PLASMA ADIPONECTIN LEVEL IN TYPE 2 DIABETIC AND NON-DIABETIC PATIENTS

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LIST OF ABBREVIATIONS USED

(In alphabetical order)

ADA	- American Diabetic Association
ADP	- Adenosine diphosphate
AGE	- Advanced glycosylation end product.
AMP	- Adenosine monophosphate
ATP	- Adenosine triphosphate
BMI	- Body mass index
cAMP	- cyclic Adenosine monophosphate
CAD	- Coronary artery diseases
CDC	- Centre for disease control
DBP	- Diastolic blood pressure
DCCF	- Diabetes control and complication trial
DM	- Diabetes mellitus
ECG	- Electrocardiogram
ELISA	- Enzyme linked immuno sorbent assay
FBS	- Fasting blood sugar
FPG	- Fasting plasma glucose
GLUT	- Glucose transport protein unit
HbA1C	- Glycosylated haemoglobin
HDL	- High density lipoprotein
HNF	- Hepatocyte nuclear transcription factor.
HYT	- Hypertension
IAPP	- Islet amyloid polypeptide
ICMR	- Indian Council of Medical Research
IRS	- Insulin receptor substrate
MODY	- Maturity onset diabetes in young
NEFA's	- Non- essential fatty acids
PG	- Plasma glucose
PI	-3 kinase- Phosphatidyl inositol-3 kinase
PPBS	- Post prandial blood sugar
SBP	- Systolic blood pressure
SPSS	- Statistical Package for the Social Sciences
SUR	- Sulfonylurea receptors
UKPDS	- United Kingdom Prospective Diabetes Study
WHO	- World Health Organisation
WHR	- Waist Hip Ratio

INTRODUCTION

INTRODUCTION

Type 2 diabetes mellitus is the most common form of diabetes, a disorder characterised by high blood glucose. Pathophysiological abnormalities noted in type 2 diabetes mellitus are impaired insulin secretion, peripheral insulin resistance and excessive hepatic glucose production. Along with type 2 diabetes mellitus, obesity and cardiovascular diseases are commom[1]. The association of obesity with development of type 2 diabetes mellitus may be partly mediated by altered secretion of adipokines by adipose tissue, which is a complex, metabolically highly active organ. Factors secreted by adipocytes are leptin, adiponectin, plasminogen activator inhibitor -1 and resistin.[2]

Adiponectin is a collagen like protein solely secreted by adipocytes. Accumulating evidence from animal and human study demonstrates that adiponectin plays an important role in the pathophysiology of insulin resistance, diabetes, lipid metabolism and inflammation and thus risk of cardiovascular diseases.[3]

It has been reported that reduction in plasma adiponectin levels may be related to elevation of insulin resistance and/or hyperinsulinemia associated with diabetes.

Adiponectin mimics the vascular as well as metabolic action of insulin. It inhibits macrophage transformation into foam cells as well as their phagocytic activity.[4]

In addition, adiponectin diminishes oxidized low density lipoprotein accumulation in the blood vessel wall and increases nitric oxide production in endothelial cells.[5]

It is suggested that adiponectin via these mechanisms may not only protect against atherosclerosis but also retards its progression.

The ability of adiponectin to increase insulin sensitivity in conjunction with its anti-inflammatory and anti-atherogenic properties have made this novel adipocytokine a promising therapeutic tool for future.[6]

Adiponectin accounts for approximately 0.01% of all plasma proteins, at around 5-10 µg/dl. Adiponectin levels differ in different geographical area. Thus, we aimed to study the adiponectin levels in this part of the country and in diabetes mellitus and to examine the relationship between adiponectin, glycemic control and lipid profile through determining its level in different study groups of patients and to assess the relationship between adiponectin and obesity as well as atherosclerosis related cardiovascular disease in type 2 diabetes mellitus patients.

HISTORICAL REVIEW

Table: 1 Diabetes Timeline Table[7,8,9,10]

1552 B.C	Earliest known record of diabetes mentioned on 3rd Dynasty Egyptian papyrus by physician Hesy-Ra; mentions polyuria (frequent urination) as a symptom.
1st Century A.D	Diabetes described by Arateus as “the melting down of flesh and limbs into urine.''
164 A.D	Greek physician Galen of Pergamum mistakenly diagnoses diabetes as an ailment of the kidneys.
Up to 11th Century	Diabetes commonly diagnosed by ''water tasters'' who drank the urine of those suspected of having diabetes: the urine of people with diabetes was thought to be sweet-tasting. The Latin word for honey (referring to its sweetness), “mellitus' is added to the term diabetes as a result.

16th Century	Paracelsus identifies diabetes as a serious general disorder.
Early 19th Century	First chemical tests developed to indicate and measure the presence of sugar in the urine.
Late 1850s	French physician, Priorry, advises diabetes patients to eat extra large quantities of sugar as a treatment.
1870s	French physician, Bouchardat, notices the disappearance of glycosuria in his diabetes patients during the rationing of food in Paris while under siege by Germany during the Franco-Prussian war; formulates idea of individualized diets for his diabetes patients.
19th Century	French researcher, Claude Bernard studies the workings of the pancreas and the glycogen metabolism of the liver. Czech researcher, I.V. Pavlov, discovers the links between the nervous system and gastric secretion, making an important contribution to science's knowledge of the physiology of the digestive system.
Late 19th Century	Italin diabetes specialist, Catoni, isolates his patients under lock and key in order to get them to follow their diets.
1869	Paul Langerhans, a German medical student announces in a dissertation that the pancreas contains two systems of cells. One set secretes the normal pancreatic juice; the function of the other was unknown. Several years later these cells were identified as the “islets of Langerhans”.
1889	Oskar Minkowski and Joseph von Mering at the University of Strasburg, Austria, first removed the pancreas from a dog to determine the effect of an absent pancreas on digestion.
November 14, 1891	Frederick Banting born near Alliston, Ontario. His parents, devout Methodist, try to pressure their son into joining the ministry; instead, in 1912, Banting enrolls in medicine at the University of Toronto.
February 28, 1899	Charles Best born in West Pembroke, Maine.

1900-1915	"Fad" diabetes diets include: the "oat-cure" (in which the majority of diet was made up of oatmeal), the milk diet, the rice cure, "potato therapy" and even the use of opium.
1908	German scientist, Georg Zuelzer develops the first injectable pancreatic extract to suppress glycosuria; however, there are extreme side effects to the treatment.
1910-1920	Frederick Madison Allen and Elliot P. Joslin emerge as the two leading diabetes specialists in the United States. Joslin believes diabetes to be "the best of the chronic diseases" because it was ''clean, seldom unsightly, not contagious, often painless and susceptible to treatment"
c. 1913	Allen, after three years of diabetes study, publishes "Studies Concerning Glycosuria and Diabetes", a book which is significant for the revolution in diabetes therapy that developed from it.
1919	Frederick Allen publishes Total Dietary Regulation in the treatment of Diabetes, citing exhaustive case records of 76 of the 100 diabetes patients he observed, becomes the director of diabetes research at the Rockefeller Institute.
1919-20	Allen establishes the first treatment clinic in the USA, The psychiatric Institute in New Jersey to treat patients with diabetes. High blood pressure and Bright's disease, wealthy and desperate patients flock to it.
July 1, 1920	Dr. Banting opens his first office in London, Ontario. He receives his first patient on July 29th; his total earnings for his first month of work is $4.00.
October 31, 1920	Dr. Banting conceives of the idea of insulin after reading Moses Barron's "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis" in the November issue of "Surgery, Gynaecology and Obstetrics". For the next year with the assistance of Best, Collip and Macleod, Dr. Banting continues his research using a variety of different extracts on de-pancreatized dogs.

December 30, 1921	Dr. Banting presents a paper entitled "The beneficial influences of Certain Pancreatic Extracts on Pancreatic Diabetes", summarizing his work to this point at a session of the American Physiological Society at Yale University. Among the attendees are Allen and Joslin. Little praise or congratulation is received.
January 23, 1922	One of Dr. Collip's insulin extracts first tested on a human being, a 14-year-old boy named Leonard Thompson, in Toronto; treatment considered success by the end of the following February.
May 21, 1922	James Havens becomes the first American successfully treated with insulin.
May 30, 1922	Eli Lilly and Company and the University of Toronto enter a deal for the mass production of insulin in North America.
October 25 1923	Dr. Banting and his colleague Prof. Macleod are awarded the Nobel Prize in Physiology or Medicine. Dr. Banting shares his award with Best: Prof. Macleod shares his award with Dr. Collip.
1934	Dr. Banting is knighted, becoming Sir Frederick Banting.
1940s	Link is made between diabetes and long-term complications (kidney and eye disease).
1941	On February 21, Sir Frederick Banting is killed in an airplane crash over Newfoundland while en route to England.
1944	Standard insulin syringe is developed, helping to make diabetes management more uniform.
1946	Dr. Best co-founds a diabetes association under the name Diabetic Association of Ontario. It later comes to be known as the Canadian Diabetes Association.
1950s	Insulin zinc proportions were developed by Hallas - Moller and coworkers as lente (slow acting) insulin.
1953	Nova Scotia and Alberta established provincial diabetes organizations. Canadian Diabetes Association is formally established.
1955	Oral drugs are introduced to help lower blood glucose levels.
1956	L'Association Diabete Quebec is established. Sanger identified amino acid sequence of beef, pork and sheep.

1959	Two major types of diabetes are recognized: type I (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes.
1960s	Nicol and Smith identified amino acid sequence in humans. The purity of insulin is improved. Home testing for sugar levels in urine increases level of control for people with diabetes.
1966	First pancreas transplant performed at the University of Manitoba.
1983	First biosynthetic human insulin is introduced.
1986	Insulin pen delivery system is introduced.
1989	Opening of the Banting Museum and Education Centre in London, Ontario; Her Majesty Queen Elizabeth the Queen Mother lights the Flame of Hope.
1993	Diabetes Control and Complications Trial (DCCT) report is published. The DCCT results clearly demonstrate that intensive therapy (more frequent doses and self-adjustment according to individual activity and eating patterns) delays the onset and progression of long term complications in individuals with type 1 diabetes
1995	DES launches its first education awareness Campaign. The Canadian Diabetes Association launches its website. It is an award-winning source of diabetes-related information for people all over the world.
1996	75th Anniversary of the discovery of insulin celebrated around the world.
	The Canadian Diabetes Association presents a symposium entitled "75 Years of Progress in Diabetes care, Management and Treatment."
1998	The United Kingdom Prospective Diabetes Study (UKPDS) is published. UKPDS results clearly identify the importance of good glucose control and good blood pressure control in the delay and/or prevention of complications in type2 diabetes. Clinical Practice Guidelines for the Management of Diabetes in Canada are released by the Canadian Diabetes Association.
1999	Guidelines for the Nutritional Management of Diabetes is released.
2011	ADA-Diagnostic Criteria

EPIDEMIOLOGY

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably because of increasing obesity, reduced activity levels as countries are becoming more industrialized, and the aging of the population.

In 2010, the prevalence of diabetes ranged from 11.6 to 30.9 % .10 countries with the highest prevalence are Naurua, United Arab Emirates, Saudi Arabia, Mauritius, Bahrain, Reunion, Kuwait, Oman, Tonga, Malaysia—in descending prevalence; (Fig. 1.) In the most recent estimate for the United States (2010), the Centers for Disease Control and Prevention (CDC) estimated that 25.8 million persons, or 8.3% of the population, had diabetes (27% of the individuals with diabetes were undiagnosed). Approximately 1.6 million individuals >20 years of age were newly diagnosed with diabetes in 2010. DM increases with aging. In 2010, the prevalence of DM in the United States was estimated to be 0.2% in individuals aged <20 years and 11.3% in individuals aged >20 years. In individuals aged >65 years, the prevalence of DM was 26.9%. The prevalence is similar in men and women throughout most age ranges (11.8% and 10.8%, respectively, in individuals aged >20 years). Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be aged 45–64 years.

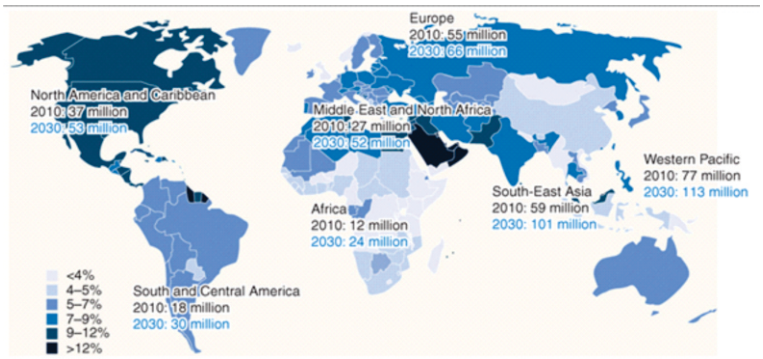

Figure: 1.Worldwide prevalence of diabetes mellitus. Comparative prevalence(%) of estimates of diabetes (20–79 years), 2010.

PREVALENCE OF DIABETES GLOBALLY AND IN INDIA.[11]

The prevalence of diabetes in adult population worldwide was estimated to be 4% in 1995 and will rise to 5.4% by the year 2025. It is higher in developed countries. The number of adult diabetics were 135 million in 1995 and will rise to 300 million by 2025. The major part of this numerical estimate will occur in developing countries. There will be 42% increase from 51 to 72 million in developed nations and 170% increase from 84 to 228 million in the developing countries. Thus by the year 2025 more than 75% of people with diabetes will reside in developing countries as compared to 62% in 1995. The countries with largest number of people with diabetes will be India, China and USA by the year 2025.

In developing countries as compared to developed ones, majority of the people with diabetes range from 45 years to 62 years. In the developed countries the range is at about 65 years. This pattern will further accentuate by the year 2025. There are going to be more women with diabetes than men in the developed countries. There is a trend for increased population of diabetics in urban areas.

THE MALE TO FEMALE RATIO[11]

In the year 1995 for the world as whole there were more women diabetics than men, 73 million women and 62 million men. In the developing countries there are equal number of men and women with diabetes numbering to 42 million each. In India there is male excess with 11 million men as compared to 8 million women.

These results suggest that for the world as a whole between 1995 and 2025, the adult population will increase by 64%, prevalence of diabetes in adults will increase by 35% and number of people with diabetes by 122%.

For developed countries there will be an increase by 11% in adult population and a 27% increase in prevalence of adult diabetes and a 42% increase in number of people with diabetes.

For the developing countries there will be 92% increase in adult population and 48% increase in prevalence of adult diabetes and 170% increase in number of people with diabetes.

PREVALENCE OF DIABETES IN INDIANS

A study was conducted in selected Indian population in the Indian Institute of Technology, Chennai[12]. A total of 1198 persons of whom 743 (62%) were males and 455 (38%) were females, in 116 patients of whom 80 males (69%) and 36 females (31%) having diabetes were diagnosed. The remaining 1082 (90.3%) of whom 663 (61.3%) males, 419 (38.7%) females were screened by OGTT. Among the males, 450 (67.9%) were normal, 155 (23.4%) had impaired glucose tolerance and 58 (8.7%) had diabetes.

In this study prevalence was 9.7% and 7.7% for the known and newly detected type 2 diabetes.

In another study conducted in Chennai[13] with 26,066 people of whom 13,366 were males and 12,700 were females. The crude as well as age adjusted prevalence of diabetes was 4.9% for the people aged over 20 years. The estimated crude prevalence of diabetes was 10.5%.

A study conducted in Dombivilli by S .V. Iyer[14] in a sample subject of 520 subjects aged over 20 years, the prevalence of diabetes was 4.61% as per the WHO criteria and was 7.5% as per the American Diabetological Association Criteria.The prevalence after 2-hour post glucose load was 6.15%. The mean glucose level increased with age and BMI.

The prevalence of IGT was 8.6% below 50 years of age. It is increased to 23.4% in the age group of 50 and above.

PREVALENCE OF DIABETES IN KARNATAKA STATE[15]

A study was conducted in Kudremukh of Karnataka state where the population included the executives, skilled and unskilled workers employed by the Kudremukh iron ore Company.

Of the 3314 subjects registered at the hospital who were aged 20 years and above, 1676 were men and 1638 were women. Among 678 people of whom 346 were men and 332 women were tested for diabetes, diabetes was present in 34 people, 5% of whom 20 were men, 14 were women. Impaired glucose tolerance was present in 15.2% of whom 8 were men, 7 were women.

Thus, a total of 49.7% had abnormal glucose tolerance. All patients had NIDDM. The crude prevalence rate was 6% in men and 4% in women, this was seen more in the younger women population and increased to 7% when adjusted to age ratio. The peak prevalence was seen in 55-64 age groups.

REVIEW OF LITERATURE

CLASSIFICATION OF DIABETES MELLITUS[16,17]

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria, such as age of onset or type of therapy. The two broad categories of DM are designated as type 1 and type 2.Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic process progresses. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications. Now that pharmacologic agents are available to target specific metabolic derangements, type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Table 2: Spectrum of glucose homeostasis and diabetes mellitus (DM).[17]

Type of Diabetes	Normal glucose tolerance	Hyperglycemia			
		Pre-diabetes*	Diabetes Mellitus		
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control	Insulin required for survival
Type 1					
Type 2					
Other specific types					
Gestational Diabetes					
Time (years)					
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)		
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)		
A1C	<5.6%	5.7–6.4%	≥6.5%		

The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). Arrows indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge and the A1C for the different categories of glucose tolerance are shown at the lower part of the figure 2. These values do not apply to the diagnosis of gestational DM. The World Health Organization uses an FPG of 110–125 mg/dL for the prediabetes category. Some types of DM may or may not require insulin for survival. *Some use the term "increased risk for diabetes" (ADA) or "intermediate hyperglycemia" (WHO) rather than "prediabetes." *(Adapted from the American Diabetes Association, 2007)*

Table 3. Etiologic Classification of Diabetes Mellitus[17]

I.	Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
A.	Immune-mediated
B.	Idiopathic
II.	Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III.	Other specific types of diabetes
A.	Genetic defects of beta cell function characterized by mutations in:
1.	Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
2.	Glucokinase (MODY 2)
3.	HNF-1 (MODY 3)
4.	Insulin promoter factor-1 (IPF-1; MODY 4)
5.	HNF-1 (MODY 5)
6.	NeuroD1 (MODY 6)
7.	Mitochondrial DNA
8.	Subunits of ATP-sensitive potassium channel
9.	Proinsulin or insulin
B.	Genetic defects in insulin action
1.	Type A insulin resistance
2.	Leprechaunism

3. Rabson-Mendenhall syndrome 4. Lipodystrophy syndromes C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase D. Endocrinopathies—Acromegaly, Cushing's syndrome, Glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, beta-adrenergic agonists, thiazides, hydantoins, asparaginase, alpha-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine F. Infections—congenital rubella, cytomegalovirus, coxsackievirus G. Uncommon forms of immune-mediated diabetes— "stiff-person" syndrome, anti-insulin receptor antibodies H. Other genetic syndromes sometimes associated with diabetes—Wolfram's syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Source: Adapted from American Diabetes Association, 2011.

THE DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS[69]

Table 4. Criteria for the Diagnosis of Diabetes Mellitus. ADA 2011

Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL)[a] *or*
Fasting plasma glucose 7.0 mmol/L (126 mg/dL)[b] *or*
HbA1C > 6.5%[c] *or*
Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[d]

[a]Random is defined as without regard to time since the last meal. [b]Fasting is defined as no caloric intake for atleast 8h. [c]The test should be performed in laboratory certified according to HbA1C standards of the Diabetes Control and Complications Trial. [d]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use.

Source: American Diabetes Association, 2011.

Insulin Biosynthesis, Secretion, and Action[18]

NORMAL INSULIN METABOLISM AND THE GLUCOSE HOMEOSTASIS

Biosynthesis

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the amino-terminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor. Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and co-secreted from secretory granules in the beta cells. Because C peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia. Pancreatic beta cells co-secrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino-acid peptide, along with insulin. The role of IAPP in normal physiology is incompletely defined, but it is the major component of the amyloid fibrils found in the islets of patients with type 2 diabetes, and an analogue is sometimes used in treating type 1 and type 2 DM.

Human insulin is produced by recombinant DNA technology; structural alterations at one or more amino acid residues modify its physical and pharmacologic characteristics.

Secretion

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides and neurotransmitters also influence insulin secretion. Glucose levels >3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by a facilitative glucose transporter. Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which

inhibits the activity of an ATP-sensitive K^+ channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (e.g., sulfonyl-ureas, meglitinides); the other is an inwardly rectifying K^+ channel protein (Kir6.2). Inhibition of this K^+ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium) and stimulates insulin secretion. Insulin secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80–150 min. Incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion. Glucagon-like peptide1 (GLP-1), the most potent incretin is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level. Incretin analogues, are used to enhance endogenous insulin secretion.

Insulin secretion is modulated such that glucose production and utilization rise or fall to maintain normal blood glucose levels. The human insulin m-RNA is transcribed. Translocation of message occurs in the rough endoplasmic reticulum yielding a pre-pro insulin, there follows a proteolytic cleavage of pre-peptide sequences to yield a pro insulin, and in the golgi apparatus cleavage of the C-peptides to yield insulin sequence, both insulin and C-peptides are stored in secretory granules and secreted together after a physiological stimulus. The release of insulin from the beta cells is biphasic in manner involving the two pools of insulin. A rise in blood glucose levels results in the glucose uptake into beta cell, is facilitated by an insulin dependent glucose transport protein GLUT-2 and leading to an immediate release of insulin presumably that is stored in beta cell granules, if the secretory response persists a delayed and protracted response will follow, which involves the active secretion of insulin. The most important stimulus that triggers insulin release is glucose which also potentiates the insulin synthesis.

The calcium efflux, alpha adrenergic stimulus, cAMP, glucagon like peptides are also involved in insulin secretion. Intestinal hormones, amino acids such as leucine, arginine also stimulate insulin release but not synthesis.

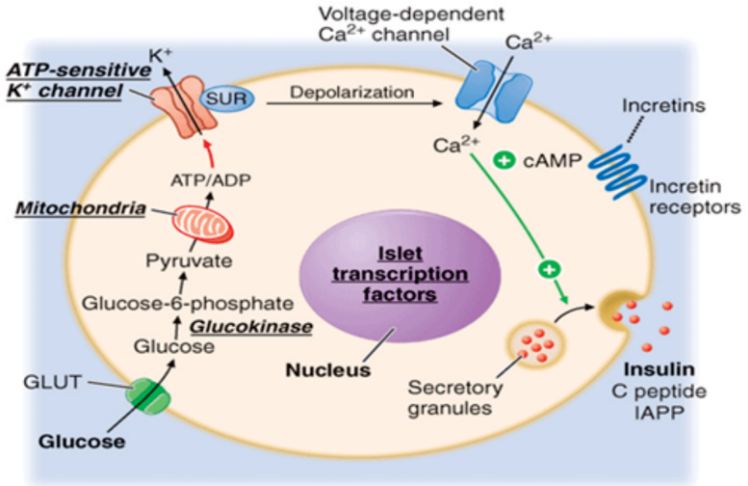

Figure 2. Mechanisms of glucose-stimulated insulin secretion and abnormalities in diabetes.

Glucose and other nutrients regulate insulin secretion by the pancreatic beta cells. Glucose is transported by a glucose transporter (GLUT1 in humans, GLUT2 in rodents); subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR (sulfonylurea receptor) is the binding site for some drugs that act as insulin secretagogues. Mutations in the events or proteins underlined are a cause of maturity-onset diabetes of the young (MODY) or other forms of diabetes. SUR(sulfonylurea receptor), ATP(adenosine triphosphate), ADP(adenosine diphosphate), cAMP(cyclic adenosine monophosphate), IAPP(islet amyloid polypeptide or amylin).[69]

Action

Insulin is a major anabolic hormone and is required for;

1) Transmembrane transport of glucose and amino acids
2) Glycogen formation in liver and skeletal muscles
3) Glucose conversion to triglycerides
4) Nucleic acid synthesis
5) Protein synthesis

One of the most important functions of insulin is glucose transport into the following cells.

1) Striated and myocardial cells
2) Fibroblasts
3) Fat cells which represent two third of body mass

In addition to these metabolic functions, insulin like growth hormones initiate DNA synthesis in certain cells and stimulate their growth and differentiation. Insulin interacts with its target cells by binding to the insulin like receptors composed of two glycoproteins- alpha and beta. Since the amount of insulin bound to the cells is affected by the availability of receptors, their numerous functions are important in regulating the action of insulin. Receptor bound insulin triggers number of intracellular responses including activation or inhibition of insulin sensitive enzymes in the mitochondria, protein synthesis and DNA synthesis.

Once insulin is secreted into the portal venous system, 50% is removed and degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in the target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signalling molecules, such as insulin receptor substrates (IRS). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidylinositol-3'-kinase (PI-3-kinase) pathway stimulates translocation of a facilitative glucose transporter (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signalling pathways induce glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

The GLUT-4 in muscles and the adipose tissue is the major insulin regulator and transporter, the GLUT-2 on the other hand is present in the liver and beta cells of pancreas insulin independent and serves to facilitate rapid equiliberation of glucose between extra and intracellular compartments.

One of the earliest defects involved is translocation of glucose transport protein unit (GLUT) from the golgiapparatus to the plasma membranes, thus facilitating celluar uptake of glucose. There are several forms of GLUTs which differ in their tissue distribution, affinity for glucose and sensitivity to insulin.

Hepatic production of glucose is regulated by number of hormones. Conversely, after glucose enter the cells, it is metabolized by oxidation to carbondioxide and water or is stored by non oxidative metabolism as glycogen synthesis, defects in all these regulator steps in glucose homeostasis namely insulin secretion glucose transport, glucose production, glucose utilization are found in patients of type-2-diabetes.

TYPE - 2 DM

PATHOGENESIS OF DIABETES MELLITUS AND ITS COMPLICATIONS [19,20,21,22,23,24]

Diabetes mellitus represent a group of metabolic disorders in which there is impaired glucose utilization including hyperglycemia. A defective insulin secretion response underlies glucose utilization. Fat and protein metabolism are also affected.

PATHOGENESIS OF TYPE-2-DIABETES[19,20,21]

Genetic factors: These are of greater importance in type-2-diabetes than in type-1-diabetes. Among the identical twins the concordance rate was above 90%.

However, like type-1-diabetes, it is not HLA associated except a weak link among the Pima Indian. There is no evidence of autoimmune mechanism except a few subgroups. The mode of inheritance is largely unknown in the maturity onset diabetes which is autosomal dominant and linked to chromosomes 7, 20 and 12. The defect in chromosome has been traced to mutations in gene encoding the glucose phosphorylation enzyme, glucokinase which serves as part of glucose sensing mechanism, regulating insulin secretion in pancreatic beta cells. There is also evidence that a subgroup of patients with type-2-diabetes between polymorphic alleles of glycogen synthetase, which is the rate limiting step for glucose conversion to glycogen storage in the muscle cells.

Two metabolic defects that characterize type-2-diabetes are:

1. Derangement of insulin secretion that is insufficient relative to glucose load.
2. An inability of peripheral tissues to respond to insulin (insulin resistance).

The primary abnormality of an insulin secreting defect verses insulin resistance is a matter of confusion and most of the people have both.

Insulin deficiency: Early in the course of type-2-diabetes, insulin secretion appears to be normal and the plasma insulin levels are not reduced. However, subtle defect in beta cell function are found. In the normal individuals insulin secretion occurs in a pulsatile manner whereas in a diabetic, normal pulsatile or oscillatory pattern is lost. At about same time when the blood sugar reaches about 115 mg/dl, the rapid first phase of insulin secretion caused by chronic hyperglycemia, referred to as glucose toxicity is due to reduction of GLUT-2 transporters, which facilitate glucose entry into beta cells. In due course of time most patients develop mild to moderate insulin deficiency. Assessment of insulin deficiency in type 2 diabetes is complicated by the occurrence of obesity. Even in the absence of diabetes the obesity is associated with insulin resistance and hyperinsulinemia. However, when obese type 2 diabetics are compared with weight matched non diabetics, the insulin levels of obese diabetics are below those obeserved in obese non diabetics suggesting a relative insulin deficiency. Further more in patients with moderately severe type2 diabetes, it is possible to demonstrate an absolute deficiency of insulin.

Insulin resistance: In most patients with type-2-diabetes insulin deficiency is not of sufficient extent to explain the metabolic disturbances.It is logical to suspect impairment of tissue responses to insulin. Indeed, there is abundant evidence that insulin resistance is the major factor in the pathogenesis of diabetes. It is a complex phenomenon which is not restricted to diabetes. In both cases of obesity and pregnancy, insulin sensitivity of tissues is decreased even in the absence of diabetes. Hence the obesity and pregnancy may unmask the sub clinical type-2-diabetes by increasing the insulin resistance. Obesity an extremely important diabetogenic influence and not surprisingly over 80% of diabetics are obese. This insulin resistance can he reduced with weight loss in early stage.

Cellular basis of insulin resistance: Although unclear there is decrease in the number of receptors and more importantly post receptor defects including the impaired signalling. Binding of insulin to its receptors leads to translocation of GLUTS, particularly GLUT-4 in the muscles and fat tissues. This may account for insulin resistance in obesity and type2 diabetes.

We can conclude that most patients with type-2-diabetes have a relative or absolute deficiency of insulin. However, this is milder compared to type-1-diabetes and is not an early feature of this disease. The cause for insulin deficiency in type-2-diabetes is unknown. Unlike type-1-diabetes there is no evidence of viral or auto immune mediation. According to one of the views, all the somatic cells of diabetics, including the pancreatic beta cells are genetically vulnerable to injury, leading to accelerated cell turnover and the premature aging and ultimately to a modest reduction in beta cells.

In addition to insulin resistance there is increased glucose production in the liver further aggravating the hyperglycemia.

To summarize, type-2-diabetes is a complex disease, multifactorial in origin involving both impaired insulin release and end organ insensitivity. Insulin resistance is frequently associated with obesity and produces excessive stress on beta cells which may fail in the face of sustained need or state of hyper insulinemia, genetic factors being more involved in Maturity Onset Diabetes in young (MODY). But in most cases of type-2-diabetes how this fits into the puzzle remains unclear.

Relevant chemical and biological properties of advanced glycosylation end (AGE) products.[19]

Chemical properties:

1) Cross link polypeptides of some proteins e.g. Collagen
2) Trap non glycosylated proteins e.g. LDL Immunoglobulins, complements.
3) Confer resistance to proteolytic digestion
4) Inactivate nitric oxides
5) Bind nucleic acids.

Biological properties

1) Bind to AGE receptors on monocytes and mesangial cells and induce

a) Monocyte emigration
b) Cytokine and growth factor secretion
c) Procoagulant activity
d) Enhanced cellular proliferation
e) Enhanced extra cellular matrix production.

2) Intracellular hyperglycemia with disturbance in polyol pathway.

In some tissues for e.g. Nerves, lens, kidneys and blood vessels that do not require insulin for glucose transport, hyperglcemia leads to increase in intracellular glucose. The excess of glucose is metabolized to sorbitol, a polyol by the enzyme aldolase reductase and eventually to fructose. The accumulated sorbitol and fructose lead to increased intracelluar osmolarity and influx of water and eventually to osmotic cell damage. Sorbitol accumulation is associated with decrease in myo-inositol content resulting in decreased phosphoinositide metabolism, diacyl glycerol, protein kinase C, sodium potassium ATPase activity.

METABOLIC DERANGEMENTS IN DIABETES

Insulin is a major anabolic hormone in the body and derangements in insulin functions affect not only glucose metabolism but also fat and protein metabolism. Unopposed secretion of counter regulatory hormones-glucagon, growth hormone and epinephrine is now thought to play a role in these metabolic derangements which are most severe in diabetes. The assimilation of glucose into muscle and adipose tissues is sharply diminished or even abolished, not only does the storage of glycogen in the liver and muscle increase but also the reserves are depleted in glycogenolysis. The fasting hyperglycemia may reach levels many times greater than normal and when the circulating glucose exceeds the renal threshold, glycosuria ensues. The excessive glycosuria induces an osmotic diuresis and polyuria which cause a profound loss of water and electrolytes.

MORPHOLOGY OF DIABETES AND ITS COMPLICATIONS

The important morphological changes in diabetes are related to its systemic complications since they are major cause of morbidity and mortality. There is extreme variability among patients in the time of onset,

the severity of these complications and the particular organs involved. In most patients regardless of the type of diabetes when the disease is present over 15 years, morphological changes are present in basement membrane of small vessels (microangiopathy) kidneys, retina, nerves and other tissues and the clinical evidence of dysfunction of these organs present.

Islet changes in the lesions in pancreas are neither constant nor pathognomic. One or more of the changes may occur.

1) Reduction in size and number of islets. This is most often seen in type-1-diabetes and particularly in rapidly progressive disease. Most of the islets are small, inconspicuous and easily detected on routine staining sections.
2) Increase in size and number of cells. This may be seen in diabetic or non diabetic infants of diabetic mother. Presumably maternal hyperglycemia leads to fetal hyperglycemia and compensatory hyperglycemia of fetal islets.
3) Beta cell degranulation. This is encountercd in type-1-diabetes and thought to represent depletion of secretory stores of insulin in damaged cells.
4) Fibrosis of islets.
5) Amyloid replacements of islets by an amorphous substance having fibrillar substructure characteristics of amyloid deposits are composed of polypeptide amylin called as islet amyloid polypeptide (IAPP). Both the collagenous and amyloid deposits occur at first about the microcirculation within the islets and progressively extend to obliterate the surrounding cells. These are more common in type-2-diabetes.
6) Leukocyte infiltration may take one of the two forms. The most common pattern is heavy lymphocytic infiltration within the islet cells called the insulitis.

The susceptibility of a diabetic to atherosclerosis is due to the following factors.

1) Hyperlipidemia occurs in one third to half of patients, but even those with normal lipid levels also have severe atherosclerosis.
2) HDL levels are low in diabetics which enhance susceptibility to

atherosclerosis.

3) Non enzymatic glycation of LDL renders it more recognizable by the LDL receptors, while the HDL is more easily degradable which enhances atherogenesis.
4) Increased platelet adhesion and aggregation.
5) Obesity is present in most diabetics.
6) Hypertension is also common in diabetes which can aggravate atherogenesis.

Whatever the mechanisms, all diabetics who have had disease for 10 years and more irrespective of their age of onset are likely to develop significant atherosclerosis.

INSULIN RESISTANCE SYNDROME [25,26,27,28,29,30,31,32,33]

The insulin resistance syndrome comprises a spectrum of disorders, with hyperglycemia representing one of the most readily diagnosed features. The *metabolic syndrome*, the *insulin resistance syndrome*, or *syndrome X* are terms used to describe a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia (decreased HDL and elevated triglycerides), obesity, type 2 diabetes or IGT/IFG, and accelerated cardiovascular disease.

The various studies done worldwide show that diabetes is a multifactorial disease. The Neele's thrifty genotype or fasting or feasting hypothesis shows that an individual harbours the genes for diabetes at birth which become expressive when the apt environment arrives. The probable cause for Indian epidemic of diabetes is at the intrauterine level.

Most of the Indian new born babies are small compared to the western new born babies. However the major deficit was in the non fat tissue that is the abdominal viscera, skeletal muscle, but the fat at subscapular skin fold was well preserved. This suggests that besides the obligatory preservation of brain, the mal-nourished fetus favors adipose tissue deposition at the expense of muscle and the abdominal viscera which include liver, pancreas and kidney. In the metabolic terms, net lipogenesis rather than structural protein synthesis was favored in the small babies of small mother. The thin but centrally obese phenotype of an adult with type-2-diabetic Indians seem to be let down in utero. Poorly developed liver,

pancreas and kidney could have relevance to the occurrence of number of disorders of the future.

A study conducted at the South Hampton has shown that poor intrauterine growth and adult diabetes and the coronary artery disease are interrelated, the major cause of fetal malnutrition is maternal malnutrition.

Maternal malnutrition in India is amongst the poorest and Indian babies are one of the smaller in the world. Upto one third are less than 2500gms at birth due to intrauterine growth retardation.

A study conducted at the KEM hospital at Pune showed that at the age of four years, circulating glucose and the insulin concentrations 30 minutes after an oral glucose were related inversely to the birth weight and directly to the current weight and the skin fold thickness.

Thus, poor intrauterine growth coupled with subsequent obesity was[34] associated with disturbance in glucose insulin metabolism, suggestive of insulin resistance. This is the earliest age at which a relationship of poor intrauterine growth with disturbed glucose and insulin metabolism are demonstrated. These children were again studied at the age of 8 years. The combination of being small at birth but big at the age of 8 years was associated not only with higher glucose and the insulin concentration but also with insulin resistance syndrome features. There were higher blood insulin levels and also triglycerides. Not only the weight and fat mass at 8 years were related but also the height, so that the taller children who were born small were also insulin resistant. It appears that catch up growth in low birth weight babies is associated with development in insulin resistance syndrome.

Another study at Holsworth memorial hospital in Mysore by[35] Dr. Caroline Fall and her colleagues traced five hundred individuals born in that hospital and living in the surrounding areas. At the mean age of 45 years, non fatal coronary artery diseases such as angina and Q wave abnormalities were increased in men and women who were born small for height, weight and head circumferance. In men, small birth weight was related to hyperinsulinemia. Diabetes was increased in those who were

short and heavy at birth and born to relatively heavy mother. These individuals were insulin deficient after a dose of oral glucose. There is however marked urban to rural gradient in the prevalence of insulin resistance syndrome and the rapid rise in the prevalence of urban Indians over the last five decades which is difficult to explain by thrifty phenotype alone. Intrauterine malnutrition and low birth weight have existed in India for a very long period and are common in villages where the diabetes is uncommon. The striking difference is due to obesity in the urban population. Higher rates of diabetes in the overseas first generation Indians migrated to western countries in comparison to their natives in India is higher. This is due to life style adaptation.

Thus a combination of poor intrauterine growth reflected by small babies[36] at birth and later on adapting one self to the affluent and western life style with consumption of high caloric food and lesser physical exercise leads to obesity which can in turn lead to insulin resistance syndrome.

The post natal obesity seems to be more detrimental in small babies adapted to the life of scarcity inutero. This is the bases of adaptation and dysadaptation hypothesis of the insulin resistance and diabetes. This explains high risk of diabetes in India and other developing population at a relatively low BMI (body mass index). Thus being small at birth predisposes and subsequent over weight precipitates diabetes.

Thus the epidemic index of the ratio of impaired glucose tolerance (IGT) to total glucose intolerance (TGI) correlates well with duration of diabetes. Thus, higher the prevalence of IGT to TGI in a population, greater the potential for type 2 - diabetes in that population.

In India, the prevalence of IGT in both rural and urban population is around 8%. The prevalence of diabetes varies over four times in the urban population. This implies that as the nutrition standards improve and urbanization creeps into rural settings, the population of IGT will be converted to overt diabetes. This is again found in migrant Indians abroad.

The features of insulin resistance syndrome detectable clinically-

The third report of expert panel on detection, evaluation and treatment of high cholesterol detected in adults has put forth the following guidelines.

The diagnosis of metabolic syndrome is made when three or more risk determinants given below are present.

RISK FACTORS:

1) Abdominal ObesityWaist circumference
   a) Men > 102 cms (>40 inches)
   b) Women> 88 cms (>34.5 inches)
2) Triglycerides> 150 mg/dl
3) HDL cholesterol
   a) Men < 40 mg / dl
   b) Women< 50 mg / dl
4) Blood Pressure> 130 / 85 mmHg
5) Fasting glucose> 110 mg / dl

Factors associated with increased likelihood of insulin resistance

- Strong family history of diabetes
- History of gestational diabetes
- Polycystic ovarian disease
- Impaired glucose metabolism
- Obesity, BMI of >30kg / m^2
- Increased waist hip ratio (WHR), 0.9 to 1 in men and 0.8 in women.

ADIPONECTIN IN DIABETES

Adiponectin is highly and specifically expressed in differentiated adipocytes and circulates at high levels in the bloodstream. Adiponectin is an approximately 30 kDa polypeptide containing an N-terminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal globular domain.[37]

Adiponectin is a 244 amino acid protein that is synthesized exclusively in adipose tissue. Growing evidence suggests that adiponectin is an important determinant of insulin resistance since it acts either hormonally or locally on adipocytes to alter insulin signalling and influences glucose and lipid metabolism. Circulating levels of adiponectin is also associated with better lipid profile, particularly higher levels of HDL cholesterol and lower triglycerides, decreased inflammation and improved glycemic control.[38]

A strong and consistent inverse association between adiponectin and both insulin resistance and inflammatory states has been established. Plasma adiponectin declines before the onset of obesity and insulin resistance in nonhuman primates, suggesting that hypoadiponectinemia contributes to the pathogenesis of these conditions. Adiponectin levels are low with insulin resistance due to either obesity or lipodystrophy, and administration of adiponectin improves metabolic parameters in these conditions. Conversely, adiponectin levels increase when insulin sensitivity improves, as occurs after weight reduction or treatment with insulin-sensitizing drugs.

In the liver, adiponectin enhances insulin sensitivity, decreases influx of NEFAs, increases fatty acid oxidation, and reduces hepatic glucose output. In muscle, adiponectin stimulates glucose use and fatty acid oxidation. Within the vascular wall, adiponectin inhibits monocyte adhesion by decreasing expression of adhesion molecules, inhibits macrophage transformation to foam cells by inhibiting expression of scavenger receptors, and decreases proliferation of migrating smooth muscle cells in response to growth factors. In addition, adiponectin increases nitric oxide production in endothelial cells and stimulates angiogenesis. These effects are mediated via increased phosphorylation of the insulin receptor; activation of AMP activated protein kinase, and modulation of the nuclear factor-B pathway. Taken together, these studies suggest that adiponectin is a unique adipocyte-derived hormone with antidiabetic, antiinflammatory, and antiatherogenic effects.[39]

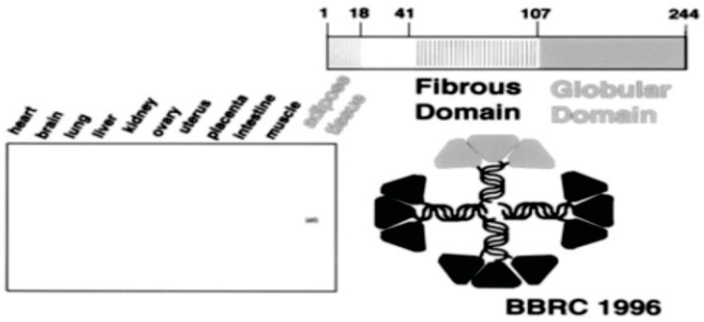

Figure: 3. Structure and adipose tissue-specific expression of adiponectin gene

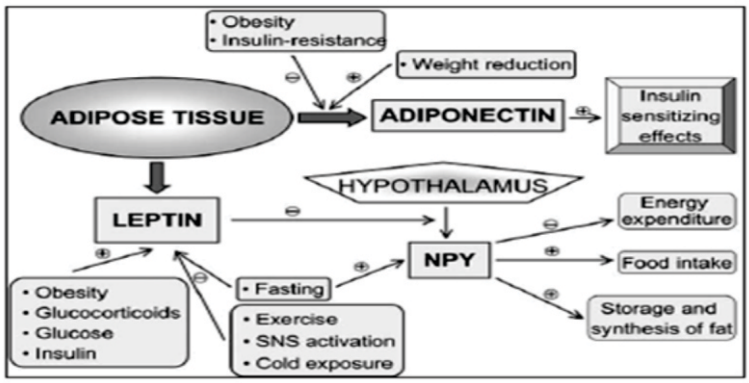

Figure 4. Role of adipokines.[39,40]

Adipose tissue secretes leptin in states of food deprivation, SNS stimulation, exercise and cold exposure. Leptin secretion from adipose tissue is inhibited by obesity states, glucocorticoids, glucose and insulin. Leptin reaches hypothalamus, where in turn it inhibits secretion of NPY that normally reduces energy expenditure, enhances appetite and stimulates synthesis and storage of fat. Adiponectin normally sensitizes tissues for insulin effects. Obesity and insulin resistance negatively regulate adiponectin secretion from adipose tissue, whereas weight reduction enhances its secretion.

In the year 2003 there were identified two receptors for adiponectin. AdipoR1 is a receptor for the globular adiponectin and it is found in the skeletal muscles. AdipoR2 is a receptor for the entire adiponectin molecule and is found in the liver.

Toshimasa Yamauchi and colleagues,[41] using molecular cloning techniques, recently identified the genes for adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) on human chromosomes 1p36 and 12p13, respectively. The receptors contain seven transmembrane domains but are structurally and functionally distinct from the classic G-protein-coupled receptors. AdipoR1 is expressed ubiquitously but is most abundant in skeletal muscle, whereas AdipoR2 predominates in liver. The two receptors share only about 67% homology to each other and appear to have different binding affinity for globular or full-length adiponectin, such that the globular form has greater effects on the AdipoR1, whereas both

globular and full length forms have more moderate effects on the AdipoR2 isoform. Tissue specificity of receptor distribution and differential ligand interactions could be an important opportunity for precise regulation of related, but distinct, physiological pathways. Human and murine cDNAs show high homology for both receptor subtypes (96·8% for AdipoR1 and 95·2% for AdipoR2), and conservation across species from yeast to human beings further supports the fundamental relevance of the signalling pathways in metabolism.

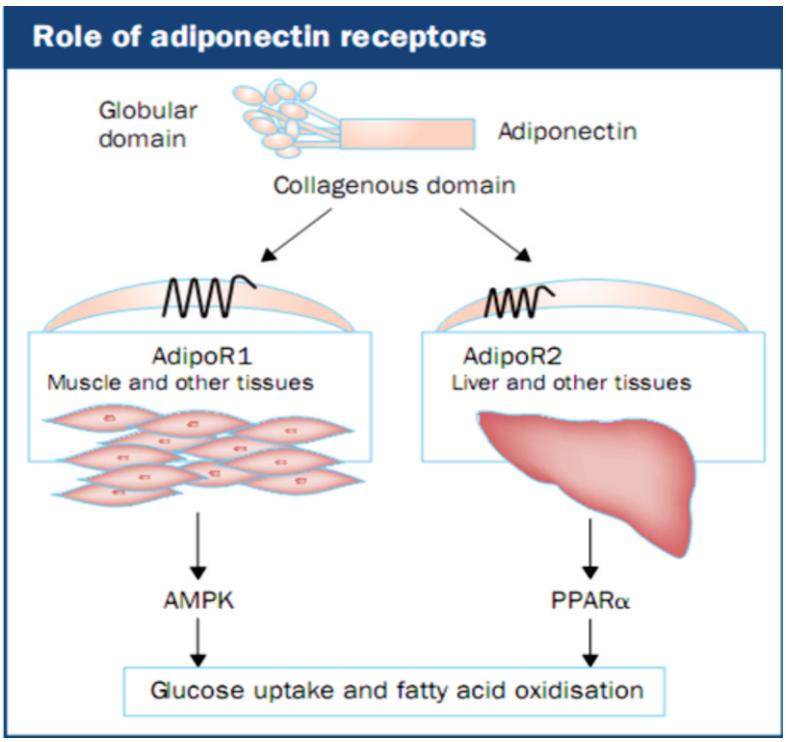

Figure 5: Role of Adiponectin receptors

Both globular and full-length adiponectin increase phosphorylation of AMP-activated kinase, an enzyme that has a role in the insulin-sensitising and glucose-lowering actions of exercise[42] and of the biguanide metformin,[43] and which may be involved in the actions of thiazolidindione agents in muscle tissues.[44] In addition, adiponectin seems to increase activity of peroxisome proliferator-activated receptor . Activation of these pathways results in decreased hepatic glucose production,[45] increased glucose uptake and fatty acid oxidation in muscle[46,41,47] and may mediate

the cardiovascular effects.[48] Identification of adiponectin and cloning of the adiponectin receptors will permit a clearer understanding of the role of adiponectin in normal and abnormal physiology, which may ultimately lead to novel therapies for diabetes and insulin resistance syndromes.

Discovery of Adiponectin and Its Clinical Significance

Adiponectin was identified in the adipose tissue in the year 1996. 40% of expressed genes in adipose tissue are unknown or, novel genes. The gene that was expressed most abundantly and specifically in adipose tissue was also a novel gene.[49]

The molecule encoded by this gene, adipose most abundant gene transcript-1, possesses a signal peptide, collagen-like motif and globular domain, and has the significant homology with collagen X nand VIII and complement factor C1q (**Figure: 4**).[49]

The term was matrix-like protein, the adiponectin. The mouse homologue of adiponectin has been cloned as ACRP30 and AdipoQ [50,51] .

Plasma levels of adiponectin in humans are substantially high, up to 5 to 10 microg/mL on an average[52]. Interestingly, plasma levels are negatively correlated with body mass index, whereas leptin, another adipose tissue-specific secretory protein, is known to increase with body mass index.[53] The negative correlation is stronger between adiponectin levels and visceral adiposity than between the protein and subcutaneous adiposity. It has been reported that TNF-alpha is a strong inhibitor of adiponectin promoter activity.[54] The negative correlation between visceral adiposity and adiponectin levels might be explained by the increased secretion from the accumulated visceral fat . Diabetic patients with macroangiopathy also have lower levels of adiponectin than those without macroangiopathy[55].

Lindsay et al[56] also demonstrated that plasma levels of adiponectin were lower in Pima Indians, a unique cohort with high prevalence of obesity, with diabetes. They also demonstrated that plasma levels of adiponectin are strongly correlated with insulin sensitivity evaluated by glucose disposal rate[57]. These results suggest that adiponectin has an important role in insulin actions and hypoadiponectinemia may result in insulin resistance and diabetes mellitus.

Although it has not been clarified whether hypoadiponectinemia observed in diabetic patients is genetic or is attributed to visceral fat accumulation, adiponectin may play a crucial role in the development of diabetes mellitus and high adiponectin levels should protect the impairment of glucose metabolism, as demonstrated in the study of Pima Indians.

Recent studies have also shown that subjects with hypertension have lower levels of plasma adiponectin.[58] The more important significance of adiponectin is that this protein shows lower levels in ischemic heart disease.[59]

Kaplan-Meyer analysis in subjects with renal insufficiency demonstrated that the subjects with hypoadiponectinemia died of cardiac events more frequently during 4 years of observation.[60]

These data suggest that hypoadiponectinemia might be a novel and important risk factor of atherosclerotic disease[59]

Cell Biological Functions of Adiponectin

A large amount of adiponectin flows with the blood stream inside the vascular walls. It would be interesting to know whether adiponectin can enter into vascular walls.

Immunohistochemical examination using anti- adiponectin antibody demonstrated that there is no existence of adiponectin in the untreated normal vascular walls in rabbit.

However, markedly positive immunohistochemical stain was detected in the balloon-injured vascular walls.[61]

Because adiponectin has been shown to have an ability to bind subendothelial collagen, such as collagen V, VIII, and X, endothelial injury may induce the entering of adiponectin into subendothelial space by binding to these collagens.

Antiatherogenic Function Of Adiponectin.

Adiponectin has potential inhibitory activities of atherogenic cellular phenomena.

Physiological concentration of adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, including intracellular adhesion molecule-1 , vascular cellular adhesion molecule-1, and E-selectin.[71]

Adiponectin was shown to inhibit the TNF- alpha induced nuclear factor-kappa B activation through the inhibition of I kappa B phosphorylation , which might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells.[72]

Adiponectin also inhibits the expression of the scavenger receptor class A-1 (SR-A) of macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation.[73]

In addition, adiponectin inhibits the proliferation and migration of smooth muscle cells. This inhibition was shown to be attributable to the binding competition to platelet-derived growth factor-BB receptor of adiponectin and the inhibition of signal transduction through extracellular signal-related kinase (ERK).[74] From these vascular cellular functions, adiponectin may have a potential antiatherogenicity.

In humans, many offensive factors are present, including oxidized LDL, inflammatory stimuli, and chemical substances that may induce vascular injuries. At that time, adiponectin secreted from adipose tissues may go into the injured arteries and protect against the development of atherogenic vascular changes (Figure 7).

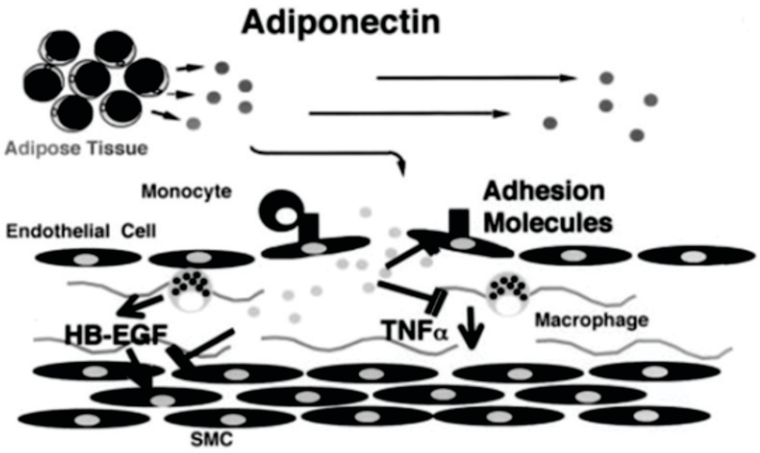

Figure -6 . Molecular Mechanism Of Antiatherogenic Function Of Adiponectin.

Therefore, adiponectin might be likened firefighters who put out the fire of the vascular walls while it is still small. When the plasma levels of adiponectin are decreased in the subjects with visceral fat accumulation, the small fire may become bigger and bigger because of the shortage of firefighters.

DIABETICS AND CARDIOVASCULAR RISK[62,63,64,65]

The strong heart study[66] showed that prevalence ratio of definite myocardial infarction were 3.8 for diabetic women and 1.9 for diabetic men: prevalence ratio for definite coronary heart disease was 4:6 and 1.8 respectively. This data showed that diabetic women have larger adverse difference in several cardiovascular diseases. Women with diabetes compared with their non diabetic counter parts, were more obese, and there was greater increase in central adiposity than was seen when comparing diabetic versus non-diabetic. In the present study, waist circumference was reflective of body fat distribution in the abdominal area, including both subcutaneous and visceral apidose tissue mass. An analysis of waist circumference provided data similar to that of waist -hip ratio (with p=0.0015) giving evidence to support the possibility that it is the amount of abdominal fat that differs in individuals with diabetes. Several reports have shown that visceral fat mass, as measured by computed tomography is more strongly associated with risk factors of myocardial

infarction than other components of waist circumference and there are many studies showing that waist circumference is significantly associated with coronary heart disease.

Thus the greater difference associated with diabetes in waist-to-hip ratio in women compared to men could definitely contribute to greater impact of diabetes on cardiovascular diseases in women. This data also indicates that diabetic women - compared to their non diabetic counterparts, have more adverse lipoprotein changes than do the non diabetic one, including the greater decrease of HDL cholesterol, apoAl, LDL size, and greater increase in apo B. Sex difference in diabetic associated lipoprotein levels have been observed in several other studies also. In the Rancho Bernado cohort, diabetic women had greater increase in total and LDL cholesterol and greater decrease in HDL cholesterol than did the diabetic men.

In the San Antonio heart study, diabetes in Mexican American women was associated with greater increase in LDL cholesterol and decreased HDL cholesterol.

Women especially those who are premenopausal, generally have lipoprotein profile that is less atherogenic than that of non diabetic men, as well as lower levels of blood pressure and fibrinogen and less abdominal obesity These may all be explained by the presence of estrogen, which raises the HDL cholesterol, and lowers LDL cholesterol, central fat distribution and blood pressure levels. Insulin resistance has been linked to hyperandrogenicity and lower estrogen concentrations. Thus insulin resistance and its accompanying hormonal changes in diabetic women may reverse the usually favorable cardiovascular disease risk profile and result in constellation of risk factors that greatly accelerate the atherosclerotic process.

In postmenopausal women, the protective effects of estrogen with higher HDL cholesterol and lower LDL cholesterol will be reversed and these women will be more prone for cardiovascular risks, especially diabetic dyslipidemia and progressive antherosclerosis.

Atherosclerotic diseases are the leading cause of death in developed countries and part of developing countries.[67] Therefore, measures against

atherosclerosis are the biggest medical subject in the 21st century. Many epidemiological studies have been performed to clarify the pathogenesis of atherosclerosis and have revealed the importance of hyperlipidemia as the strongest risk factor for this disease. Recently, the contribution of LDL to the development of atherosclerosis and HDL to its prevention has been well demonstrated with cell biological investigations. The crucial roles of oxidized LDL in atherosclerotic cellular changes have been especially well recognized. However, when we consider the subjects who suffer from atherosclerotic diseases, lipid abnormalities can only partly explain the prevalence of the development of atherosclerosis.

Atherosclerotic cellular changes consist of basically the following 3 cellular phenomena: Monocyte adhesion to endothelial cells by the expression of adhesion molecules,oxidized LDL uptake of macrophages through scavenger receptors, and proliferation of migrated smooth muscle cells by the action of platelet-derived growth factors or heparin binding endothelial growth factor–like growth factor.

DIABETES AND THE METABOLIC SYNDROME[75]

There is growing interest in multiple risk factor syndrome, in which clustering of diabetes mellitus,hyperlipidemia ,and especially hypertriglyceridemia and hypertension is observed in each subject. Multiple risk factor syndrome has been also called syndrome X, deadly quartet visceral fat syndrome, and, recently, metabolic syndrome[68,69,70].

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM). The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension.

<table>
<tr><th colspan="4">NCEP:ATPIII 2001 and IDF Criteria for the Metabolic Syndrome[75]</th></tr>
<tr><th>NCEP:ATPIII 2001</th><th colspan="3">IDF Criteria for Central Adiposity[a]</th></tr>
<tr><th>Three or more of the following:</th><th colspan="3">Waist circumference</th></tr>
<tr><td>Central obesity: Waist circumference >102 cm (M), >88 cm (F)</td><td>Men</td><td>Women</td><td>Ethnicity</td></tr>
<tr><td>Hypertriglyceridemia: Triglycerides 150 mg/dL or specific medication</td><td>94 cm</td><td>80 cm</td><td>Europid, Sub-Saharan African, Eastern and Middle Eastern</td></tr>
<tr><td>Low HDL cholesterol: <40 mg/dL and <50 mg/dL, respectively, or specific medication</td><td>90 cm</td><td>80 cm</td><td>South Asian, Chinese, and ethnic South and Central American</td></tr>
<tr><td>Hypertension: Blood pressure 30 mm systolic or 85 mm diastolic or specific medication</td><td>85 cm</td><td>90 cm</td><td>Japanese</td></tr>
<tr><td rowspan="4">Fasting plasma glucose 100 mg/dL or specific medication or previously diagnosed Type 2 diabetes</td><td colspan="3">Two or more of the following:</td></tr>
<tr><td colspan="3">Fasting triglycerides >150 mg/dL or specific medication</td></tr>
<tr><td colspan="3">HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication</td></tr>
<tr><td colspan="3">Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication</td></tr>
<tr><td></td><td colspan="3">Fasting plasma glucose 100 mg/dL or previously diagnosed Type 2 diabetes</td></tr>
</table>

In this analysis, the following thresholds for waist circumference were used: White men, 94 cm; African-American men, 94 cm; Mexican-American men, 90 cm; white women, 80 cm; African-American women, 80 cm; Mexican-American women, 80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cut points (94 cm for men and 80 cm for women) and once based on South Asian cut points (90 cm for men and 80 cm for women) were used. For participants who were considered "other Hispanic," the IDF thresholds for ethnic South and Central Americans were

used. ***Abbreviations:*** HDL, high-density lipoprotein; IDF, International Diabetes Foundation; NCEP:ATPIII, National Cholesterol Education Program, Adult Treatment Panel III.

Although insulin resistance has been considered a key factor for clustering of multiple risk factors, the precise mechanism by which these common metabolic and circulatory disorders cluster in one individual and also why this pathophysiological state is so atherogenic have not been fully clarified by the levels of molecular basis. Clinical studies on the morbidities of obesity suggest that the extent of fat accumulation is not necessarily a determinant of development of obesity-related diseases but that body fat distribution is a more important factor for morbidity.

Adiponectin in Metabolic Syndrome[75]

Adiponectin is reduced in the metabolic syndrome. The relative contribution of adiponectin deficiency versus overabundance of proinflammatory cytokines is unclear.

SUMMARY

Adipose specific adiponectin levels are lesser in diabetes and its associated complications like CAD, HTN and obesity. As age advances, adiponectin level decreases. Females have higher adiponectin levels than males, both in diabetic and nondiabetic. Diabetics have lesser levels of adiponectin level compared to non diabetics.. Diabetics with hypertension have lower levels of adiponectin compared to non diabetics with hypertension. Diabetics with CAD have lower levels of adiponectin compared to non diabetics with CAD. Obese diabetics have lower levels of adiponectin levels than non obese diabetics. Adiponectin is inversely proportional to levels of triglyceride and LDL cholesterol , and directly proportional to levels of HDL cholesterol.

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