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Diabetes Mellitus: Its Epidemiology and Pathogenesis: A Global Focus on Type 2

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SUMMARY

Diabetes mellitus enjoys pandemic status. Majority of patients will suffer, life threatening complications resulting from microvascular and macrovascular damage associated with diabetic nephropathy, cardiovascular and cerebrovascular disease, dyslipidemias and a plethora of intracellular and extracellular biochemical abnormalities. New theories regarding its pathogenesis and specially those for type 2 have emerged over the years. This review focuses on the different aspects of epidemiology, pathogenesis and presentations of type 2 diabetes mellitus.

GLOBAL STATISTICS AND EPIDEMIOLOGY

Diabetes mellitus is a noticeable modern day scourge. The diabetic population has grown relentlessly from more than 124 million people in 1994 to over 177 million in 2004, currently at 285 million[1] with conservative projections to 366 million[2] and extreme ones to 438 million by the year 2030[1]. At present more than 92.4 million Asian people are effected. India, China and the U.S are ranked the highest in the world with affectees at 31.7,20.8 and 17.7 million respectively expected to increase to 79.4, 42.3 and 30.3 million in the same order[3,4]

The majority of affected individuals in these nations will be 35-64 years of age and those in the developed nations 65 years or more[1]. Globally, morbidity and mortality figures reflect some 3.2 million people die of diabetes each year and 6 people die of diabetes related ailments each minute[3]. It is ranked second in causation of loss of vision and nephropathy worldwide. Diabetics have 2-4 times more heart disease at an earlier age and a two times higher risk of stroke than non-diabetics. It was the seventh major instigant of mortality in the U.S. with 231,404 deaths reported each year[5].

Based on World Health Organization estimates Pakistan ranked eighth for diabetes with 4.3 million individuals suffering from diabetes in 1995. At that time it occurred in 10% of Pakistan's population affecting both sexes 25 years or above. 64% of diabetics were females and approximately 15% of diabetic population comprised of children and young adults. Impaired G.T.T. was seen in over 13% of women and over 7% of men, 56% of females also developed gestational diabetes during pregnancy[6-9]

These figures could not be updated due to absence of any new survey at the national level. However this increase continued according to international studies with Pakistan ranking 6th in a list of 10 nations with the number of diabetics reaching 5.2 million in 2000[4]. In case of persistence of the same trend, Pakistan will rise unfortunately to 4th position with 14.5 million diabetic patients by the year 2025[10].

Diabetes mellitus the disease

Diabetes mellitus pathologically is a consortium of syndromes symbolized by casual hyperglycemia (fasting plasma glucose >7.0 mmol/l,

or plasma glucose > 11.1 mmol/l, two hours after a meal [11] resulting from absolute or relative inadequacy of insulin secretion, impairment of insulin action (receptor desensitization and post receptor deregulation) or both[12]. Physiologically there is deranged metabolism of lipids, proteins and carbohydrates and a risk of vascular complications[13]. In addition there is evidence that decreased muscle glucose uptake and reduced insulin secretory response to glucose predict diabetes[14]. Increased hepatic glucose production[15], associated hypercholestrolemia and hyper-triglyceridemia are present[16]. The disease forms encompassing the diagnosis of diabetes mellitus are divided into categories: Type 1 (approximately 5% diabetics) Type 2 (95% diabetics), Type three 'others' and Type 4 'gestational diabetes mellitus [17].

The most representative symptoms of diabetes include polyuria, polydipsia, polyphagia and idiopathic decrease im weight, without postural hypotension, parasthesias, muscle weakness, impotence and more severely hypotension even in recumbent position. Other symptoms include repeated infections, poor healing of wounds, foggy vision and numbness or absence of sensation in extremities. Untreated diabetes mellitus terminates into wide ranging short as well as long term complications and sometimes even in an emergency presentation diabetic ketoacidosis which eventally progresses to coma if untreated[18]. Incidence of type 2 diabetes in the younger population is growing rapidly which is termed, 'maturity onset diabetes of the young' (MODY1, 2, 3, 4 and X)[11]. Some early symptoms include fatigue, polydipsia, polyuria and polyphagia and in women recurrent vaginal yeast infections[19]. Type 1 diabetes incidence is higher in younger individuals lesser than 30, however its onset can occur at any age. Its biochemical presentations range from frequent ketosis, hypercholestrolemia, hypertriglyceridemia, increased LDL levels[20] and sometimes can even cause slow mental function in diabetics.

The commonly occuring long term complications are neuropathy, retinopathy, nephropathy. Diabetes is the premier cause of advanced nephropathy, coronary artery disease leading to myocardial infarction, cardiomyopathy and cerebrovascular disease leading to stroke. Chronic infections, gangrene and chronic pain are also parts of its complications[21]. Diagnostic criteria for diabetes based on the standardization of plasma glucose (Table 1) as well as glycated hemoglobin levels have witnessed tremendous progress[22] (Table 2)

Table 1: Report of Experts Committee on Diagnosis and Classification of DM 2004. Diabetes Care 27(1); 47-54. Diagnosing Diabetes

Stage	Test (mmol/L – mg/dl)		
	Fasting Plasma Glucose Test (FPG) (Preferred)	**Casual Plasma Glucose Test**	**Oral Glucose Tolerance Test (OGTT) 75 gram load**
Diabetes	Fasting Plasma Glucose (FPG) greater than or equal to 7.0 / 126	Casual Plasma Glucose greater than or equal to 11.1 / 200 plus symptoms	Two-hour plasma glucose (2hPG) greater than or equal to 11.1 / 200
Gestational Diabetes	Fasting Plasma Glucose (FPG) greater than or equal to 7.0 / 126	Note above	Two-hour plasma glucose (2hPG) greater than or equal to 8.6 / 155
Impaired Glucose Tolerance (Pre-Diabetes)	Impaired Fasting Glucose (IFG) = FPG greater than or equal to 6.1 / 110 and less than 7.0 / 126	Note above	Impaired Glucose Tolerance (IGT) = 2hPG greater than or equal to 7.8 / 140 and less than 11.1 / 200
Normal	Fasting Plasma Glucose (FPG) less than 6.1/ 110		Two-hour plasma glucose (2hPG) less than 7.8 / 140

American Diabetes Association 2004 suggests normal fasting blood glucose less than 5.6mmol/ 100mg/dl & Impaired Fasting Glucose ≥ 5.6 mmol / 100 mg/dl but less than 7.0 mmol / 126 mg/dl.

Table 2: American Diabetes Association HbA1C Benchmarks.

Diabetes	A1C level is 6.5%(47mmol/ml) or higher
Pre-Diabetes	A1c is 5.7%-6.4% (39-46 mmol/ml)

Hb A1C guidelines by ADA (Standards of Medical Care in Diabetes: 2010)

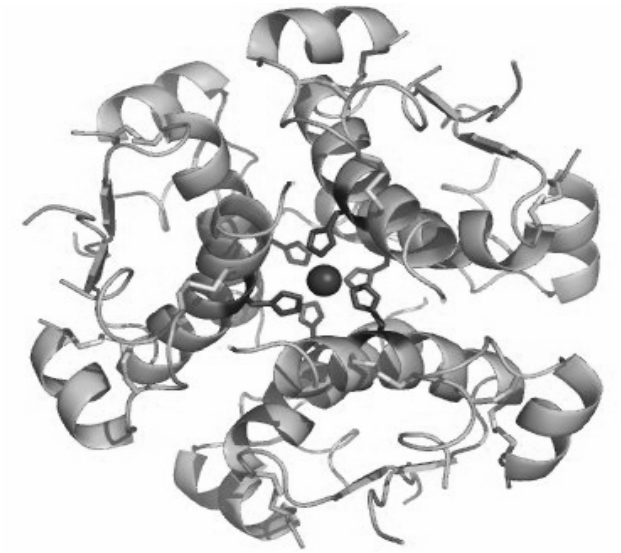

Fig. 1: Computer-generated hexameric assembly of insulin molecules, showing the threefold symmetry, with the zinc ions, and the histidine residues involved in binding. Chang X, Jorgensen AM, Bardrum P, Led JJ (August 1997). "Solution structures of the R6 human insulin hexamer". Biochemistry 36 (31): 9409–22.

TYPE 2 DIABETES: FROM NORMAL METABOLIC PHYSIOLOGY TO DIABETIC PATHOLOGY: THE INSULIN MOLECULE

Type 2 DM is a heterogenous conglomerate of metabolic disorders noticeable for hyperglycemia due to decremental insulin effect in the presence or absence of insulin secretion[23] and therefore insulin's role in maintaining metabolic balance is undeniable. Physiologically a protein (51 amino acids) anabolic hormone, with a mol wt of 5808 daltons arranged in two chains (A and B) joined by disulphide bridges, it is produced by the pancreatic beta cells of islets of Langerhans.It has a hexameric assembly with zinc and histidine residues (Fig. 1). Its basal level is maintained at 30-90pmol/L which rises upto 360-450pmol/L[13] during meals. Insulin promotes synthesis (from circulating nutrients) and storage of glycogen, triglycerides and proteins in its major target tissues: liver, fat and muscle which are reversed to a large extent in diabetes. Some of its other actions include increased potassium uptake in muscle,improved vascular compliance, especially in microarteries; augmentation of HCL secretion in stomach[24]. Insulin effects on the human brain include improvement of memory (especially verbal) and learning[25]. Reducing caloric intake and normalizing insulin levels may slow down a number of biological aging processes and enhance longevity. Postprandial levels of insulin inhibit autophagy completely while playing an important role in the anti-geriatric caloric reduction mechanism[26]. Intranasal insulin administration elevates cerebral insulin signaling and resultantly also enhances immediate thermoregulatory and glucoregulatory response to food intake, suggesting the vital role and control of central nervous insulin in human energy homeostasis[27].

Insulin release from the beta pancreatic cells occurs in phases stimulated greatly by a number of factors e.g increased blood glucose which enters through the glucose transporter GLUT 2, mannose, incretins: glucose dependent insulinotropic peptide GIP and glucagon like peptide GLP-1, amino acids leucine and argininine, gastrin, secretin, vasoactive intestinal peptide released by the enteroendocrine cells of the intestinal mucosa, vagal nerve stimulation and to a lesser extent by glucagon[24]. Alpha 2 adrenergic agonists clonidine and methyl dopa inhibit the release of insulin. In counterbalance ,circulating adrenaline activates β_2-receptors on the β-cells in the pancreatic islets to enhance insulin secretion which allows for GLUT-4 translocation in the muscle and adipose tissue. Canonical pathway of insulin secretion from B cells involving K ATP-dependent mechanism has now been supplemented by the pyruvate carboxylase mediated anaplerotic pathway[28]. These pathways involve exchange of pyruvate with several citric acid cycle intermediates and subsequent activation of mitochondrial metabolic cycles and energy production[29,30]. Inhibitory signals include somatostatin, leptin and chronically elevated glucose and fatty acid levels [24].

Diagnostically, impaired first-phase insulin release in diabetes is demonstrated in the glucose tolerance test by a significant hyperglycemia at 30 minutes, a significant decline in blood glycemia in 60 minutes and a gradual rise to baseline levels during estimations, repeated after every hour[20].

Insulin molecule is degraded primarily by liver, kidney and muscle[31]. There is a 50% first pass metabolism of insulin by the liver and the rest is

transcytosed, while renal metabolism removes most of the insulin from systemic circulation. Insulin is filtered by renal glomeruli and reabsorbed by the renal tubules which also degrade it. Degradation usually involves cellular internalization of the insulin-receptor complex, and action by thiol metalloproteinases[13]. The half life of insulin in plasma is about ~ 4–6 minutes) in normal subjects and patients with uncomplicated diabetes. This may be increased in diabetics who develop anti insulin antibodies to exogenously administered insulin[31,32.]

INSULIN SIGNALLING

General concept

Mammalian insulin receptor gene has two isoforms IR b binding to insulin and found in most well known insulin responsive organs ie liver, skeletal muscle and adipose tissues, IR a predominating in fetal and hematopoietic tissues with equal binding affinity for both insulin and IGF2[33].The human insulin receptor belongs to the superfamily of tyrosine kinases comprising of two extracellular alpha subunits and two transmembrane b subunits[34]. The activated receptors undergo autophosphorylation, which appear to activate their tyrosine kinase activity towards substrate proteins principally Gab-1 and Shc within the membrane, a caveolar pool of insulin receptor phosphorylates (Caveolar), APS (adaptor protein) and Cbl associated protein and all four IRS (insulin receptor substrates) 1 through 4[35]. These tyrosine phosphorylated proteins interact with signaling cascades via Sh2 and SH3domains recruiting such proteins as SHP2, Grb2 associated binder and SOS, resulting in activation of MAP kinases and PI3 – kinase which transduce many of insulin's cellular effects (mitogenesis, protein synthesis, glycogen synthesis, GLUT (glucose transporter translocation) among others[36]. A polymorphism in the human IRS1, G972R is linked with insulin resistance and enhanced risk of type 2 DM acting as inhibitor of the insulin receptor tyrosine kinase [37].

Pathogenesis of type 2 diabetes

Development of insulin resistance, though linked with hyperinsulinemia, significantly predicts the progression of diabetes mellitus. This is linked with coronary heart disease, hypertriglyceridemia decreased HDL cholesterol, with variation in levels of glucose intolerance termed as "Syndrome X"[38] & sleep disorder[39].There is a continuous relationship between steady state plasma glucose and insulin resistance syndrome disease outcomes mentioned above, such as hypertension, malignancy, heart disease and stroke[40]. There is also an associated risk of malignancy such breast cancer with a worst outcome[41], and prostate cancers[42]. Women with insulin resistance may have hormonal abnormalities such as increased ovarian testosterone secretion. Other biochemical changes coexisting with insulin resistance include reduced low density lipoprotein particle diameter[43] and the post prandial accumulation of remnant lipoproteins[44]. Furthermore, decreased endothelium dependent vasodilatation is seen due to lack of NO[45,47] with increased mononuclear cell adhesion[46], along with increased plasma cellular adhesion molecule amounts, and plasma asymmetric dimethyl arginine[46]. Augmented prothrombotic factors including increased plasminogen activator inhibitor 1 (PAI-1) and fibrinogen are noted[48]. Inflammatory markers including C-reactive protein and leukocyte count are also elevated. There is abnormal uric acid metabolism with decreased renal water clearance and increased plasma uric acid[49]. Hemodynamic changes with increased sympathetic nervous system activities[50] and increased renal sodium retention are also seen. Similarly fatty liver, independent of overall obesity is associated with insulin resistance, hypertension and hypertriglyceridemia[51]. Angiotensin 2 also contributes to insulin resistance while its receptor blockade by losartan in latest large l trials in diabetic patients was noticed to decrease risk of diabetes development [52]

EMERGING THEORIES

Very recently theories on T2DM pathogenesis have started to represent a multiorgan direction which range from defects in insulin-linked glucose uptake by skeletal muscle, an abnormality in secretory activities of adipocytes, poorly functioning pancreatic β-cells, altered reception /

reaction towards increased glucose levels in the brain, an abnormal accumulation of lipids, due to reduced lipid oxidative capacity and increased amounts of in circulation free fatty acids (FFAs)[53,54]. These enhanced FFA levels initiate insulin resistance, particularly in skeletal muscle, by diminishing insulin-stimulated glucose uptake, probably due to enhanced lipid levels within the muscle cell[55,56]. Mitochondrial dysfunction could also be a plausible candidate in the altered skeletal muscle response to lipids. Overweight, physical inertia and genetic tendencies all play their role in the altered lipid metabolism. The details of these compensatory processes and the precise point in the pathogenesis of T2DM where these fail and the reasons of this failure are elusive (Fig. 2).

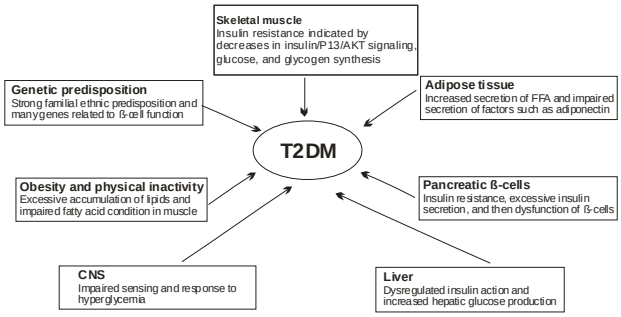

Fig. 2: Roles of Different Organs, Tissues, Physical Activity & Genes in T2DM

The skeletal muscle is responsible for insulin driven glucose removal of upto 75% from the systemic circulation, resultantly dysfunctions in skeletal tissue are important in destablising glucose homeostasis in patients with type 2 diabetes mellitus[57]. The phosphorylation of insulin receptor by tyrosine appears to be upto mark or decreased in normal weight type 2 diabetics[58]. Angiotensin 2 signalling cascade also effectively modulates the phosphorylation of insulin receptor substrate 1 in the insulin signaling pathway primarily but not exclusively at the GLUT 4 translocation site[59]. In addition to this impaired downstream signaling from PI3-kinase activation lead to increased oxidative stress in skeletal muscle in mice and is involved angiotensin 2 induced insulin resistance[60]. Type 2 diabetic subjects also exhibit faulty insulin-stimulated tyrosine phosphorylation of IRS1 in skeletal muscle. A coincidental dysfunction is noticed at the level of PI3K in musculature of type 2 diabetics[58].

Storgaard reported that insulin signaling defects contribute partially to altered insulin activity in glucose transport and glycogen production in patients before they develop type 2 diabetes[61]. The faulty behaviour of the insulin receptor or insulin receptor substrate is a usual character of insulin resistance. Mechanisms for this negative regulation could encompass tumor necrosis factor alpha mediated downregulation of mRNA transcription[62,63], proteosome-involved degradation of insulin receptor[64], and phosphatase-associated dephosphorylation[65,66] or kinase-linked serine/ threonine phosphorylation[67,68]. These signaling abnormalities could result in an impaired glucose transport in type 2 skeletal muscles[64]. A significant lack of amplification of glucagon like peptide in response to hyperglycemia was noted in obese middle aged type 2 diabetics[69]. Type 2 diabetes mellitus linked with impaired metabolic adaptibility regarding shift from lipid metabolism to glucose oxidation under insulin action has been detected as well[70].

Adipose tissue

The stimulation of AT1 receptors simulates increase in adipose cell size in the animal model. Therefore blockage of the renin angiotensin receptors using angiotensin receptor blocker should improve insulin resistance[71]. Angiopoeitin-like protein 2 is a key adipocyte derived inflammatory mediator linking obesity to insulin resistance[72]. Levels of TRAP a protein secreted by the immune cells in fat tissue are found to be raised in obese humans, which may signal a decrease in insulin sensitivity[73]. An Australian human study analysed fat tissue removed in lapband surgery and revealed that macrophages in fat tissue are producing cytokines that prevent cells from responding to insulin causing insulin resistance[74].

Adipocyte GLUT4 expression is diminished in type 2 diabetic patients [75] resulting in production of factors that are responsible for inter organ biochemical connectivity, such as serum retinol-binding protein-4 (RBP4) which enhanced liver

expression of phosphoenolpyruvate carboxykinase, a gluconeogenic enzyme and depreciated the insulin muscle response. Adipose tissue surrounding the organs and elsewhere secretes a variety of chemicals such as adiponectin, leptin, resistin, interleukin 6, tumor necrosis factorα, visfatin, with capability to alter the overall insulin physiological effects[76,77]. Decreasing protein kinase C delta activity reduces inflammation by down regulating interleukin 6 in animal mouse adipose tissue[78]. A reduction of signaling downstream of the insulin receptor may be a primary mechanism through which these inflammatory biochemicals causes insulin resistance. Adipose tissue and its self contained macrophages act by endocrinal and paracrinal signaling to facilitate inflammation and reduce insulin responsivity[77, 79].

Pancreatic β-cells

In type 2 diabetes mellitus diversified factors and pathways including endoplasmic reticulum stress[80], elevated longstanding blood sugar levels, inflammatory cytokines[81,82] or dyslipedemia[83], oxidative stress[84] are also responsible for reducing β-cell mass, their ability to function effectively in overcoming insulin resistance and eventually lead to β-cell degeneration[85]. Insulin resistance activates oxidative stress pathway protein CHOP, causing apoptosis and cell death in the beta cell in mouse model[86]. Small clusters (oligomers) of toxic islet amyloid polypeptides (IAPP) form inside beta cell membranes may also play a role in apoptosis & beta cell dysfunction characteristic of type 2 diabetes[87]. Decreased insulin receptor substrate 2 expression may also result in β-cell death[88]. Insulin receptor substrate 2 serine/threonine phosphorylation as mentioned earlier with resultant IRS2 ubiquitination and proteosomal degradation, therefore appears to link both defects in insulin signaling and insulin secretion[89]. In addition decreased β-cell insulin sensitivity appears an initial pathognomic feature in type 2 diabetes mellitus[90, 91].

Liver

The liver is a vital player in storage, formation and utilization of glucose and lipids. Hepatic lipid metabolism involves biochemical processes ranging from synthesis of fatty acids and oxidation to cholesterol, bile acids and lipoprotein formation. These metabolic pathways are closely regulated and coordinated to maintain glucose and lipid homeostasis in normal physiological circumstances[92]. Resultantly, insulin (anabolic) and glucagon (catabolic) set liver as the prime target. Free fatty acids enhance hyperglycemia causing insulin secretion. Altered hepatic insulin behavior in terms of sensitivity and action has profound importance regarding pathological progression of type 2 diabetes mellitus[93]. The liver X receptors LXR α and LXR β[94] which are nuclear hormone receptors function as integrators of lipid,metabolic and inflammatory signaling[95], have also exhibited importance in maintaining glucose balance and β cell function. LXR agonist administration augmented both baseline and provoked insulin secretion via enhanced attachment of PDX-1 pancreatic and duodenal factor homeobox1 to the proximal insulin promoter[96]. This also promoted insulin expression and a corresponding enhancement in the anareplosis gene expression which reversed the process of cholesterol transport[97,98] alongwith increase in pyruvate carboxylase activity a prime controller of cycling of pyruvate and anaplerotic flux independant of intra islet lipid accumulation[99]. Insulin receptor substrate 1 and 2 have a co-operativity in the control of insulin signaling in the liver and in gluconeogenesis, glycogen production, and lipid metabolism gene expression[93]. These function in turn rest on insulin receptor, substrate proteins themselves and are regulated by their expression levels and post translational modifications. Therefore it is not surprising that poor functioning of these IRS proteins not only lead to after meal peaks in glucose levels but also to enhanced hepatic gluconeogenesis and altered lipid synthesis all features of type 2 diabetes and insulin resistance[99-101].

Small intestine

Glucagon like peptide1 secreted by mucosa of the small intestine and its insulinotrophic activity is mediated through GLP1 receptors on pancreatic β cells[102]. In T2DM patients or pre diabetics this

response is defective as reduced concentrations of postprandial GLP1 contributes to a blunted insulin secretory response to meals[103, 104].

CNS

The central nervous system has central command authority in maintaining and modulating glucose hemostasis via a plethora of of chemical signals (neural, hormonal, and nutrient) which it senses and integrates, to regulate glucose output and uptake by the liver and peripheral tissues respectively[104]. Data from experimentation on animals have revealed that hyperphagy and increasing weight reduce the sensing and responding capacity of the central nervous system to variations in the levels of energy metabolites, whereas specific CNS treatments or procedures reduce insulin resistance and hyperglycemia[105]. Therefore insulin action on its receptors in the brain regulate peripheral glucose and fat metabolism in mice[106].

Obesity

Presence or absence of obesity subdivides Type 2 diabetes into two subgroups, the majority being obese (80-90%) and usually middle aged. Type 2 diabetes tends to be familial. The tendency of developing Type 2 diabetes grows for each pound added to body weight by 4%. This results in hyperglycemia and hyperinsulinemia in the body[107]. Hyperactivity of the systemic and adipose tissue specific rennin angiotensin systems is associated with obesity. The rennin angiotensin system has been implicated with the control of glucose homeostasis, providing a causal link among obesity diabetes and hypertension[108,109]. Interestingly however not all obese individuals are type 2 diabetic which could be due to mutation of the Brd2 gene linked to energy metabolism which in mice caused severe obesity without type 2 diabetes[110].

Within the sarcoplasm of skeletal muscle of obese individuals, the imbalance between uptake and oxidation results in profound collection of triacylglycerol, long-chain acyl-CoAs, diacylglycerols, and ceramides[111]. And here too as in the liver and pancreatic β cells elevated circulating fatty acids have been linked to faulty insulin action and resultantly poor glucose handling[112]. Also seen in human and animal skeletal muscle model of insulin resistance is diacylglycerol associated activation of protein kinase C, resulting in impairment of the insulin physiological effect through insulin receptor substrate 1 serine phosphorylation[113, 114].

Physical activity

Routine daily physical activity and alterations in dietary preferences and habits is inversely linked to the risk of developing type 2 diabetes mellitus[111]. Latest research has revealed enhancement of mitochondrial oxidative capacity with post moderate to strenuous exercise and can accelerate insulin-stimulated glucose uptake into skeletal muscle[115].

Genetic analysis

A **s**pate of genetic studies has been ongoing revealing many aspects of genetic involvement in type 2 diabetes. One such research points to a modification of the hexokinase resulting in development of Type 2 diabetes in people under the age of 25 called maturity onset diabetes of the young (MODY)[111].

The familial genetic tree provides useful clinical assessment of the potential and risks of type 2 diabetes mellitus amongst family members with enhanced risk of 40 to 70% of developing type 2 diabetes in children of a single or both diabetic parents respectively.While risk is substantially lower in the general population, approximately 7%, it is doubled in first degree relatives[116]. There are chances of developing monogenic disease such as MODY1–6 under 25 years of age or polygenic disease such as common type 2 diabetes mellitus[120]. These genes are known to be active in the hepatic, intestinal, renal and pancreatic tissue[13]. In type 2 diabetes about 20 common genetic variants of loci are known out of which namely eight genes such as TCF7L2, KCNJ11, HHEX, SLC30A8, CDKAL1, CDKN2A/2B, IGF2BP2 , KCNQ and PPARG effect the capacity of β cells to react to insulin resistance by enhancing insulin secretion[117]. One CAPN10 gene is involved in glucose transport; MC4R and FTO genes have been associated with obesity while; for eight other loci their importance remains undefined[118]. Thus, type 2 diabetes mellitus is the culmination of a multiorgan disease, in which a

cooperativity of malfunctions exist which are noticeably early direct or indirect defects in skeletal muscle, adipocytes, hepatocytes, β-cells of pancreas, and the central nervous system.

Mitochondria and reactive oxygen species

Reactive oxygen species and involvement of oxidative stress markers may regulate insulin resistance[118,119]. Data reveals depreceation in insulin action and enhancement of reactive oxygen species levels upon in vitro treatment of 3T3-L1 adipocyte tumor necrosis factor alpha or dexamethasone[120]. While, opposing antioxidant, or transgenic reactive oxygen species removing enzyme therapy, both decreased insulin resistance to tumor necrosis factor alpha or dexamethasone-treated 3T3-L1 adipocytes with variable effect. Decreased mitochondrial oxidative phosphorylation has been lately revealed in diabetic patients, using microarray for localizating underworking genes, PGC1 (PPARGC1A and NRF1 involved in oxidative phosphorylation[121,122]. Angiotensin 2 probably plays a role in decreasing mitochondrial content possibly through AT1 receptor enhancement of their lysis and AT2 receptor dependant direct decrease of their biological formation[123]. Other human data presents a shared responsibility of weak mitochondrial lipid metabolism, mitochondrial dysfunction, reduced numerical strength of skeletal muscle mitochondria, 38% less mitochondrial density of muscle fibres in insulin resistant individuals as compared with controls, and enhanced intramyocellular fat content associated with defects in mitochondrial activity, have all been suggested in type 2 diabetes mellitus patients[124 - 126]. It is evidenced that the cause for PKC activation and in turn blockage of serine/tyrosine phosphorylation is linked to inactivation of insulin receptor substrate 1. This phenomenon may occur at the cellular level or may lie at the subcellular mitochondrial level, by virtue of mitochondrial diminished fatty acid metabolism either due to deprecated mitochondrial activity and/or reduced mitochondrial numbers. All these steps would eventually reduce downstream intracellular signaling, imperative for attachment of GLUT4 transporter to the plasma membrane and eventually decrease glucose uptake in skeletal muscle[127].

Interlinked biochemical pathways participating in hyperglycemic microvascular pathogenesis in DM

Interlinked biochemical pathways within cells share responsibility for development of diabetic microvascular damage alongwith insulin dependent uptake of glucose by the increased expression of the glucose transporter (GLUT 1) into capillary endothelial and mesangial cells[128]. Poor glycemic contol remains a visible risk factor in progression of vasculature pathology in type 1 and type 2 DM. Increased cytosolic glucose lead to enhanced concentrations of triosephosphates, glyceraldehyde-3-phosphate and dihydroxyacetonephosphate and downregulation of GAPDH the house keeping enzyme[129] (Fig.3)..These inturn initiate numerous pathways of biochemical malfunction such as incremental levels of diacylglycerol de novo, activation of protein kinase Cβ, enhancement of the polyol pathway, induction of the hexosamine pathway, incremental flux through the glycerophosphate shuttle and consequently mitochondrial malfunction with oxidative stress, metabolic pseudohypoxia and formation of advanced glycation endproducts[130] (Fig.3). Other fortifying pathways are also activated by activated PKC such as activation associated uncoupling of eNOS endothelial nitrous oxide synthase by increased oxygen radical production[131,132] and

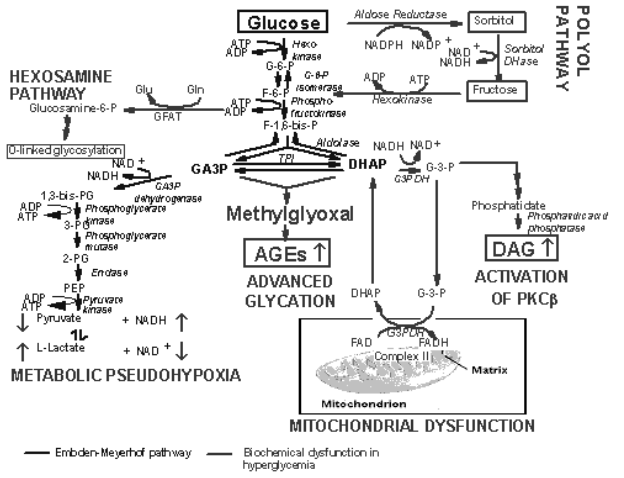

Fig. 3: **Pathways of hyperglycemic damage in diabetes mellitus type 2. (Adapted from the Diabetic control and Complications, New Engl. J. Med. 1993).**

activation of poly (ADP- ribose) polymerase in response to oxidative and probably glycation damage to DNA[133] and AGE receptor (RAGE) mediated vascular cell activation[130] (Fig.3) Accumulation of triosephosphates is the starter for these processes[134] and a plan to reverse this, could alleviate multiple pathways of biochemical dysfunction.

And, finally more recently dysfunctional thiamine dependant enzymes pyruvate dehydrogenase, alphaketoglutarate dehydrogenase of the krebs cycle and transketolase involved in the reductive pentose pathway have also been reported in type 2 diabetics which could prove to be another vital link in type 2 diabetes pathogenesis.[135 - 137]

CONCLUSION

Type 2 diabetes now needs to be viewed as a multiorgan, multitissue,enzymatic and biochemical dysfunction with a genetic basis.New and diverse approaches towards its therepeutics are the need of the hour based on this data.

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REFERENCES

1. International Diabetes Federation Diabetes Atlas, IDF, 2009.
2. WHO/International Diabetes Federation, Launch of Diabetes action now. 2004
3. Screening for Type 2 Diabetes. Report of a World Health Organization and International Diabetes Federation meeting. © World Health Organization 2003.
4. Wild S, Roglic G, Green A, Sicere R: Global prevalence of diabetes estimates for 2000 and projections for 2030. Diabetes Care, 2004; 27(5): 1047-53.
5. Centers for Disease Control. National Diabetes Fact Sheet. 2007.
6. Shera AS, Rafique G, Khwaja IA, Baqai S, Khan IA, et al. Pakistan National Health Survey:prevalence of glucose intolerance and associated factors in North West Frontier Province (NWFP) of Pakistan. J Pak Med Assoc 1999;49(9):206-11.
7. Shera AS, Rafique G, Khawaja IA, Baqai I, King H. Pakistan National Diabetic Survey: prevalence ofglucose intolerance and associated factors in Balochistan province. Diabetes Res Clin Pract 1999;44(1):49-58.
8. Samad A. Shera. Personal Communication. Diabetic Association of Pakistan, Karachi, Pakistan (Dec 23, 03).
9. First National Action Plan for Prevention of Diabetes; Diabetes Association of Pakistan. http://www.dap.org.pk/achivements2.htm
10. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care, 1998; 121: 1414–31
11. Goodman Gillman. Insulin, Oral Hypoglycaemic agents and the endocrine pancreas. The Pharmacological Basis of Therapeutics Tenth Edition, 2001; 61:1686-1710.
12. Katzung BG. Basic and clinical pharmacology. Eighth edition 2004. Pancreatic Hormones and Anti Diabetic Drugs. 711-734.
13. Goodman Gillman. Insulin, Oral hypoglycaemic agents and the pharmacology of endocrine pancreas. The Pharmacological Basis of Therapeutics Eleventh Edition. 2006; 60: 1613-46.
14. Lillioja S. Mott DM, Spraul M. Insulin resistance and Insulin secretary dysfunction as precursor of non insulin dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med, 1993; 329:1988-92.
15. Stumvoll M, Goldstein BJ & van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet, 2005; 365:1333–46.
16. Edelman SV. Type II diabetes mellitus. Adv

Intern Med. 1998;43:449-500.
17. Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 2003 26: 3160-67
18. Praveen J.K, Micheal Clark. Clinical. Diabetes Mellitus, 2005; 832-57.
19. Margolis Saudek CD. The John Hopkins white papers Diabetes mellitus. Baltimore, 1996: Medletter Associates.
20. Ganong WF. Endocrine Functions of the pancreas and regulation of carbohydrate metabolism. Review of Medical Physiology. 20th Edition. New York: Mc Graw Hill, 2001; 328-333.
21. Stratton M, Adler AL, Neil HAW, Mathews DR., Manley SE, et al. Association of glycaemic with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): 1-6
22. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2011; 34 (1): S11-S61
23. Das SK & Elbein SC The genetic basis of type 2 diabetes. Cellscience, 2006;2:100–31
24. Katzung BG. Pancreatic hormones and Antidiabetic Drugs. Basic and Clinical Pharmacology.11th edition Philadelphia W. B Saunders.2009:727-52
25. Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, et al. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 2004; 29(10): 1326–34.
26. Bergamini E. Cavallini G, Donati A, Gori Z. The role of macroautophagy in the ageing process, anti-ageingintervention and age-associated diseases. Int J Biochem Cell Biol, 2004; 36: 2392–04
27. Benedict C, Brede S, Schith HB, Lehnert H, Schultes B, et al. Intranasal insulin enhances postprandial thermogenesis and lowers postprandial serum insulin levels in healthy men. Diabetes, 2010;60 (1): 114–118.
28. Tarasov A, Dusonchet J, Ashcroft F. Metabolic Regulation of the Pancreatic CellATP-Sensitive K Channel A Pas de Deux. Diabetes, 2004;53:S113-S122.
29. JensenMV, Joseph JW, Ronnebaum SM, Shawn C, Burgess A, Dean Sherry, et al. Metabolic cycling in control of glucose-stimulated insulin secretion. Am J Physiol Endocrinol Metab; 295:E1287-E97
30. Ronnebaum SM, Joseph JW, Ilkayeva O, Burgess SC, Lu D, et al. Chronic Suppression of Acetyl-CoA Carboxylase 1 in β-Cells Impairs Insulin Secretion via Inhibition of Glucose Rather Than Lipid Metabolism. J Biol Chem, 2008.283:14248-256
31. Duckworth, W.C. Insulin degradation: Mechanisms, products and significance. Endocr Rev, 1988; 9:319-45
32. Palmer BF, Ismail N, Henrich LW. Carbohydrate and insulin metabolism in chronic kidney disease.Upto date On Line, 2010.
33. Louvi A, Accili D. & Efstratiadis A. Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. Develop Biol, 1997; 189:33–48.
34. White MF. Insulin signaling in health and disease. Science, 2003; 302:1710–11.
35. White MF. IRS Proteins and the common path to diabetes. Am J Physiol Endocrinol Metab, 2002; 283:E413-E22.
36. De Mytes P. The structural basis of insulin and insulin-like growth factor-1 receptor signaling. Diabetologia, 1994 ;37:S135-S148
37. McGettrick AJ, Feener EP, Kahn CR. Human insulin receptor substrate-1 (IRS-1) polymorphism G972R causes IRS-1 to associate with the insulin receptor and inhibit receptor autophosphorylation. J Biol Chem. 2005; 280(8):6441-6.
38. Reaven G. Insulin Resistance .Why is it important? What is the link between it and cardiovascular disease. 12th annual meeting and clinical congress of the American Association of Clinical Endocrinologists 2003.
39. Punjabi N. Sleep disordered breathing, glucose intolerance and insulin resistance.The Sleep Heart Study. Am J Epidemiol, 2004; 160:521-30.
40. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin

resistance, independent of obesity, in polycystic ovary syndrome. Diabetes, 1989; 38:1165-74

41. Goodwin PJ, Ennis M, Pritchard KI. Fasting insulin and outcome in early-stage breast cancer: results of a propective cohort study. J Clin Oncol, 2002; 20:42-51
42. Hsing AW, Chua S Jr, Gao YT. Prostate cancer risk and serum levels of insulin and leptin: A population-based study. J Natl Cancer Inst, 2001; 93:783-89
43. Reaven GM, Chen YD, Jeppeson J. Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoproteinparticles. J Clin Invest, 1993; 92:141-46.
44. Abbasi F, McLaughlin T, Lamendola C, Lipinska I, Tofler G, Reaven GM. Comparison of plasminogen activator inhibitor-1 concentration in insulin-resistant versus insulin sensitive healthy women. Arterioscler Thromb Vasc Biol, 1999; 19: 2818-21.
45. Hseuh WA Quinones MJ. Role of endothelial dysfunction in endothelial resistance. Division of Endocrinology. Diabetes and Hypertension University of California-Los Angeles,School of Medicine. Am J Cardiol, 2003; 92(4A) :10J-17J.
46. Chen NG, Abbasi F, Lamendolda C. Mononuclear cell adherence to cultured endothelium is enhanced by hypertension and insulin resistance in health non diabetic volunteers. Circulation, 1999; 100:940-43.
47. Sturhlinger MC, Abbasi F, Chu JW. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA, 2002;287:1420-26.
48. Abbasi F, McLaughlin T, Lamendola C, Lipinska I, Tofler G, et al. Comparision of plasminogen activator inhibitor-1 concentration in insulin-resistant versus insulin sensitive healthy women. Arterioscler Thromb Vasc Biol, 1999;19: 2818-21.
49. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA, 1991;266:3008-11.
50. Facchini FS, Stoohs RA, Reaven GM. Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens, 1996;9:1013-17.
51. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab. 2002; 87:3023-028.
52. Lindholm LH, Ibsen H, Borch Johnson K. Risk of new set diabetes in the Losartan Intervention for Endpoint Reduction In Hypertension Study. J Hypertens, 2002;20: 1879-86.
53. Kelley DE & Simoneau JA Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. J Clin Invest, 1994;94:2349–56
54. Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, Saris WH & van Baak MA. Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. Diabetes, 2000;49:2102–107.

54b. Blaak EE, Wagenmakers AJ, Glatz JF, Wolffenbuttel BH, Kemerink GJ, Langenberg CJ, Heidendal GA & Saris WH. Plasma FFA utilization and fatty acid-binding protein content are diminished in type 2 diabetic muscle. Am J Physiol Endocrinol Metab, 2000; 279:E146–E154.

55. Boden G. Free fatty acids, insulin resistance, and type 2 diabetes mellitus. EMBO Reports, 1999; 3:323– 8.
56. Santomauro AT, Boden G, Silva ME, Rocha DM, Santos RF, et al. Overnight lowering of free fatty acids with Acipimox improves insulin resistance and glucose tolerance in obese diabetic and non-diabetic subjects. Diabetes 1999; 48:1836–41.
57. Bjornholm M, Zierath JR. Insulin signal transduction in human skeletal muscles: identifying the defects in Type II diabetes. Biochem Soc Trans 2005; 33:354-7.

58. Zierath JR, Krook A. & Wallberg-Henriksson H. Insulin action and insulin resistance in human skeletal muscle. Diabetologia, 2000; 43:821–35.
59. Folli F, Kahn CR, Bouchie J, Hansen H, Feener EP. Angiotensin II inhibits insulin signaling in aortic smooth muscle cells at multiple levels: A role for serine phosphorylation in insulin/angiotensin II crosstalk. J Clinic Invest, 1997;100:2158-69.
60. Ogihara T, Asano T, Ando K, Sakoda H, Anai M, et al. High-salt diet enhances insulin signaling and induces insulin resistance in Dahl salt-sensitive rats. Hypertension. 2002; 40:83–89.
61. Storgaard H, Song XM, Jensen CB, Madsbad S, Bjornholm M, et al. Insulin signal transduction in skeletal muscle from glucose-intolerant relatives with type 2 diabetes. Diabetes, 2001; 50: 2770-78.
62. Frittitta L, Youngren JF, Sbraccia P, D'Adamo M, Buongiorno A, et al. Increased adipose tissue PC-1 protein content, but not tumour necrosis factor-alpha gene expression, is associated with a reduction of both whole body insulin sensitivity and insulin receptor tyrosine-kinase activity. Diabetologia 1997; 40:282–89.
63. Moller DE Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab, 2000; 11: 212–17.
64. Zhande R, Mitchell JJ, Wu J. & Sun XJ Molecular mechanism of insulin-induced degradation of insulin receptor substrate 1. Mol Cell Biol, 2002;22:1016–26.
65. Bandyopadhyay D, Kusari A, Kenner KA, Liu F, Chernoff J, et al. Protein–tyrosine phosphatase 1B complexes with the insulin receptor in vivo and is tyrosine-phosphorylated in the presence of insulin. J Biol Chem, 1997;272:1639–45.
66. Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, et al. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. Science 1999; 283: 1544–48.
67. Aguirre V, Uchida T, Yenush L, Davis R. & White MF. The c-Jun NH (2)-terminal kinase promotes insulin resistance during association with Insulin receptor substrate-1 and phosphorylation of Ser (307). J Biol Chem, 2000; 275: 9047–54.
68. Yu C, Chen Y, Cline GW, Zhang D, Zong H, et al. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. J Biol Chem, 2002;277:50230–36.
69. Visboll T, Agerso H, Kramp T, et al. Similar elimination rates of glucagon like peptide s in obeses type 2 diabetics patients and healthy subjects. J Clin Endocrinol Metab, 2003;88:220-24.
70. Kelley DE & Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes, 2000;49:677–83.
71. Zorad S, Fickova M, Zelezna B. The role of angiotension II and ts receptors in regulation of adipose tissue metabolism and cellularity. Gen Physiol Biophys, 1995;14:383-91.
72. Yuichi Oike. Fat to Chronic Inflammation. Science Daily. Cell Press, 2009
73. Lang P, Hermelen VV, Ryden M, Kaaman M, Parini P, et al. Monomeric tartrate resistend acid phophatase induces insulin sensitive obesity. PLoS one.2008
74. Wentworth JM, Naselli G, Brown WA, Doyle N, Phipson B, et al. Preinflammatory CD11c + CD206 + adipose tissues macrophages are associated with insulin resistance in human obesity. Diabetes, 2010; 59(7):1648.
75. Shepherd PR. & Kahn BB. Glucose transporters and insulin action –implications for insulin resistance and diabetes mellitus. N Eng J Med, 1999;341:248–57
76. Gimeno RE & Klaman LD Adipose tissue as an active endocrine organ: recent advances. Curr Opin Pharmacol, 2005;5:122–28.
77. Wellen KE & Hotamisligil GS Inflammation, stress, and diabetes. J Clin Invest, 2005;115: 1111–19
78. Wallerstedt E, Smith U, Andersson CX. Protein kinase C-Omega is involved in the inflammatory effect of IL-6 in mouse adipose

cells. Diabetologia, 2010;53(5):946.
79. De Luca C. & Olefsky JM. Stressed out about obesity and insulin resistance. Nat Med, 2006; 12:41–42
80. Harding HP & Ron D. Endoplasmic reticulum stress and the development of diabetes: A review. Diabetes, 2002; 51, S455–S61.
81. Donath MY, Storling J, Maedler K. & Mandrup-Poulsen T Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. J Mol Med, 2003; 81: 455–470.
82. Donath MY. & Halban PA. Decreased beta-cell mass in diabetes: significance, mechanisms and therapeutic implications. Diabetologia, 2004; 47: 581–89.
83. Poitout V. & Robertson RP. Minireview: secondary beta-cell failure in type 2 diabetes–a convergence of glucotoxicity and lipotoxicity. Endocrinology 2002;143:339–42.
84. Kaneto H, Nakatani Y, Kawamori D, Miyatsuka T, Matsuoka TA, et al. Role of oxidative stress, endoplasmic reticulum stress, and c-Jun N-terminal kinase in pancreatic beta-cell dysfunction and insulin resistance. Int J Biochem Cell Biol, 2006; 38: 782–93.
85. Rhodes CJ. Type 2 diabetes – a matter of beta-cell life and death? Science, 2005; 307:380–84.
86. Song B, Scheuner D, Ron D, Pennathur S, and Kaufman RJ. Chop deletion reduces oxidative stress, improves β cell function, and promotes cell survival in multiple mouse models of diabetes. American Society for Clinical Investigation. J Clin Invest. 2008; 118: 3378–89.
87. Gurlo T, Ryazantsev S, Huang C-J, Yeh MW, Reber HA, et al. Evidence for proteotoxicity in beta cells in type 2 diabetes, toxic lslet Amyloid polypeptide Oligomers from interacellularly in the secretory pathway. Am J Path, 2010;176: 861-69.
88. Hennige AM, Burks DJ, Ozcan U, Kulkarni RN, Ye J, et al. Upregulation of insulin receptor substrate-2 in pancreatic beta cells prevents diabetes. J Clin Invest, 2003;112: 1521–32.
89. Werner ED, Lee J, Hansen L, Yuan M & Shoelson SE Insulin resistance due to phosphorylation of insulin receptor substrate-1 at serine 302. J Biol Chem, 2004;279: 35298–305
90. Ferrannini E. Insulin resistance versus insulin deficiency in non-insulin dependent diabetes mellitus: problems and prospects. Endo Revs, 1998; 19:477–90.
91. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia, 2003; 46:3–19.
91b Kahn SE, Hull RL & Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature, 2006; 444:840–46.
92. Raddatz D & Ramadori G Carbohydrate metabolism and the liver: actual aspects from physiology and disease. Zeitschrift fu¨r Gastroenterologie, 2007;45: 51–62.
93. Fritsche L,Weigert C, Haring HU & Lehmann R. How insulin receptor substrate proteins regulate the metabolic capacity of the liver – implications for health and disease. Curr Med Chem, 2008; 15:1316–29
94. Varga G, Su C. Biodrugs 2007;21:117-24.
95. Edwards P. A., Kennedy M. A., Mak P. A. LXRs; oxysterol-activated nuclear receptors that regulate genes controlling lipid homeostasis. Vascul. Pharmacol, 2002;38, 249–56
96. Ogihara T, Chuang JC. Liver X Receptor agonists augment human islet function through activation of anaplerotic pathways and glycerolipid/free fatty acid cycling. J Biol Chem, 2010; 285(8): 5392- 5404.
97. Gerin I, Dolinsky VW, Shackman JG, Kennedy RT, Chiang SH, et al. LXRbeta is required for adipocyte growth, glucose homeostasis, and beta cell function. J. Biol. Chem. 2005;280:23024-31
98. Efanov AM, Sewing S, Bokvist K, Gromada. Liver X receptor activation stimulates insulin secretion via modulation of glucose and lipid metabolism in pancreatic β-cells. J Diabetes,

2004;53: S75-S78
99. Taniguchi CM, Ueki K & Kahn R Complementary roles of IRS-1 and IRS-2 in the hepatic regulation of metabolism. Ind J Med Res, 2005;115: 718–27.
100. Dong X, Park S, Lin X, Copps K, Yi X et al. Irs1 and Irs2 signaling is essential for hepatic glucose homeostasis and systemic growth. J Clin Invest, 2006;116:101–14.
101. Simmgen M, Knauf C, Lopez M, Choudhury AI, Charalambous M, et al. Liver-specific deletion of insulin receptor substrate 2 does not impair hepatic glucose and lipid metabolism in mice. *Diabetologia*, 2006;49: 552–61.
102. Drucker DJ. Glycogen-like peptides. Diabetes 1998**;**47: 159-69.
103. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. Am J Physiol Endocrinol Metab, 2004**;** 287: E1953-59
104. Deacon Carolyn F, Holst Jens J. Dipeptidyl Peptidase-4 Inhibition – Advances in our Understanding of Diabetes Management. US Endocrinol; 4(II), Eur Endocrinol ;4 (II)
105. Sandoval DA, Obici S & Seeley RJ. Targeting the CNS to treat type 2 diabetes. Nature Reviews. Drug Discovery, 2009**;** 8; 386–98.
106. Jens C. Brüning. Linda Koch, Wunderlich F.T, Seibler J, Könner A.C, Hampel B, et al. Central insulin action regulates peripheral glucose and fat metabolism in mice**.** J Clin Invest; 2008;118(6):2132–47.
107. BennetD Brown F.Clinical Pharmacology.9th edition. Treatment of diabetes mellitus. Precautions with Oral Agents.2003,25:689
108. Boustany CM, Bhardwaj K, Daugherty AX. Activation of systemic and adipose rennin angiotensin system in rats with diet induced obesity and hypertension. Am J Physiol Regul Integr Comp Physiol, 2008**;**287:R943-R949.
109. Schmeider RE, Hilger KF, Schlaich MP. Renin angiotensin sustem and cardiovascular risk. Lancet, 2007;369:1208-19
110. Wang F, Liu H, Blanton W, et al. Brd2 disruption in mice causes severe obesity without Type 2 diabetes. Biochem J, 2009; 425:71-83.
111. Venables MC & Jeukendrup AE. Physical inactivity and obesity: links with insulin resistance and type 2 diabetes mellitus. Int J Exp Diab Res, 2009;25:S18–S23.
112. Belfort R, Mandarino L, Kashyap S, Wirfel K, Pratipanawatr T, et al. Dose–response effect of elevated plasma free fatty acid on insulin signaling. Diabetes, 2005**;** 54:1640–48.
113. Itani SI, Ruderman NB, Schmieder F & Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and I kappa B-alpha. Diabetes, 2002;51:2005–2011.
114. Yu C, Chen Y, Cline GW, Zhang D, Zong H, et al. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1(IRS-1)-associated phosphatidy-linositol 3-kinase activity in muscle. J Biol Chem, 2002**;**277:50230–236.
115. Thyfault JP, Cree MG, Zheng D, Zwetsloot JJ, Tapscott EB, et al. Contraction of insulin-resistant muscle normalizes insulin action in association with increased mitochondrial activity and fatty acid catabolism. Am J Physiol. Cell Physiology, 2007; 292:C729–C739.
116. Majithia AR & Florez JC. Clinical translation of genetic predictors for type 2 diabetes. Curr Opin Endocrinol Diabetes and Obesity, 2009; 16: 100–106
117. Ridderstrale M & Groop L. Genetic dissection of type 2 diabetes. Mol Cell Endocrinol, 2009**;** 297 **:**10–17.
118. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004**;**114:1752–61.
119. Lin Y, Berg AH, Iyengar P, Lam TK, Giacca A, Combs TP, Rajala MW, Du X, Rollman B, Li W, et al. The hyperglycemia-induced inflammatory response in adipocytes: the role of reactive oxygen species. J Biol Chem 2005; 280**:** 4617-26.
120. Houstis N, Rosen ED & Lander ES. Reactive

oxygen species have a causal role in multiple forms of insulin resistance. Nature, 2006;440: 944–48.
121. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, et al. PGC-1a responsive genes involved in oxidative phosphorylation are coordinately down regulated in human diabetes. Nat Gen, 2003;34:267–73.
122. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. |PNAS, 2003**;** 100**:** 8466–71.
123. Masanori Mitsuishi. Angiotensin II Reduces Mitochondrial Content in Skeletal Muscle and Affects Glyemic Control. Diabetes, 2009;58:710–717
124. Maechler P & Wollheim CB Mitochondrial function in normal and diabetic beta-cells. Nature, 2001;414:807–12
125. Petersen KF, Dufour S, Befroy D, Garcia R & Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Eng J Med, 2004**;** 350**:** 664–71
126. Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, Neschen S, White MF, Bilz S, Sono S et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin resistant offspring of type 2 diabetic parents. J Clin Invest, 2005**;**115:3587–93.
127. Lowell BB & Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science 2005**;** 307:384–87.
128. Heilig CW, Concepcion LA, Riser BL, Freytag SO, Zhu M, et al. Overexpression of glucose transporters in rat mesangial cells cultured in a normal glucose mellieu mimics the diabetic phenotype. J. Clin. Invest. 1995**;** 96: 1802-14.
129. Du X, Matsumura T, Edelstein D, Rodetti L, Zsengeller Z, et al. Inhibition of GAPDH activity by poli (ADP-ribode) polymerase activities three major pathways of hyperglycemic damage in endothelial cells. J. Clin. Invest, 2003**;**112: 1049- 57.
130. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes, 2000;54:1615-25.
131. Lassegue B and Clempus RE. Vascular NAD (P) H oxidases: specific features, expressions, and regulation. Am. J. Physiol, 2003;285: R227-R297.
132. Guzik TJ, Mussa S, Gastaldi D et al. Mechanisms of increased vascular superperoxide production in human diabetes mellitus. Circulation, 2002;105:1656-1662.
133. Soriano FG, Virag L, Jagtap P et al. Diabetic endothelial dysfunction: the role of poly(ADP-ribose) polymerase activation. Nat Med, 2001;**7**:108-13.
134. Thornalley PJ, Jahan I, Ng R. Suppression of' the accumulation of' triosephosphates and increased formation of methylglyoxal in human red blood cells during hyperglycaemia by thiamine in vitro. Biochem, 2001;129:543-49
135. Curto M, Novi RF, Rabbone I and derangements in obese subjects and newly diagnosed NIDDM patients and derangements of pyruvate dehydrogenase in their circulatory lymphocytes. Int J Obes Relat Metab Disord, 21(12):1137-1142
136. Des Jardins, Roger. F. Butterworth. Role of mitochondrial dysfunction and oxidative stress in the pathogenesis of selective neuronal loss in wernickes encephalopathy. Mol Neurobiol. 31: 1-3, 17-25
137. Pekovich SR, Martin PR and Singleton CK. Thiamine deficiency decreses steady-state tranketolase and pyruvate dehydrogenase but not a ketoglutrate dehydrogenases mRNA levels in three human cells type. J Nutr, 1998; 128**:** 683-87.

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