90 %, IGT: 106 %, obesity: 40 % and central obesity: 35 %, but hypertension decreased by 11 % during the last 12 years. In women age, waist, body mass index (BMI), hypertension, low education, and living environment; in men age, BMI, and hypertension were independently associated with an increased prevalence of diabetes. In women current smoking, and in men being single were associated with a reduced risk. These results from one of the largest nationally representative surveys carried out so far show that diabetes has rapidly become a major public health challenge in Turkey (Ilhan Satman, 2013)

Body Fat Distribution and Hyperinsulinemia as Risk Factors for Diabetes and Cardiovascular Disease

(*Arteriosclerosis* 6:123-130, 1986)

Michael P. Stern and Steven M. Haffner showed that differences In body fat distribution between diabetics and non-diabetics have been recognized for several decades; diabetics have a more centralized or upper body fat pattern than non-diabetics. Recently, attention has focused on fat patterning and also on hyperinsulinemia as possible risk factors for cardiovascular disease, as well. The case for Insulin as a cardiovascular risk factor Is bolstered by theoretical considerations related to Its possibly atherogenic effects on serum and arterial wall lipids. Empirical evidence for fat patterning and hyperinsulinemia as cardiovascular risk factors rests on six prospective epidemiologic studies, three on fat patterning and three on Insulin. Although provocative, none of these studies can be regarded as definitive. In none was a dose-response effect demonstrated, and there are various Inconsistencies within and across the studies. Moreover, In none of the studies were hyperinsulinemia and fat patterning evaluated simultaneously. This Is of particular importance In view of the well-documented Interrelationships between these two variables. For example, Insulin resistance and hyperinsulinemia have been found to be greater In women with upper body obesity compared to women with lower body obesity of equivalent degree. Considerable progress has been made recently In understanding the mechanisms of the differential metabolic effects of these two types of obesity. The extent to which fat patterning and hyperinsullnemia are genetic or acquired has
received relatively little attention. Further research on this question Is warranted since elucidation of any environmental Influences on these variables mights uggest new clinical and public health control measures. (Michael P. Stern, 1986)

Pre-natal and early life risk factors for childhood onset diabetes mellitus: a record linkage study

International Journal of Epidemiology, 27.444-149, 1998

Michael E Jones *et al* using data from the Oxford Record Linkage Study (ORLS) and conducted a case control study to examine pre-natal and early life risk factors for childhood and adolescent onset diabetes mellitus. They identified 160 boys and 155 girls born 1965-1986 and admitted to hospital with a diagnosis of diabetes during 1965-1987 in the ORLS area. Up to eight controls were matched to each case on sex, year of birth and hospital or place of birth. We linked the hospital records for each child to all of that child's hospital records and to his or her mother's maternity record. There were no significant associations between subsequent diabetes and birthweight, gestational age, birth weight for gestational age, maternal age and parity. There were increased risks with not breastfeeding (relative risk [RR] = 1.33; 95% CI: 0.76-2.34), and with diabetes recorded in the mother during pregnancy (RR = 5.87; 95% CI: 0.90-38.3), but these were not statistically significant. There was a significantly raised risk with pre-eclampsia or eclampsia during pregnancy (RR = 1.48; 95% CI : 1.05-2.10). Pre-eclampsia may be the result of an immunogenic incompatibility between mother and fetus, and this early immunological disturbance might be related to incidence of diabetes in later life. Older maternal age has usually been associated with an increased risk of a child developing IDDM. However one study found the opposite, 13 and among mothers with diabetes the risk in offspring decreases with maternal age. The analyses identified pre-eclampsia or eclampsia as a significant risk factor for diabetes in the offspring. Diabetes in the mother was also associated with a large increased risk in the children, although the numbers of affected mothers was small and the assodation was not statistically significant. The interpretation of the results presented here, however, depends on the validity of using routine data sources to identify cases and controls and to provide exposure information. (Michael E Jones, 1998)

Chapter Five

Methodology

Methodology

Research Design

The study was a review study. The paper was based on the information collected from various journal

Sample Size

Sample size was 50 journal

Study period

Study period was 1 year (June,2015-June 2016)

Sample characteristics and data collection

The Sample was collected from various journal like Diabetes Care , European Journal Epidemiology, Diabetologia, American Journal of Nutrition , Diabetes Metabolism Research and Review, International Journal of Endocrinology, Springer, Elsevier journal etc.

Inclusion Criteria

- Patient/ subject only with Diabetes mellitus was taken for these research.
- age from 18 years up to 65 years was included in this study.
- Both male and female patient was included in this study.

Exclusion Criteria

- Patient with additional clinical complication were excluded from this study.

Data Analysis

The data were put on a tabular form and it was analyzed statistically like frequency counts and simple percentages by using Microsoft Excel.

Chapter Six

Results

Risk Factor (Socio economic factor)

source	Income
Xiao- ren et al,1995	2%
Source	**Family history**
Manjun A mohan ,etal 2015	6%
June M. Chan,etal, 1993	
P. Ravikumar etal, 2011	
Source	**Education**
Xiao- ren et al,1995	12%
Carlotta saccerdote etal, 2012	
P. Ravikumar etal, 2011	
Yazdarpanah et al, 2016	
Manjun A mohan ,etal 2015	
Cristia meisinger, 2009	
Source	**Smoking**
N.M choetal, 204	4%
June M. Chan,etal, 1993	
Source	**Physical activity**
Xiao- ren et al,1995	8%
P. Ravikumar etal, 2011	
Viswonathan mohan etal,2008	
Cristia meisinger, 2009	
Source	**Dietary factor**
Mohren jangorlani, etal,2015	6%
Isao Muraki etal , 2016	
S.D gardeno, 2012	

Risk Factors (Physiological factors)

Source	IGT
Goran et al, 1962	6%
Nam H.cho etal, 2009	
Yazdarpanah et al, 2016	
Source	**Obesity**
Mohren jangorlani, etal,2015 Manjun A mohan ,etal 2015 June M. Chan,etal, 1993 Xiao- ren et al,1995 Gorow, etal 1962 Viswonathan mohan etal,2008 Isao muraki, 2006 Liweichan, 2006 Mj knol, 2016 S.D gardeno, 2012	22%
D. S Prasad etal,2012	
Source	**Blood Cholesterol level**
Mohren jangorlani, etal,2015	6%
Manjun A mohan ,etal 2015	
Gorow, etal 1962	
Source	**Metabolic abnormalities**
Mohren jangorlani, etal,2015	4%
S.D gardeno, 2012	
Source	**Low sex hormone binding globuline**
Gorow, etal 1962	2%

Risk Factors of Diabetes Mellitus (Disease)

Source	Hypertension
D. S Prasad etal,2012	12%
Xiao- ren et al,1995	
Enzo bonora et al, 2004	
P. Ravikumar etal, 2011	
Monju A mohan, 2015	
Lewichan, 2004	
Cristia meisinger, 2009	
Source	**Dislipidemia**
Gorow, etal 1962	6%
Liweichan, 2006	
Cristia meisinger, 2009	

Out of 50 journal % of risk factor

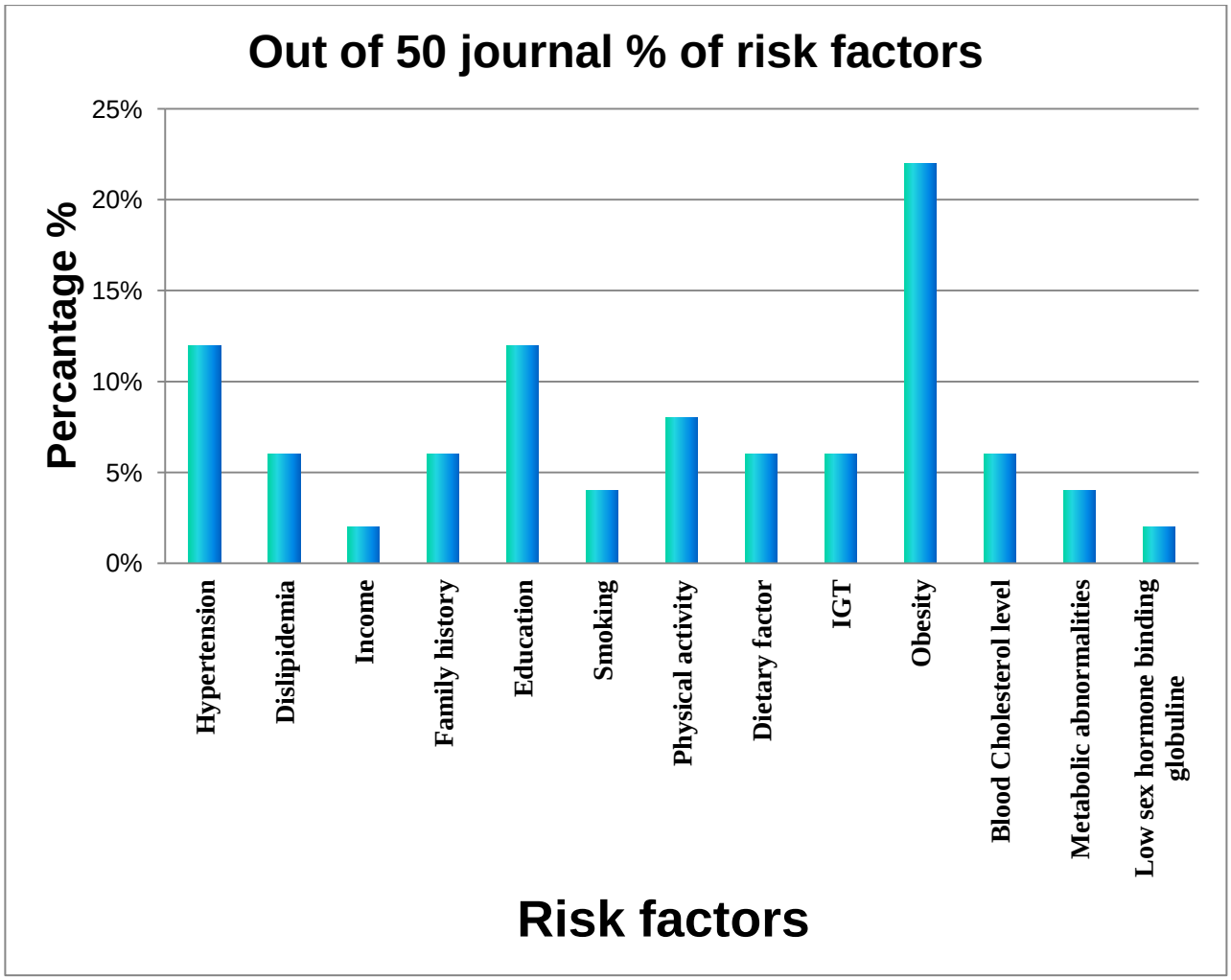


Fig: Percentage of risk factors which are prone to develop diabetes mellitus (Out of 50 journal)

Chapter Seven

Discussion

Discussion

Sex (Gender): A Polymorphism (Pro12 Ala) is correlated with increased insulin sensitivity and reduced risk for type-2 diabetes by promoting better suppression of lipid oxidation leading to more glucose deposal. But polymorphism activities difference is found in males but not found in females. [National Institute of Health and Clinical Excellence (NICE)] A clear result was found in Scottish research result, men developing type-2 diabetes at a lower BMI than woman of similar age. Men may be less sensitive to insulin than women or more tend to store fat more readily around liver and other organs rather than under the skin as women do.

Age & BMI: Have done a number of studies in the last few years to define the metabolic abnormalities which occur in older age. On the other hand, maximum people over 45 years gain fat around the liver or other organs. Body immune system can fall into disorder. Due to obesity or excess fat deposition decrease the insulin secretion and increases insulin resistance with increasing age. So risks of diabetes increase as get older. (Dr. Grydon Meneilly, MD,FRCP. Spring Equinox 2000 diabetes in the Elderly Vol-2 No.1) This may be because tend to exercise less, loss muscle mass and gain weight mean fatty cells that are problematic for insulin sensitivity. In Particular fat around abdomen releases chemicals that can upset the body's metabolic system. It is well known that more fatty acid, the more resistant cell become to insulin.

Blood Group: Many studies on the relationship between blood groups and certain diseases have recently been published. It has been shown that blood group-A is quite frequent in patient with cancer of stomach, pancreas or esophagus (Aridetal 1954), while blood group-O is common in patients suffering from peptic ulcer (Ref: Aridetal 1954) (clarke etal 1955) is firmly established, whereas association between blood groups and diabetes series has not been confirmed. But various studies shown that B+ Blood group are more suffer by diabetes than other group.

Inhabitant & Working Style: It is really alarming for urban peoples that they are in more risk for diabetes than rural people. Every study has shown that due to urbanization, some demographic changes has occur such as physical activities, diet pattern, food habit, so people gain obesity that is the main risk factor to develop diabetes mellitus. Obesity that is the main risk factor to develop diabetes (http://www.medicalnewstoday.com/info/diabetes). But physical activities help to control weight and uses of glucose as energy make cells more sensitive to insulin. Exercise causes skeletal muscle to be more sensitive to insulin, the chemical signal that tells cells to absorb glucose. On the other hand exercise related works change muscle fiber with higher capillary density that can increase sensitivity and responsive to insulin.

Smoking: Tobacco stimulates stress hormone that can increases insulin resistance. From American study Nicotine increase the activity of some receptors and catecholamine. But it has been reported that catecholamine impair the pathways that are related to the production of insulin. So this type of insulin

impairment can produce diabetes. On the other hand tobacco impairs brain and tissue receptor mechanisms that impair both insulin sensitivity and insulin secretion.

Family History: Family history is an important risk factor for developing a number of serious diseases including diabetes. From my study I can see that approximately 6% patients of diabetes have history of diabetes in their family especially in type-1 diabetes. According to the researcher at Jolin diabetes centre report- It immediate relative (ex. Parents, brothers, sister) has diabetes, one's risk of developing diabetes is 10 to 20 times more than the risk of the general people.

Types of Diabetes & Diagnosis Period: Data from the world health organization-Multinational project for children diabetes indicate that type-1 diabetes in rare in most Africans, American, Indian and Asian population. National diabetes clearing house (www.diabetes.trial.Net.org.) However some northern European countries including Finland and Sweden have high rates of type-1 diabetes. But actual reasons of difference are unknown. But genetic factor can play a role to develop diabetes. Type-2 diabetes is more common in older people especially in people who are overweight and occur more often in African American, Asian. Main cause of type-2 diabetes is lacking of proper exercise and diet control. (www.diabetes.trial.Net.org.) So in this case gene is a factor to develop diabetes but life style is main risk factor for diabetes.

Patient Awareness: From a study at 2011, awareness about diabetes and treatment of diabetes status among men and women with diabetes is not good. Almost 65% men and 60% women are not aware that their plasma glucose is elevated. But according to various articles, increasing awareness about diabetes 55% patients with diabetes are going to hospital once every two months, Maximum patients cannot control their blood sugar level. A great portion of diabetes patients are informed about diabetes. Awareness is rising in various stages but overall condition is not satisfactory. For example, world diabetes day raise global awareness of diabetes- its escalating rates around the world and how to prevent the illness in most cases. The activities of the WHO and other organization to set norms and standards, promote surveillance, encourage prevention, raise awareness and strength prevention and control of diabetes .World diabetes day on the 14 November of every year has grown from humble beginning to become a globally calibrated event to increase awareness about diabetes comprising hundreds of campaigns activities screening, lecture, meeting and more. On the other hand in Bangladesh various types of organization has been working to grownup awareness about diabetes hospital based doctors and press also playing a great role arranging various types of program such as yell, seminar, talk show. Also poster, free diabetes test and doctors counseling is valuable factors to grow awareness about prevalence of diabetes and prevention of diabetes related problems by controlling of diabetes

Chapter Eight

Conclusion

CONCLUSION

Diabetes poses a major health problem globally and is one of the top five leading causes of death in most developed countries. A substantial body of evidence suggests that it could reach epidemic proportions, particularly in developing and newly industrialized countries. This study suggest that age, sex, inhabitant family history of diabetes and life style modification related result such as increased BMI, overweight, stress, food habit, overall diabetes management system, limitation of management system related logistics such as available specialist, complete care hospital, awareness growing forces, lacking of overall balancing capacity among patients, disease and disease management are the main causes behind the diabetes mellitus. Therefore the findings from this review article can manage prevalence of diabetes mellitus . So, identification of risk factors and rate, disease pattern & tendency of people against diabetes, knowledge about disease & disease management protocols and proper action plan against this disease by government organization, nongovernment-organization, media and general people can reduce the risk of this threat.

Chapter Nine

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