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Pathogenesis of Type 2 Diabetes Mellitus

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1. Introduction

The natural history of type 2 diabetes (T2DM) has been well described in multiple populations. Patients with T2DM have inherited genes from parents that make their tissues resistant to insulin. Insulin resistance (IR) in muscle and liver and β-cell failure represent the core pathophysiologic defects in development of T2DM. Age, genes, IR, lipotoxicity, glucotoxicity, amyloid deposition and abnormal incretin are factors playing a role in progressive β-cells dysfunction. The progressive decline in insulin secretion, decrease of the pancreatic β- cell mass and function and the presence of IR will contribute in changing the state of the dysglycemia from normal to, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and end with overt diabetes [1].

2. Glucose metabolism

Excessive hepatic glucose output is an important factor in the fasting hyperglycemia of patients with T2DM. Following administration of isotope in healthy subjects and in patients with T2DM, the overall hepatic glucose output was an increase by twofold and the gluconeogenesis more than threefold in patients compare with the controls. This finding demonstrated the increased in gluconeogenesis is the predominant mechanism responsible for increased hepatic glucose output in patients with T2DM and it is correlated with fasting plasma glucose level. [2]. Insulin controls the hepatic glucose production and promotes glucose utilization by the skeletal muscle. There is a correlation between the hepatic glucose production and the fasting glucose, in normal subjects, the postabsorptive hepatic glucose production is increased. But in

patients with T2DM, the main causes are increased mostly by gluconeogenesis and to less extent by glycogenolysis by the liver. The Increased production of gluconeogenic precursors (lactate, alanine, and glycerol) and hyperglucagonemia with increased hepatic FFA acid oxidation might be responsible for glucogenesis. There is also a reduction in suppression of hepatic glucose production after carbohydrate ingestion which plays a role in the impairment in postprandial glucose homeostasis in T2DM [3].

The increased of the glycogenolysis and the decreased in the hepatic glucose uptake by glucagon will produce hyperglycemic phenotype associated with insulin deficiency and IR. In the overnight fasted, it is essential in countering the suppressive effects of basal insulin to maintain appropriate levels of glycogenolysis, fasting hepatic glucose production and blood glucose. Glycogenolysis is also increased by the counter-regulatory hormones response to hypoglycemia and in exercise [4]. Insulin and glucagon secretion are determined by plasma glucose concentration which is widely fluctuated according to the demand such as exercise and supply as taking high carbohydrate meal. In the resting postabsorptive state, the glyco-genolysis and gluconeogenesis are equal or in balance in hepatic glucose release. This is a key regulated process. In the postprandial state, suppression of liver glucose output and stimula-tion of skeletal muscle glucose uptake are the most important factors. Under stressful condi-tions, the counter-regulatory hormones of the hypoglycemia secretion are increased with increased of the sympathetic nervous system activity. Their actions to increase hepatic glucose output and to suppress tissue glucose uptake are partly mediated by increases in tissue fatty acid oxidation. In T2DM, the fasting hyperglycaemia resulted from increased gluconeogenesis while, the postprandial hyperglycemia occurs due to impaired suppression of glycogenolysis and impaired skeletal muscle glucose uptake [5].

In normal subjects the fasting plasma glucose levels are constant from day to day. This constancy is due to a close co-ordination between glucose production by the liver and glucose uptake in peripheral tissues. In T2DM, fasting hyperglycemia to less extent is correlated with increased hepatic glucose production due to impaired hepatic sensitivity to insulin. But, it is largely due to reduced insulin secretion and increased glucagon secretion. Though the basal immunoreactive insulin and glucagon levels in patients with T2DM may appear normal compared with the normal subjects, the islet function testing at matched glucose levels reveals impairments of the basal, steady-state, and stimulated insulin and glucagon secretion due to a reduction in β- cells secretory capacity and a reduced ability of glucose to suppress glucagon release. Islet α- and β-cells functions are reduced by more than 50% in T2DM by the time that clinical fasting hyperglycemia develops (140 mg/dL) [6]. The efficiency of glucose uptake by the peripheral tissues is also impaired due to a combination of decreased insulin secretion and defective of the cellular insulin action [6, 7]. The defective in first phase glucose induced insulin secretion is followed by fasting hyperglycemia and the progressive failure in pancreatic β-cells function is matched by rising glucose levels to maintain basal and second-phase insulin output. The glucose is not only directly regulated insulin synthesis and secretion. But, moderated all other islet signals, including other substrates, hormones, and neural factors. In T2DM the defects are in first-phase insulin secretion and in the deficiency of the ability of glucose to

potentiate other islet nonglucose β-cell secretagogues. In T2DM patients, the resulting hyperglycemia does not correct the first phase of insulin secretion defect. However, it compensates for the defective glucose potentiation, maintains nearly normal basal insulin levels and insulin responses to nonglucose secretagogues [8].

The major primary reduction of suppression in the output of the endogenous hepatic glucose release and the minor effect of the splanchnic glucose sequestration in these patients are the cause of increasing in systemic glucose delivery which subsequently responsible for the postprandial hyperglycemia [9, 10].

The fasting hyperglycemia is mainly caused by the increased of the released hepatic glucose production. This mechanism is increased in psotabsorptive state and exhibits a positive correlation with fasting glucose level [3, 7 11].

The increase of the glucogenesis in the postprandial state represents the primary mechanism responsible for impaired suppression of hepatic glucose production [3]. The increased in the rate of glucose release by the liver results in part from impaired hepatic sensitivity to insulin, but it is largely due to reduced insulin secretion and increased glucagon secretion [6]. The degree of fasting hyperglycemia in a given patient with T2DM is closely related to the degree of impaired pancreatic β-cells responsiveness to glucose.

The fasting insulin secretion in normal subject and in patients with T2DM is comparable. But, there is a marked impairment of insulin secretion in patients with DM in relation to the degree of hyperglycemia. This is demonstrating the closed feedback loop operating between glucose levels and pancreatic β-cells which regulates the relationship of insulin secretion and hepatic glucose production [11]. The glucose uptake by peripheral tissue is impaired due to a combination of decreased insulin secretion and defective in cellular insulin action [6, 7].

The amyloid deposition process is associated with disproportionate hyperproinsulinemia. The amylin in transgenic mice develops islet amyloid deposits and hyperglycemia. This is suggestive the process of amyloid fibril formation impairs the function of the β-cells and eventual death. The progressive loss of β-cell function in T2DM, initially reflected by the loss in first-phase insulin secretion, followed by a decrease in the maximal capacity of glucose to potentiate all non-glucose signals. Finally, a defective steady-state and basal insulin secretion develops, leading to complete β-cells failure requiring insulin therapy [12].

The conclusion is, T2DM is characterized by a steady-state re-regulation of plasma glucose concentration at an elevated level in which islet cells dysfunction play a necessary role [7].

3. Insulin secretion, function and impairment

Insulin is synthesized and produced by β- cells in the pancreas. It is a peptide hormone regulates the metabolism of fat and carbohydrate in the body. It helps glucose absorption from the circulation by fat tissue and skeletal muscles. Figures 1 [13] and 2 [14].
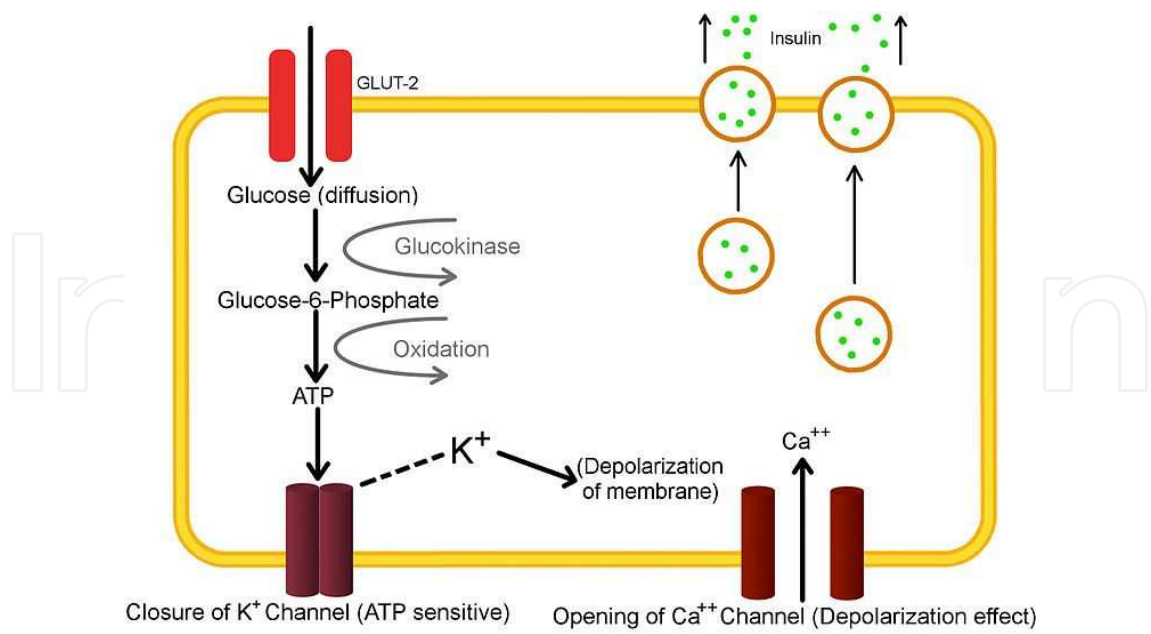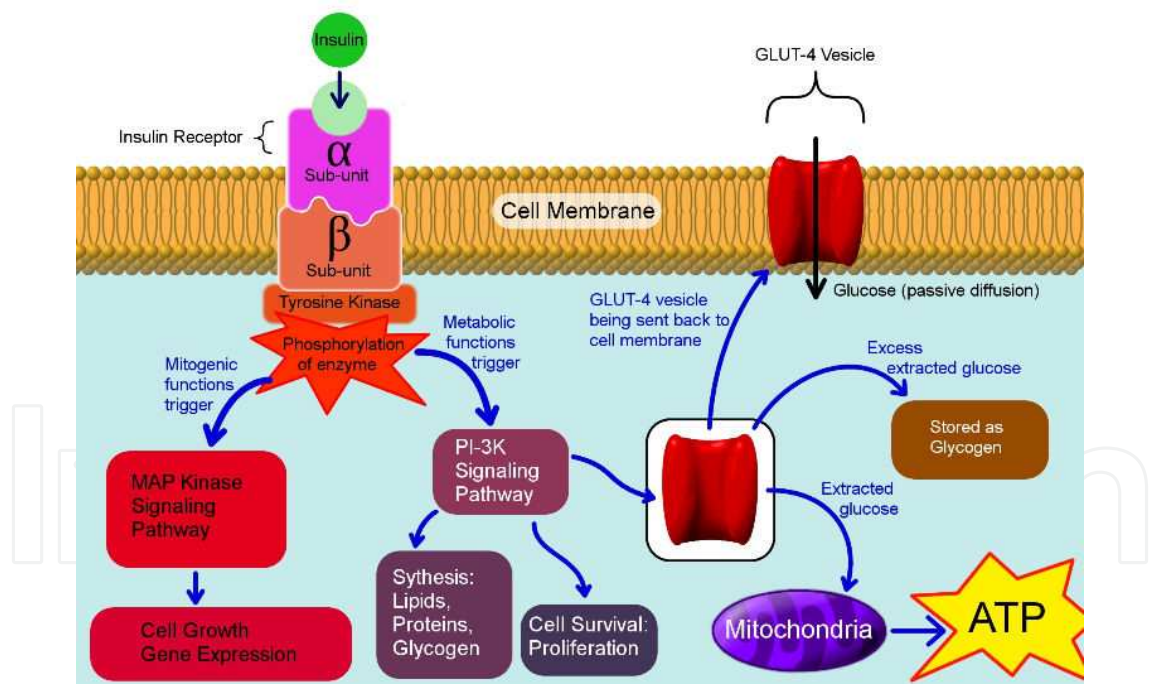
Figure 1. Insulin secretion [13].

Figure 2. Insulin functions [14].

Pancreatic β-cells secrete insulin in two phases, first and second phase (biphasic manner). The loss of first phase is an independent predictor of T2DM onset. In patients with T2DM, the restoration of this phase suppresses the hepatic glucose output and improves the blood glucose concentration [15]. There are many metabolic abnormalities precede the clinical picture of

T2DM as demonstrated in a study of normal first- degree subjects who had relatives with T2DM. Following intravenous glucose infusion, these subjects showed a reduced first phase insulin secretion with decreased ability of the β-cells to respond to successive increase or decrease in glucose with mild elevation in 2hours post challenge glucose level [16]. In patients with T2DM, the earliest detectable defect and exhaustion of β- cells function appeared in the reduction of the first-phase insulin secretion. This phase is brief burst and spike lasting for about 10 minutes followed by plateau second phase lasted for 2-3 hours. The reductions in both phases occur equally early and precede development of IR [17]. The fasting plasma insulin concentration is often a marker of insulin sensitivity (IS) and the changing in acute insulin secretion following glucose challenge is an early observation of progressive pancreatic defect. Glucotoxicity and lipototoxicity are contributor factors in progressive and the continuous decline in pancreatic function [1, 18].

Insulin is secreted from the secretory cells by priming reaction. Each cell contains thousands of secretory vesicles/granules. Less than <5% of these cells exist to release the readily pool insulin by exocytosis followed by minimal latency of immediate releasable pool of insulin. The bulk of granules in the cell (>95%) exist in a non-releasable reserve pool of insulin, which must undergo a series of ATP-, Ca^{2+}-, and temperature-dependent reactions to release insulin [19].

The prevalence of Gestational diabetes (GDM) is 2-3% of all pregnant women. GDM women have the same second –phase insulin response as women with normal oral GTT. But, the first phase-insulin secretion is reduced with intravenous glucose and has a later peak rise with OGTT. Both groups showed a decreased in IS by 50-70%, this is back to normal in postpartum period in women with normal OGTT but this is not in women with GDM. In the same period, the latter group also demonstrated a persistent and excessive proinsulin secretion. Women with GDM have also a substantial increase in insulin secretion with OGTT or a meal compared to the same women in postpartum period. But this rise is less in women with GDM compared with pregnant women who retain normal OGTT [20].

The glycemic progression from normal to IGT mainly due to IR and from this state to overt DM depends primarily on β-cells failure in addition to progression to severe IR. Two studies, San Antonio and Hoorn Study showed the high fasting proinsulin reflects the β-cells dysfunction and the progression to DM. IR is determined by fasting hyperinsulinemia and lower glucose removal. Therefore, the 2 hours blood glucose level following oral glucose load is the most powerful in prediction of development of T2DM. IR and progressive β-cells dysfunction are the two important defects in development of the disease [21]. IFG and IGT are intermediate states in glucose metabolism that exist between normal GT and overt diabetes are related to these defects in addition to the reduction in early-phase insulin secretion. But, subjects with IGT also have impaired late-phase insulin secretion. The latter group also demonstrated a significant higher muscle IR and low hepatic IR while subjects with IFG have severe hepatic IR with normal or near-normal muscle IS [22]. The insulin secretion and glucose homeostasis in the first phaase insulin secretion is determined by a complex pathawy of multiple signals including hypoxia inducible factor 1α, von Hippel-Lindau, factor inhibiting HIF, nicotinamide phospho-ribosyl-transferase, and the sirtuin family in addition to many other novel regulatory factors are crucial [15].

4. Insulin resistance

Patients with T2DM have high whole body glucose production and glucogenesis but low glycogenolysis compared with normal subjects. In patients with IR, there is impairment of glucose transport and insulin signaling in target tissues with release of inflammatory markers from the adipose tissue [23, 24]. The glucose, FFA, autonomic nerves, fat-derived hormones and the gut hormone glucagon-like peptide-1 (GLP-1) are mediators sending signals to the β-cells to respond to IR. The maintenance of normal glucose and lipid metabolism is by the reciprocal relation of IR to IS and insulin secretion. Hyperbolic relation is the best description of the curvilinear relation between IS and secretion. This relation is impaired with failure of these signals to act on β-cells to secret insulin ends with subsequent development of dysglycemia (Impaired Fasting glucose- IFG, impaired Glucose tolerance –IGT and DM) [25].

Obesity is the most common cause of IR and T2DM. Simply being overweight (BMI >25) raises the risk of developing T2DM by a factor of 3 [26].

The main components of IR are dysglycemia, dyslipidemia, obesity, hypertension and hyperinsulinemia. Therefore, it is the key feature of metabolic syndrome (MS) and vascular complications (cardiovascular and stroke). IR components once are acquired, those with genetic predisposition will develop the full picture of the disorder suggesting the final phenotypic expression involves both genetic and acquired influences. The most important environmental factor in IR is central obesity which is mainly caused by intake of high fat, and refined carbohydrate without physical activity. These are exacerbated by genetic predisposition but IR could be reduced with minimizing dietary intake and regular exercise [27].

The three potential mechanisms of the controlling glucose metabolism in the skeletal muscles are the glycogen synthase, the hexokinase and the major insulin-stimulated glucose transporter GLUT4. Therefore, defects in glycogen synthesis in the skeletal muscles playing a major role in the pathogenesis of IR [28]. The decrease in the ability of normal responding skeletal muscles to circulating insulin levels or concentrations is main principle of development of IR which could precede the overt T2DM by 10 to 20years [28].

T2DM is characterized by increased hepatic glucose output, increased peripheral resistance to insulin action (due to receptor and postreceptor defects) and impaired insulin secretion.

Two major variants of insulin receptor abnormalities associated with acanthosis nigricans, hyperinsulinemia and marked hyperandrogenism. The classic type A IR syndrome, which is due to genetic defect in the insulin-signaling system such as mutation in the insulin receptor gene [29] and type B IR syndrome, which results from autoantibodies to the insulin receptor [30].

Many factors could enhance IR include, obesity, inflammation and inflammatory markers, defects in genes and drugs. These will be demonstrated further in this chapter.

5. The role of obesity and inflammatory markers in insulin resistance and T2DM

Obesity has a substantial negative effect on life expectancy and longevity. It reduces the length of life in severely obese people by an estimation of 5 to 20 years. This negative effect should be addressed in the health public policy [31]. Obesity, IR, and T2DM are growing health concerns, and the incidence and the prevalence of these diseases are increasing worldwide [32, 33]. Obesity will cause a decline in life expectancy for the first time in recent history due to numerous co-morbid disorders [31] and it is a risk factor for many human diseases [34]. Obesity is associated with an increased risk of developing IR and T2DM [34, 35]. The primary defects in obese individuals are the dysfunction of adipocyte and adipose tissue [34].

IR in obese subjects is determined by the release of high amounts of non-esterified FA, glycerol, hormones, pro-inflammatory cytokines and many other factors from adipose or fat tissue. This is followed by dysfunction of pancreatic β- cells and failure to secret insulin to control blood glucose levels. These metabolic and inflammatory changes are critical in defining the risk and the development of T2DM. [35]. There is a clear hyperbolic relationship between IS and insulin secretion by the β-cells of the pancreas. This demonstrates the concept of a feedback loop governs the interaction between the β-cells function and IS tissues. This helpful in explain that patients or subjects with IR have significant increase in insulin response compared with low responses in IS group [11, 36].

IR is a characteristic feature of T2DM and obesity, and the majority of patients with T2DM are obese. Obesity has a major impact to cause IR in subjects without DM. IR is the primary defect in obese elderly and middle aged patients with T2DM despite, adequate circulating insulin. But, in the second group the impairment of insulin release and the alteration of hepatic glucose output are other defects contributing to the development of the disease [37, 38, 39]. The intra-abdominal fat is a major determinant of IR among other distributed fat in the body while the dysfunction of the β- cells is correlated with reduction of β-cells mass and subsequently reduction in IS. The genetic and the molecular basis of these pathological abnormalities are there. But, not fully understood. As mentioned, the progressive declining or failure of the β-cells function and IS are associated with development of T2DM. Prior to the onset of T2DM, there are stages from normal glucose concentration to dysglycemia (IFG, IGT) emphasizing in number of ethnic group the OGTT response is a major determinant of β-cells function [25, 36]. The elevations in plasma FFA concentrations in obese subjects and in patients with T2DM inhibit insulin stimulated peripheral glucose uptake (fat and skeletal muscle) and glycogen synthesis [40, 41].

The impairment of adipose tissue functions in obese subjects caused by interaction of genetic and environmental factors and subsequently leads to obesity medical co-morbidities. However, not all obese patients develop the same complications. The adipocyte dysfunctions or impairment occur in form of ectopic fat deposition, adipocyte hypertrophy, hypoxia, changes in the cellular composition with a variety of stresses and inflammatory processes in the fat tissue (release a proinflammatory, atherogenic, and diabetogenic adipokine pattern), increased

lipid storage and impaired IS [33]. Obese individuals have large or expanded fat mass and have high or elevated plasma concentration fatty acids [42, 43, 44].

Glucose uptake rather than intracellular glucose metabolism has been implicated as the rate-limiting step for FA-induced IR [45].

In adipose tissue, the glucocorticoids can be produced locally from inactive 11-keto forms through the enzyme 11beta hydroxysteroid dehydrogenase type 1 (11beta HSD-1). In obese human, the glucocorticoids are normal. However, the excess of glucocorticoids produce visceral obesity, IR and DM. In mice, the transgenic mice overexpressing 11beta HSD-1 selectively in adipose tissue was exaggerated by high fat diet showed an increase in the level of corticosterone in adipose tissue by increased adipocyte 11beta HSD-1 activity. This could have the same effect in human[46] suggesting that increases in endogenous 11β-HSD1 in the adipose tissue of obese humans and rodents [47,48] contribute to obesity-associated IR, in part due to increased delivery of glucocorticoids to the liver via the portal vein. The c-Jun amino-terminal kinases (JNKs) interfere with insulin action and it is crucial mediator of obesity and IR. In obese mouse, the JNK activity is abnormally elevated and the absence of JNK1 results in decreased adiposity and improved IS. Therefore, it is a potential target for therapeutics [49].

The activation of JNK1 leads to serine phosphorylation of IRS-1 that impairs insulin action [50, 51]. In addition, IKK-β is a mediator of TNF-induced IR [52, 53, 54, 55] demonstrated the TLR4 (Lipopolysaccharide receptor) activation by FFA, plays a critical role in innate immunity and IR in obese human and animals through activation of inflammatory pathways. In mice the lack of TLR4 will protect insulin suppression signaling and reduce insulin mediated changes in systemic glucose metabolism by lipid infusion. This indicates the effect of nutrition as environmental factor on TLR4 and subsequently on IR. The Apoptosis signal-regulating kinase 1 (ASK1) is an evolutionarily conserved mitogen-activated protein 3-kinase that activates both Jnk and p38 mitogen-activated protein kinases. The reactive oxygen species-dependent TRAF6-ASK1-p38 axis is crucial for TLR4-mediated mammalian innate immunity [53, 54]. This finding may provide an additional link between innate immunity, cellular stress, and IR. The protein tyrosine phosphatase receptor T (PTPRT) knockout mice are resistant to high-fat diet-induced obesity. The PTPRT-modulated STAT3 signaling in the regulation of high-fat diet-induced obesity [34]. Figures 3 and 4 with Table 1.

| Adipokine	Distribution	Function	Effect in obesity
Leptin	Secreted predominantly by WAT, to lesser degree, in ypothalamus, gastric epithelium, placenta & gonads.	Regulates energy intake, expenditure & feeding behavior. Also regulates storage of fat & insulin signaling.	↑ in mouse models of obesity. ↑ in human obesity & correlated with BMI & ↓ in weight loss.
Adiponektin	Secreted exclusively by adipocytes. mRNA & protein in Sc AT > Omental AT.	Improves energy homeostasis, IS & Glucose uptake. Anti-Inflammatory properties.	↓ in mouse models of obesity and IR (ob/ob and db/db).

Adipokine	Distribution	Function	Effect in obesity
	2–3 times greater secretion in females.		↓ in human obesity & T2DM patients. ↑ after weight loss
Resistin	In rodents, secreted by adipocytes. In humans, secreted predominantly by circulating macrophages & monocytes, to a lesser degree, by WAT.	Implicated in glucose metabolism, in the regulation of gluconeogenesis & IR in rodents. More roinflammatory role in humans.	↑ circulating concentrations in mouse models of obesity. ↑ in human obesity & correlated with IR in T2DM patients.
TNF-α	Expressed by macrophages & adipocytes (visceral WAT > subcutaneous WAT).	Affects insulin & glucose metabolism. Provokes IR & stimulates lipolysis.	↑ in mouse models of obesity. ↑ in human obesity & correlated with BMI
IL-6	One-third of total circulating levels are expressed predominantly by adipocytes. Also expressed in macrophages, skeletal muscle, endothelial cells & fibroblasts.	Controversial role in the development of IR. Affects glucose metabolism	↑ circulating levels in human obese subjects & correlated with adiposity & reduced with weight loss. ↑ in plasma of T2DM patients.
IL-7	Secreted by stromal & vascular endothelial cells.	Homeostatic immune cytokine. Also regulates body weight, AT mass & function, and insulin signaling.	↑ in morbidly obese subjects.
IL-8	Secreted by adipocytes (visceral WAT > SC WAT) & macrophages.	Neutrophil chemotaxis.	↑ in obese subjects & related to fat mass & TNF-α levels.
IL-1	Secreted mainly by adipocytes & macrophages.	Role in macrophages chemotaxis & thermogenesis	↑ in obese mice. ↑ in human obesity & predictive of T2DM.
IL-10	Secreted by monocytes, macrophages, dendritic cells, B & T cells.	Improves IS & glucose transport.	Attenuated in T2DM patients & ↑ with weight loss
RBP4	Secreted by adipocytes, macrophages & hepatocytes.	Affects IS, hepatic glucose output & muscle insulin signaling.	↑ circulating levels in obese subjects & correlated with BMI & IR.
MCP-1	Secreted by AT.	Affects IS & ↑ macrophage recruitment in AT and inflammation.	↑ in mouse models of obesity. ↑ in T2DM subjects.
PAI-1	Expressed by WAT.	Potent inhibitor of fibrinolytic pathway.	↑ in human obesity and T2DM subjects.

Adipokine	Distribution	Function	Effect in obesity
CXCL5	Secreted by macrophages within the stromal vascular fraction.	Interferes with insulin signaling in muscle.	Circulating levels are higher in obese IR individuals than in obese IS & ↓ after a 4-weeks period on low-calorie diet.
Visfatin	Expressed in liver, muscle, WAT, bone marrow & lymphocytes	Role in IS, insulin secretion & inflammatory properties.	↑ in obesity & correlates with visceral adiposity in humans.
Chemerin	In rodents & humans, expressed in placenta & WAT.	Regulates adipocyte development & metabolic function.	↑ circulating levels in obese & T2DM patients and correlated with body fat, glucose & lipid metabolism.
Vaspin	Secreted by WAT, hypothalamus, pancreatic islets & skin.	Improves IS.	↑ in obesity & T2DM patients
Omentin	Secreted by omental AT.	↑ IS	↓ in obesity.
Apelin	Produced in a wide range of tissues.	Improves IS mainly acting in skeletal muscle & adipocytes in mice.	↑ in obesity, IGT & T2DM patients. ↓ after weight loss following diet & bariatric surgery.
Nesfatin	Secreted in brain tissue, B cells and AT.	Central action to ↓ Appetite.	↓ in obesity.
TGFβ	Multifunctional, produced By variety of cells. Inhibitor of differentiation.	Varied role in proliferation, differentiation, apoptosis and development.	↑ ob/ob and db/db mice. ↑ preadipocyte cell proliferation as with TNFα. ↑ in obesity, T2DM patients & CVD.
Rantes	Pro -inflammatory secreted by T cells, monocytes & to lesser degree in WAT.	↑ gene expression in AT.	No correlation of serum level with obesity.
Preptin	It is a novel hormone that is co-secreted with insulin and amylin from pancreatic β-cells [60].	Synthetic prepin ↑ insulin secretion from glucose stimulated β TC6-F7 in a concentration- dependent and saturable manner [61].	Plasma preptin level ↑ with higher BMI [62]. It is ↑ in patients with T2DM compared with patients with IGT and normal subjects [61].
Uncoupling protein 2	It is expressed in AT, skeletal muscle and tissue of immune system [63].	It protects cell function from damage and it impairs insulin secretion from β-cells [64].	Anti-oxidant in pancreatic β-cells [65]. The level and activity has impact on glucose stimulated insulin secretion [66].

Table 1. Adipokines increased in obesity and/or diabetes [58, 59].
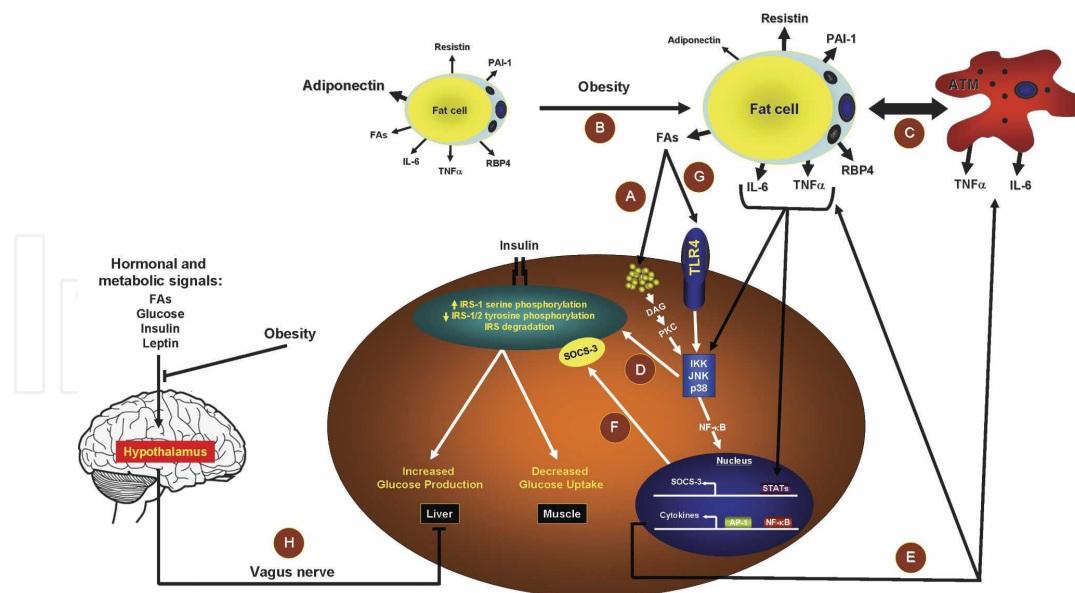
Figure 3. The molecular linked pathway between obesity and IR. (*A*) IR triggered by the increase in FAs through intracellular metabolites that activate PKC, leading to inhibit insulin signaling by activation of serine/threonine kinases. (*B*) Insulin signaling modulated by changes in adipokines secretion. (*C*) In the adipose tissue; the increased in the ATMs mediated the increase of the inflammatory cytokines that inhibit insulin signaling. (*D*) Insulin signaling inhibited by mediators (Endocrine and Inflammatory) converging on serine/threonine kinases. (*E*) IR exacerbated by activation of NF-κB heightens inflammatory responses. (*F*) Adipokines induced SOCS family proteins interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteosomal degradation inducing IR. (*G*) IR triggered by activation TLR4 and innate immune response by FAs. (*H*) Alteration in peripheral IS is related to the central response to hormonal and nutrient signals [57].
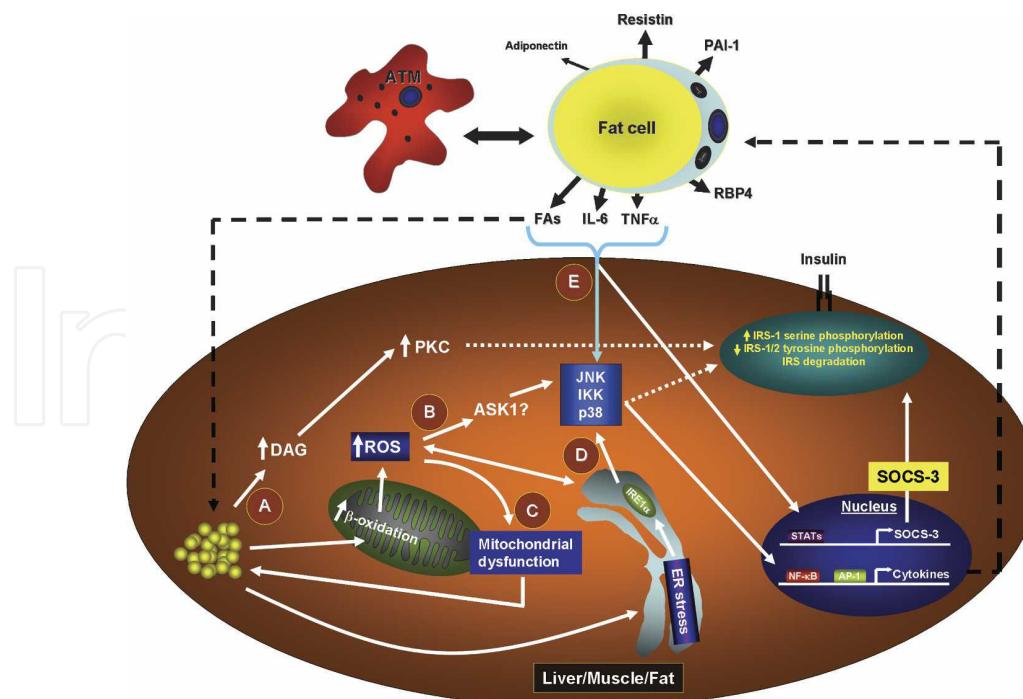
Figure 4. There are several cell-intrinsic mediators and pathways dysregulation in obesity with negative impact on IR. (*A*) Activation of PKC in the liver and muscles inhibits insulin signaling by increasing FA from ectopic adipose tissue. (*B*) Direct inhibition of insulin signaling through IRS-1 or IRS-2 serine phosphorylation or indirectly through a series of

transcriptional events mediated by NF-κB. Inhibition occurs due to activation of several serine/threoning kinases (JNK, IKK, and p38 MAPK) by excess in ROS. The later generation increased by mitochondrial β- oxidation triggered by excess fat accumulation. (*C*) IR exacerbated by mitochondrial dysfunction through increasing intracellular lipid accumulation. (*D*) Insulin signaling suppressed by activation of JNK or through a potential increase in ROS production and both activated by cellular ER stresses responses. (*E*) The cell-extrinsic modulators such as endocrine and inflammatory signals can intensified IR [57].

WAT: White adipose tissue, AT: adipose tissue, T2DM: type 2 diabetes mellitus, IR: insulin resistance, IS: insulin sensitivity, IGT: impaired glucose tolerance, TNF-α: tumor necrosis alpha, IL: interleukin, RBP4: Retinol binding protein, SC: subcutaneous, MCP-1: monocyte chemotactic protein 1, PAI: plasminogen activator inhibitor, CXCL5: chemokines molecules (CXCL5 ligand 5), TGFβ: transforming growth factor β.

6. Others

6.1. Glucose transporters

Glucose transporters (GLUT) are integral membrane proteins that mediate the transport of glucose and structurally-related substances across the cellular membranes [67].

Sugar transport catalyzed by 11 out of 14 members of the human GLUT family. There are specific characteristics of each isotypes. They are different in expression profile, substrate specificity and kinetic characteristics. Therefore, the tissue adaptation of the glucose uptake will be determined and regulated by specific tissue gene expression. GLUT4 malfunction in expression or regulation contributes to IR while GLU2 plays a role in hormonal and neuronal control by acting a glucose sensor in β-cells of the pancreas and neuronal cells [68]. GLUT1 is ubiquitously expressed with particularly high levels in human erythrocytes and in the endothelial cells lining the blood vessels of the brain. GLUT3 is expressed primarily in neurons and, together, GLUT1 and GLUT3 allow glucose to cross the blood-brain barrier and enter neurons [69].

The GLUTI, GLUT2, and GLUU3 are the major glucose transporters isoforms present in these cells and they are constitutively localized to the plasma membrane. The glucose flux across the membrane is largely dependent upon the circulating blood glucose level or concentration. In acute state, the glucose regulated the transport system in the muscles and fat cells responded within minutes to insulin [70].

GLUT4 is the primary hormonally-responsive transporter and it is the major insulin-responsive transporter [69]. GLUT4 expression is also reduced by low insulin states, such as in muscle during fasting, and in IR adipose tissue [71]. The malfunction of glucose transporter expression or regulation (GLUT4) appears to contribute to the IR syndrome [68].

7. Genes in type 2 Diabetes Mellitus

T2DM is a complex diseases arise from interactions of multiple genes with environmental factors. These genes are variables in strength, site of interaction and are different in general

population according to race and ethnicity. The diabetes genes are involved in insulin signaling, insulin secretion, IR, glucose metabolism and obesity. In addition, T2DM could be a component of many syndromes of identified inherited genes [72]. The genetic risk for T2DM changes as humans first began migrating around the world, implying a strong environmental component has affected the genetic-basis of the disease [73, 74]. Immigrants to Western developed countries, for instance, may be more prone to diabetes as compared to its lower incidence in their countries of origins [75]. In meta-analysis of different ethnicities was included in a cross –sectional data from 16 cohorts from the DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia) demonstrated; the waist-to-stature ratio in Asian was stronger than BMI is associated with DM in adjusted age group in both genders [76]. In Japanese-American the prevalence of DM was reduced among the men who had retained a more Japanese lifestyle through higher levels of physical activity and consumed more carbohydrates with less fat and animal protein in their diet. An inverse association between DM and being born in Japan was observed independent of age, body mass index, physical activity, and percentages of calories from fat or carbohydrates [77]. In Fiji population the disease pattern is determined by the modern lifestyle as in many industrial counties. The increase in mortality in this population was contributing to 6% and 30% due to DM and CVD respectively [78]. In USA, the large burden of T2DM in relative to non-Latino Whites, Latinos —those of Mexican origin in particular is related to mixed acculturation to US lifestyles and with greater time living in the States [79]. This was supported by other two studies. The first showed IR, hyperinsulineamia and T2DM with secondary lipid disturbances are the possible mechanism of higher morbidity and mortality from CHD in UK immigrants from the Indian subcontinent (South Asian) than other general population independently of the dietary fat intakes, smoking, blood pressure, or plasma lipids [80]. The second study also observed IR is the common pathogenic mechanism and is a risk factor of increasing the prevalence of CHD, T2DM, low HDL and hypertriglyceridemia in first generation immigrant Asian Indian to the USA compared with native Caucasian population [81]. The two major environmental risk factors for T2DM are obesity (≥ 120% ideal body weight or a body mass index > 30 k/m^2) and the sedentary lifestyle [82, 83]. Thus, the tremendous increase in the rates of T2DM in recent years has been attributed, primarily, to the dramatic rise in obesity worldwide [84]. Obesity is a progressive disease and up to 80% of patients with T2DM and PCOS patients can be attributed to obesity. It is a progressive condition leads to medical co-morbidities which are more prevalent with age and higher BMI, particularly in those with a central obesity [85]. In Pima Indians adolescents, the prevalence of T2DM was 50.9 per 1000 in 1967-1976 increased to 6 folds in 1987-1996. In American Indian and first nation youth, T2DM was more prevalent in 10-19 years old young group. Mainly in obese subjects with acanthosis nigiricans and had family history of the disease [86]. Sinha R, reported 25% of obese children (4 to 10 years of age) and 21%t of obese adolescents (11 to 18 years of age) had IGT and 4% of the obese adolescent has silent T2DM [87]. The increase in physical activity plays an important role in reducing risk of obesity and T2DM. The prolonged TV watching is associated with a significantly increased risk of obesity and T2DM, independent of diet and exercise. Men watching TV more than 40 hours per week have threefold of increase risk of developing T2DM compared with those less than I hour TV watching. Therefore, the public health campaign of decrease sedentary life should accompany the increase in physical activity [88].

Physical activity has also been inversely related to body mass index and IGT. Interventional studies in China, Finland and the US demonstrated the decrease in the risk of incidence and in the progression from pre-diabetes stage (IGT) to T2DM by intensive lifestyle interventions targeting diet and exercise. The Finnish Diabetes Prevention Study showed a reduction by 58% and in the china study was 31% with diet and 42% with diet and exercise. This was supported by USA study showed the same risk reduction with intensive lifestyle as in the Finnish study and also a reduction of 31% with metformin indicating that lifestyle intervention is better than drugs in T2DM prevention [89, 90, 91].

Xue Sun [92] reviewed a large-scale of association studies, and the genome-wide association studies (GWAS). Both have successfully identified multiple genes that contribute to T2DM susceptibility. Linkage analysis, candidate gene approach, large-scale association studies, and GWAS have identified approximately 70 loci conferring susceptibility to T2DM. Among them, 45 loci were identified in European populations, and the other 29 loci were identified in Asian populations, especially in East and South Asians. The immediate benefit derived from these findings was the better understanding of the pathophysiology of T2DM. A great number of studies have suggested that genetic variants in or near KCNJ11, TCF7L2, WFS1, HNF1B, IGF2BP2, CDKN2ACDKN2B, CDKAL1, SLC30A8, HHEX/IDE, KCNQ1, THADA, TSPAN8/ LGR5, DC123/CAMK1D, JAZF1, MTNR1B, DGKB/TMEM195, GCK, PROX1, ADCY5, SRR, CENTD2, ST6GAL1, HNF4A, KCNK16, FITM2-R3HDML-HNF4A, GLIS3, GRB14, ANK1, BCAR1, RASGRP1, and TMEM163 may confer T2DM risk through impaired -β-cell function [93-97] whereas PPARγ, ADAMTS9, IRS1, GCKR, RBMS1/ITGB6, PTPRD, DUSP9, HMGA2, KLF14, GRB14, ANKRD55, and GRK5 have an impact on insulin action [94,98-100]. FTO and MC4R, previously identified genes associated with obesity, appear to confer T2DM risk through their primary effects on BMI, but recent GWAS have shown that their effects on T2DM were independent of BMI, though FTO may have a small but detectable influence on T2DM risk through insulin action [101,102].

Barnet AH; concluded the higher concordance rate in identical twins than in non-identical twins regardless the age of the onset of the disease and in identical twins, the concordant for DM is usually in older age group compared with the younger [103]. In Japan, The Concordance between monozygotic twins was 83% for T2DM and was 40% between dizygotic twins for T2DM. This concordance was significantly greater in monozygotic than in dizygotic twins and among twins with later onset of DM (after the age of 20) than early onset. It was also observed, the loss of the early-phase insulin response for OGTT in T2DM co-twins [104]. The role of obesity or BMI in twins as a risk of DM varies in heterogeneous genetic background. The index twins of concordant pairs had been less obese than discordant pairs. This is suggestive obesity has a role in pathogenesis of DM in those with weaker genetic susceptibility for the disease [5].

Nonetheless, non diabetes first-degree relatives of T2DM patients have an almost three fold increased lifetime risk of T2DM in comparison to the background population [106]. In other study 40% of first-degree relatives of T2DM patients develop diabetes as compared to 6% in the general population [106]. IR is an early metabolic feature of nondiabetic first-degree relatives of T2DM patients [107,108] and also shows familial clustering in keeping with an underlying genetic predisposition [109,110]. The defects of insulin action are retained in cultured skeletal

muscle cells from IR subjects and T2DM patients [111,112] suggesting that genetic variation contributes to decreased insulin action. While IR is a common feature of T2DM, the severity and clinical importance varies considerably across the T2DM population [113].

7.1. Inherited DM: Maturity onset diabetes of the young or MODY

The transcription factor genes play a crucial role in the normal development and function of the β-cell. MODY is a distinct type of heterogeneous group of disorders caused by mutations in β-cell transcription factors. MODY is an autosomal dominant mode of inheritance β- cell dysfunction in young age group (usually before 25 years). It is difficult to distinguish between MODY and other forms of DM because of primary defect is pancreatic β-cell dysfunction in patients with MODY. There are at least nine mutations of different gens that result in MODY phenotypes which account in about 1-2% or 2-5% of patients diagnosed with DM (approximately 20000 in UK). The transcription factors hepatocyte nuclear factor HNF - α1, HNF-4α, insulin promoter factor (IPF)-1, HNF-1β, and NeuroD1 are the main identified genes in MODY. The Glucokinase (GCK) is an enzyme responsible for glucose phosphorylation, whereas HNF-1α, HNF-4α, IPF1, HNF-1β, and NEUROD1 are all transcription factors that modulate the expression of several genes involved in differentiation and function of β-cells. This enzyme is a key in blood glucose homeostasis and the defective in kinase gene metabolism implicated in the pathogenesis of DM. There is a linkage between the GCK locus on chromosome 7p and diabetes in 16 French families with MODY and the same linkage was demonstrated in a large 5-generation pedigree (BX) with 15 members with DM. Mutations in the GCK gene cause a mild, asymptomatic and non-progressive fasting hyperglycaemia from birth usually requiring no treatment. The gene on chromosome 7 (MODY2) encodes the glycolytic enzyme glucokinases plays a key role in generating the metabolic signal for insulin secretion and in integrating hepatic glucose uptake. Other linkage studies have localized other genes mutation in MODY on human chromosomes 20 (MODY1) and 12 (MODY3), with MODY2 and MODY3 being allelic with the genes encoding glucokinase. MODY1 is an encoding (hepatocyte nuclear factor) HNF-4α (gene symbol, TCF14), a member of the steroid/thyroid hormone receptor superfamily and an upstream regulator of HNF-1 α expression. This is a transcription factor involved in tissue-specific regulation of liver genes but also expressed in pancreatic islets, insulinoma cells and other tissues. Mutations in the GCK and HNF1- α/4-α genes account for up to 80% of all MODY cases, these mutations appear in different transcription factor genes result in different clinical presentations. Mutations in the genes encoding the transcription factors HNF-1α and HNF-4α cause a progressive insulin secretory defect and hyperglycemia while mutations in the GCK gene cause a mild and non-progressive disease. MODY3 form has also mutations in the gene encoding hepatocyte nuclear factor-1 α (HNF-1α, which is encoded by the gene TCF1). Mutations in HNF-1α are highly penetrant with 63%of mutation carriers having diabetes by the age of 25 years, 78.6% by 35 years, and 95.5% by 55 years resulted in progressive β- cell dysfunction with increasing treatment requirements, greater risk of complications with age and appear to be renal dysfunction, which is often diagnosed before diabetes. Mutations in HNF-4α result in same mode of β- cell deterioration in β-cells function but the diagnosis in the later age. Mutations in IPF-1 (PDX-1) are not a common cause of MODY. MODY1 form has mutations in the gene encoding hepatonuclear factor HNF-4 α (gene symbol, TCF14) is a

member of the steroid/thyroid hormone receptor superfamily and an upstream regulator of HNF-1α expression. The deficient binding of NEUROD1 or binding of a transcriptionally inactive NEUROD1 polypeptide to target promoters in pancreatic islets leads to the development of T2DM in humans. In mice, two mutations in NEUROD1 in the heterozygous state were described in development of T2DM. The truncated polypeptide lacking the carboxy-terminal trans-activation domain, a region that associates with the co-activators CBP and p300 is more severe clinically than mutation at Arg 111 in the DNA-binding domain, abolishes E-box binding activity of NEUROD1 [114-125]. Other rare forms of MODY are CEL-MODY, ABCC8, KCNJ11 and UPD6 [126]. There are many factors determined the clinical presentation of various subtype of MODY including, the severity, the course of insulin secretion defect, the risk of microvascular complications and the presence of other abnormalities or defects in diabetes patients [127].

7.2. Mitochondrial diabetes: A monogenic Diabetes Mellitus

Maternally inherited diabetes and deafness (MIDD) is a new sub-type of diabetes with mutation in mitochondrial DNA. The mitochondrial genome is passed and inherited exclusively by maternal line. In patients with T2DM there could be increase in transmission of inherited diseases by maternal line more than paternal. However, only 0.5-2.8% of patients with DM demonstrated the frequency of adenine to guanine mutation. The adenine to guanine transition mutation at position 3243 in the dihydrouridine loop of mitochondrial tRNA$^{Leu(UUR)}$ gene is specific to patients with a neurological syndrome MELAS (myopathy, encephalopathy, lactic acidosis and stroke like disease). There is also 3243 mutation is associated with the phenotypical distinct of MIDD sub-type. In a study of the genotype of patients with T2DM of North European extraction with one or more features of MIDD and/or MELAS, Two patients were identified with the mutation giving a prevalence rate of 0.13% for the whole study population, and 0.45% for the sample with phenotypic features of MIDD. Other mitochondrial gene defects and mutation of 3234 are linked to the development of T2DM [128-133].

8. The monogenic forms of Insulin Resistance (IR)

A clear genotype-phenotype association is emerging following description of more than 60 mutations in insulin receptor gene which subsequently causing IR and tend to genera extreme and severe forms of IR patients. The most abundant mutations are heterozygous leading to decreased tyrosine phosphorylation of the β-subunit of the insulin receptor.

- Type A insulin resistance syndrome, it is a heterozygous mutations in the tyrosine kinase domain of the insulin receptor gene and it is the most common phenotype. It is characterized by acanthosis nigricans and hyperandrogenism without obesity or lipoatrophy.

- Homozygous or compound heterozygous mutations lead to the Rabson–Mendelhall syndrome with severe impairment of insulin receptor function.

- Donohue syndrome (Leprechaunism) is the most extreme form of IR in humans in whom mutations resulting in complete or near-complete absence of functional insulin receptors. [134,135,136]

- Dunnigan-type familial partial lipodystrophy (FPLD) is a rare autosomal dominant form of monogenic IR. FPLD patients are born with normal fat distribution but after the onset of puberty, they lose fat from their extremities and gluteal region. The mutation of LMNA, which encodes nuclear lamin A and C on chromosome 1q21, underlies FPLD. These patients have low leptin levels and FPDL is linked to early coronary heart disease. The LMNA codon 482 missense mutation was observed to strongly associated with hyperinsulinemia, dyslipidemia, hypertension, and T2DM [137,138,139].

- The PPARγ gene, encoding the receptor through which the insulin-sensitizing drugs, the thiazolidinediones, mediate their effects the peroxisome proliferator-activated receptor gamma (PPARγ) has become a prime candidate in the search for mutations causing IR [140]. The new missense mutations in the ligand-binding domain of PPARγ were found in family (mother and her son) was heterozygous for a single nucleotide substitution with mutation at codon P467L. The mother had history of irregular period, infertility disorder, Gestational DM followed by frank DM requiring high doses of insulin (severe IR). Her son had history of early onset T2DM and hypertension. The third subject was a young female from another family presented with primary amenorrhoea, hirsutism, acanthosis nigricans and hypertension. She was heterozygous from different mutation at codon V290 of a single nucleotide substitution. These new subtypes of dominantly inherited T2DM due to defective transcription factor function resulting in impaired insulin action rather than secretion [141]. Studies to determine if mutations in the PPARγ gene predispose to diabetes in the general population show a complex relationship.

8.1. Insulin gene

Several phenotypes, including T2DM, polycystic ovary syndrome, and birth weight are associated with tandem repeat (VNTR) minisatellite 5' of the insulin gene (INS). A study analyzed this insulin gene class III VNTR minisatellite in 155 European T2DM parent-offspring trios from the British Diabetes Association demonstrated that variation within the TH-INS-IGF2 locus, most plausibly at the VNTR itself at this regulatory element is a significant determinant of T2DM susceptibility. This susceptibility is exclusively mediated by paternally derived alleles [142].

8.1.1. SUR-1gene

In Dutch population, the exon 16-3t allele of the single nucleotide polymorphisms in the sulphonylurea receptor gene (SUR1) has been reported to be associated with T2DM patients compared with the control group. But there was no association between T2DM patients and the variant in exon 18 or the combination of both variants. Other studies in Caucasian population, strong linkage disequilibrium between the exon 16 and exon 18 variants was demonstrated in patients with T2DM but was not shown in the control group [143].

8.1.2. IRS-1gene

The utilization of insulin receptor substrate (IRS)-proteins (IRS-1 and IRS-2) emerged many interactive proteins in the insulin signaling system. This can be amplified or attenuated independently insulin binding and tyrosine kinase activity, providing an extensible mechanism for signal transmission in multiple cellular backgrounds [144]. Patient with T2DM with IRS-1 variants did not differ in their degree of IR compared with patients without known IRS-1 polymorphisms. However, carriers of the codon 972 variant had significantly lower plasma levels of fasting insulin and C-peptide [145, 146]. Many other studies demonstrated several polymorphisms in the IRS-1 gene variant, a Gly-->Arg change at the codon 972 may contribute in impairment of insulin secretion and increased in prevalence among patients with T2DM [146].

8.1.3. PC-1gene

In Swedish and Finnish people, the Q allele of the human glycoprotein PC-1 gene is associated with surrogate measures of IR, but it may not be enough to increase the susceptibility to T2DM. An observation showed there was no difference in the Q allele frequency between the patients with T2DM and control group. There were higher fasting plasma glucose and 2 hours in QK genotype siblings with diabetes compared with carrier of KK genotype. While in sibling with QK genotype and without diabetes have higher fasting plasma glucose and insulin than KK genotype carrier [147].

8.2. Glycogen synthase gene

An Xbal polymorphism has been described in the glycogen synthase gene associated with IR [148]. More features of metabolic syndrome and increased susceptibility to T2DM were described in sibling with rare A2 allele of discordant sib-pair analysis [149]. A set of polymorphic microsatellite markers that span the genome was implemented in genotyping of families with this condition to essence this approach [150].

8.2.1. Calpain 10 (CAPN10) gene

Calpain gene is cytoplasmic cystiene protease requiring calcium ions for activity. CAPN10 gene was proposed as susceptibility locus of T2DM based on the initial report of association between the T2DM and CAPN10 gene [151]. It has been reported of association with T2DM in Pima Indians [152], in African Americans [153] in Mexican Americans [154], in the Botnia area of Finland, German patients [155] and in South Indians [156].

8.2.2. Foxo 1 gene

Insulin signalling downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway is at least in part controls glucose on β-cells mass and function. The activation of Akt is negatively affected the proliferation and metabolism of Foxo transcription factors. The changes in Foxo 1 transcriptional activity are associated with nutritional alteration of β-cells. Glucose-stimulated insulin secretion acts through its own receptor as the predominant mediator of these

changes in β-cells [157]. Ghrelin increases pancreatic β-cell proliferation and survival via sequential activation of phosphatidylinositol-3 kinase (PI3K) and Akt ghrelin. It protects pancreatic β-cells from lipotoxicity by inhibiting the nuclear translocation of Foxo1 [158].

8.3. Beta 3-adrenergic receptor gene

The energy balance by increasing in lipolysis and thermogenesis could be regulated by the beta 3-adrenergic receptor (beta 3-AR) gene. The ability to gain weight and the early onset of T2DM are associated with mutation in the beta 3-AR gene (Trp64Arg). But this is not in Dutch population [159]. Many studies in different ethnic groups showed an association of beta3-AR gene polymorphism with IR, obesity and its metabolic disorders such as T2DM, coronary heart disease and hypertension [160].

8.3.1. TCF7L2

The risk alleles of TCF7L2 were associated with enhanced expression of this gene in human islets as well as impaired insulin secretion both in vitro and in vivo. TCF7L2 has also been linked to altered pancreatic islet morphology as exemplified by increased individual islet size and altered α and β cell ratio/distribution within human islets [161]. TCF7L2 encodes the transcription factor TCF4 which is related to Wnt signaling pathway and which plays a critical role in the pathogenesis of T2DM. The risks of alleles in TCF7L2 were associated with hepatic but not peripheral IR and enhanced the rate of hepatic glucose production in human [162]. This is indirectly disturbing beta cells function of the pancreas.

8.3.2. SCL30A8

SCL30A8 encodes the islet specific zinc transporter ZnT-8, which delivers zinc ions from cytoplasm into intracellular insulin-containing granules and is implicated in insulin maturation and/or storage processes in β-cells [163]. The expression level of ZnT-8 was remarkably down regulated in the pancreas of db/db and Akitamice in the early stage of diabetes. Global SCL30A8 knockout mice demonstrated reduced plasma insulin, impaired glucose –stimulated insulin secretion, and markedly reduced islet zinc content [164].

8.4. Others genetic syndromes associated with diabetes

Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreichataxia, Huntington chorea, Laurence-Moon-Biedlsyndrome, Myotonicdystrophy, Porphyria and Prader-Willi syndrome.

9. Drugs induced hyperglycemia and DM

Many pharmacologic and chemical agents can predispose, induce or precipitate hyperglycemia in normal subjects with high risk of T2DM or patients with IGT and DM. The individual effect of each agent could be weak or strong and subsequently the new glycemic state will be

variable from transient to permanent. There are many mechanisms to induce diabetes by interfere with insulin production or secretion (e.g. Beta- Blockers), block insulin action (e.g. Steroids), interfere with both insulin secretion and action (e.g. Thiazides), and finally increase blood glucose using mechanisms independent of insulin's actions (e.g. Nicotinic acid) [165].

Table 2 shows the most common drugs that used in clinical practice with the mechanism of each drug or group.

Drugs	Mechanisms	Notes
Thiazide and thiazide like drugs. Chlorothiazide Chlorothalidone Hydrocholorthiazide Idapamide Methyclothiazide Metolazone	Decreases insulin release by hypokalemia [167,168] and down regulation of PPARγ Receptor.	Avoided in patients with DM and patients at risk of hyperglycemia. Use small dose if requires [167, 168].
*Spironolactone does not cause IGT even at high dosage [167].	In hypertensive elderly on Thiazide but without DM, each 0.5meq/L reduction in serum potassium was associated with 45% higher risk of new DM [169]. Increases aldosterone release and IR [170,171].	Indapamide does not interfere with blood sugar control in T2DM but higher doses that cause potassium loss may cause deterioration. Loop diuretics have been reported to reduce glucose control to a lesser extent than Thiazides [168].
Atypical antipsychotics **High risk** Clozapine Olanzapine	Wight gain [172, 173] and adiposity [174]	Risk of hyperglycemia is more in patients with obesity, age, ethnic status, and certain neuropsychiatric conditions [173].
Intermediate risk Paliperidone Quietiapine Resperidone	Sympathetic stimulation [175].	
Low risk Aripiprazole Ziprasidone	Decrease insulin action [173] and increase IR [176].	
Unknown Iloperidone	Potential Individual Polymorphisms in the leptin gene and leptin receptor gene to antipsychotic induced obesity [177].	
B- blockers Atenolol Metoprolol Propranolol	Increase fasting glucose [178].	The risk of hyperglycemia is increased in patient on B-blocker and thiazide diuretics [180].

Drugs	Mechanisms	Notes
*Carvidolol and nebivolol are not associated with hyperglycemia.	Impair insulin secretion [179]	
Corticosteroids Betamethasone acetate Cortisone Methylprednisolone Hydrocortisone Fludrocortisone Hydrocortisone Triamcinolone Prednisolone Dexamethasone	Decrease in both hepatic and extrahepatic sensitivity to insulin [182].	Identify high risk patient of hyperglycemia.
Oral contraceptive pills	Increase IR [182,183].	Risk of hyperglycemia is increased with higher doses and longer duration therapy.
Megasterol acetate [181].		Monitor the blood glucose to optimize the diabetes therapy by tablets or insulin to avoid short and long term complications of hyperglycemia.
Growth Hormone	Accelerated lipolysis resulting in increased circulating non-esterified fatty acids levels [184,185]. This may contribute to IR, hyperinsulinemia and defective glycogen synthesis [186].	Used as replacement therapy in patients with GH deficiency.
Protease inhibitors Atazanavir, Darunavir Fosamprenavir Indinavir Nelfinavir Ritonivir Saquinavir Tipranivir. Etravirine Maraviroc Raltegravir	Inhibition of GLUT4 Transporter contributes to decrease peripheral insulin sensitivity and induce IR. [187].	Lipodystrophy and Dyslipidaemia are major side effects of this group [188].
Didanosine Nucleoside reverse transcriptase inhibitor	Causes β-cell injury by pancreatitis [189].	Used in treatment of HIV infection. The risk is increased with high dose and in combination with tenofovir [190].
Antibiotics (Quinolone group)		

Drugs	Mechanisms	Notes
Gatifloxacin Temafloxacin Levofloxacin	Stimulation of insulin secretion by inhibition of pancreatic beta-cell K(ATP) channels causes hypoglycemia [192]. It may also cause hyperglycemia. [193].	Gatifloxacin was withdrawn from the market because of this effect [193]. Levofloxacin has a small effect. [192].
Rifampicin [191].	Possibly by augmenting intestinal absorption of glucose.	It is an early phase of hyperglycemia and disappeared after few days of treatment. This effect in rat [194].
Tetracyclines Tetracycline chlortetracycline	Causes hyperglycemia.	
\Calcineurin inhibitors Cyclosporine	Impair the function β-cells by impairing insulin gene expression [195-197].	The incidence of new onset DM was 14 to 16% augmented in the first post-transplantation year, declining thereafter to an annual incidence of 4 to 6%, similar to the pre-transplantation baseline rate [205, 206].
Sirolimus Tacrolimus Cyclosporine	Direct β-cells toxicity [198-200]. Decreases in IS [201].	The cumulative incidence of new onset DM was 24% at 3 yr after transplantation [205].
	Impair insulin-mediated suppression of hepatic glucose production [202]. May cause ectopic triglyceride deposition, leading to IR [203, 204]. The above aggravated by many modifiable and non-modifiable risk factors [201].	There is a synergetic effect of cyclosporine to induce DM if given with other diabetogenic drug [207].
Thalidomide [208].	Decreases insulin-stimulated peripheral glucose uptake by 31% (increased insulin resistance) Decreases glycogen synthesis by 48%.	Thalidomide, withdrawn for teratogenicity and was reintroduced in 1997 as an immunomodulator to treat erythema nodosum leprosum.
Fish oil or Omega -3 polyunsaturated fatty acids (PUFAs).	PUFAs may affect glucose metabolism through increased IS, but studies to date have been inconclusive [209].	Among all adults who use natural products, more than 37% report taking fish oil or omega-3s. [210].
Interferon α [211].	Risk of hyperglycemia only in patient with chronic hepatitis C infection.	Sustained virological responses reduce the risk of developing glucose abnormalities, especially in patients with normal glucose baseline.

Drugs	Mechanisms	Notes
Ritodrine [212].	Ritodrine induced hypokalemia.	It is selective β2- adrenergic agonist used for premature labour.
Pentamidine [213].	Inappropriate insulin release and toxicity to the islet β-cells. It may cause hypoglycemia, IGT and DM.	It is anti-protozoa agent. These effects worsening with higher doses prolong course and renal impairment.
Statins [214].	Impairing β-cell function and decreasing peripheral insulin sensitivity.	Elderly women and Asians are at particular risk.
Nicotinamide [215].	Enhanced gluconeogenesis.	Hyperglycemia may occur in both normal subjects and in patients with DM.
Diazoxide [216].	Inhibits insulin secretion	Used in treatment of insulinoma.
diphenylhydantoin [217].	Inhibiting apoptosis, increases islet insulin content, accompanied with ameliorated glucose tolerance.	It may be useful in treatment and prevention of DM.
	Inhibits insulin secretion.	Hyperglycemia is more likely to develop in subjects with other risk factors for DM.
L-Asparaginase	Non injury to β-cells [218]. In Rabbits, the anti-tumor enzyme, L-asparaginase, is produced at least in part by the suppression of insulin release [219].	It is transient hyperglycemia that ends following stop the drug.
Vacor Rodenticide poisoning [220].	It has antineoplastic activity and cause pancreatic β-cell damage.	Accidental ingestion by subjects causes severe form of diabetes Ketoacidosis.
Total Parenteral Nutrition	These patients are often critically ill and are administered preparations with high glucose content [221].	It is associated with poor outcome in severely ill patients [221,222].

Table 2. A modified and updated table of mechanisms of drugs induced hyperglycemia [166].

10. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a heterogeneous pathogenic condition affecting 2-5% of all pregnant women during pregnancy [223, 224] in other data is 5-6% [225]. GDM and T2DM share a common pathophysiological background, including β-cell dysfunction and IR [226, 227]. In addition, women with GDM are at increased risk of developing T2DM later in life [226]. The pancreatic β- cells failure and impairment is the primary characteristic of GDM. In this group of patients with diabetes, there is a genetic predisposition triggered by increased IR during pregnancy leading to malfunction of the pancreatic β-cells [224]. The clustering of the GDM within family members suggestive of genetic predisposition to the development of this disease. Furthermore, women with MODY gene mutations are reported to have GDM

more often [223,224]. In addition, the mutations in other genes include glucokinase (GCK), HLA antigens, insulin receptor (INSR), insulin-like growth factor-2 (IGF2), HNF4A, insulin gene (INS-VNTR), plasminogen activator inhibitor 1 (PAI-1), potassium inwardly rectifying channel subfamily J, member 11 (KCNJ11), hepatocyte nuclear factor-4a (HNF4A) and 1α (HNF1A) [224] suggest the susceptibility to increase the risk of GDM in certain patients.

The stimulators or the inducers of IR and phosphorylate insulin receptor substrate (IRS) proteins are activated in uncontrollable method several kinases, including inhibitor of nuclear factor κB kinase β (IKK β), c-Jun N-terminal kinase (JNK), mammalian target of rapamycin (mTOR), protein kinase C (PKC) and ribosomal S6 protein kinase (S6K). Substance P is a potent cytokine and is considered one of the crucial activators that contribute in the development of IR by impairment of insulin signaling [225]. The genetic variants in TCF7L2 is the strongest gene associated with GDM risk among other minor alleles of rs7903146 (TCF7L2), rs1225 5372 (TCF7L2), rs1799884 (-30G/A, GCK), rs5219 (E23K, KCNJ11), rs7754840 (CDKAL1), rs4402960 (IGF2BP2), rs10830963 (MTNR1B), rs1387153 (MTNR1B) and rs1801278 (Gly972Arg, IRS1) significantly associated with a higher risk of GDM. There are 12 SNPs from 10 genes are associated GDM [228].

The E23K polymorphism of KCNJ11 seems to predispose to GDM in Scandinavian women [226] and the polymorphism of TCF7L2 (rs7903146 C/T) gene, and the G972R polymorphism of the IRS1 gene, seems to predispose to GDM in Greek women [227]. In women of Han nationality in north China, The defect in sulfonylurea receptor-1 (SUR1) gene (cc and AA) may contribute to insulin hypersecretion, which might be the cause of increased body weight and decreased IS and genotype cc of SUR1 is connected with severe type of GDM [229].

In animals but not in human, Galanin inhibits glucose-stimulated insulin release [230]. In the human, the initial postprandial rise of glucose and insulin are suppressed by galanin administration [231]. Galanin and IL-6 were found to be significantly associated with IR markers in GDM, thus may play important roles in the regulation of glucose hemostasis [232].The higher level of plasma galanin is a novel biomarker for the prediction of GDM [233].

In late pregnancy the relative proinsulin secretion is mainly related to IR and does not necessarily reflect β-cell function. T2DM is not independently associated with hyperproinsulinemia as measured by the proinsulin-to-C-peptide ratio. While, in pregnant women, the increased in IR is associated with decreased proinsulin to C-peptide ratio, independently of glucose tolerance status [234].

The islet amyloid pancreatic polypeptid hypersecretion is characteristic for pregnancy and might partially decrease hyperinsulinemia in pregnancy by inhibiting insulin secretion [235].

The β- cells dysfunction and IR are the core in the pathogenesis of T2DM and both are mediated by Adiponectin. Therefore, in late pregnancy the Adiponectin is an independent factor correlated with β- cells dysfunction [236].

In pregnancy IR and GDM caused by the placental hormones and cytokines such as tumor necrosis factor alpha (TNFα), resisten and leptin. All of these are secreted by placenta independently. The human chorionic somatomammotropin (HCS), cortisol, estrogen, progester-

one, and human placental growth hormone (hPGH) are important placental hormones. Severe IR produced by overexpression of hPGH and the increase of the HCS throughout pregnancy stimulates maternal pancreatic insulin release [237].

The fall of IS during pregnancy is counteracted by increase maternal insulin secretion to maintain glucose control [238]. The insufficient insulin secretion to counteract the pregnancy-related decrease in IS is contributing in development of DM [239]. Women at high risk of GDM should have a prior conception plan to prevent DM by normalize body weight, regular physical exercise, reducing excess intake of animal protein and soft drinks, planning of pregnancy in younger ages, avoiding pollutant exposition and smoking cessation [240].

11. Uncommon diseases cause hyperglycemia and DM

11.1. Endocrine diseases

Acromegaly and hypercortisolism are frequently associated with IGT and T2DM. It is a recognized finding of occurrence of secondary T2DM with many hormonal diseases (pituitary, adrenal/or thyroid disease). Patients with Acromegaly have IR, both in the liver and in the periphery displaying hyperinsulinemia and increased glucose turnover in the basal post-absorptive states. There is increase in blood glucose level and free fatty acids due to stimulation of gluconeogenesis and lipolysis. Although, insulin growth factor-1(IGF-1) level is increased but it is unable to counteract IR induced by abnormal excess GH level. On the other hand, IS primarily enhanced in the skeletal muscles by increased IGF-1. The excess of the GH and IGF-1 in patients with Acromegaly could be controlled by somatostatin analogues (SSAs) therapy in most of the patients. On the contrast, the overall glucose tolerance might be complicated by the inhibitory effect of SSAs on pancreatic insulin secretion.

The visceral obesity and IR are induced by hypercortisolemia. It also leads to hyperglycemia and reduced glucose tolerance, determines IR and stimulates hepatic gluconeogenesis and glycogenolysis. The hyperglycemia is due to decreased insulin secretion in patients with neuroendocrine tumors (NETs), patients with pancreatic surgery and in those with pheochromocytoma. While in somatostatinoma or gluconoma the hyperglycemia is related to alteration in the counterbalance between these hormones. In the symptomatic treatment of NETs, the SSAs represent a valid therapeutic choice and it may have a significant impact on the prevalence of glucose metabolism imbalance.

Hyperthyroidism is the principally cause of hyperglycemia among thyroid disorders [241]. IR is associated positively with abnormal increase in the thyroid hormone levels [242]. The uncontrolled diabetes in patient with diabetes developing thyrotoxicosis is related to the stimulation of hepatic glucose production by thyroid hormones acting via a sympathetic pathway from the hypothalamus and FT3 influenced the transcriptional regulators of metabolic and mitochondrial genes may contribute to the development of IR. In contrast, hypothyroidism is linked to decreased IS. The thyroid hormones have insulin antagonistic effects at the liver that lead to an increase in glucose hepatic output, via an enhanced rate of gluco-

neogenesis and glycogenolysis. Lipid metabolism (lipogenesis and lipolysis) are stimulated by FT3 further aggravating the dysregulation of liver glucose and lipid metabolism predispose to IR There are several genes are involved in gluconeogenesis, glycogen metabolism, insulin signaling and many hepatic glucogenic enzymes are regulated by thyroid hormones. The thyroid hormones also could cause an increase in hepatic glucose output, through increased hepatic expression of the glucose transporter GLUT2 [243].

11.2. Polycystic ovary syndrome

The features of PCOS are hyperinsulinemia, IR and hyperandrogenesim. The later presented in those patients with hirsutism, acne, irregular periods and reproductive disorders. These features are more marked and severe in obese females and the combination of both (these features with obesity) have a synergistic effect on increased insulin secretion by β-cells and development of compensatory hyperinsulinemia. Subsequently, with the decline of the β-cell compensatory response a relative or absolute insulin secretion and production insufficiency develops which may lead to dysglycemia (IFG, IGT and T2DM). Therefore, it is well-known that PCOS and IR are considered risk factors for GDM [244]. This risk is increased in obese females, presence of family history of T2DM and to the severity of high androgenic activity. Therefore, the dysglycemia could occur in earlier age group than normal population. It could be in the 3rd or 4th decade of life and it is approximately 5 to 10 folds higher than normal population. No doubt, it is higher compared with age and weight matched control age group [245].

11.3. Pancreatic damage or β-cell damage of the pancreas

Chronic alcoholism and tropical calcified pancreatitis are most commonly associated with diabetes [247]. Pancreatic exocrine disease associated with hyperglycemia or DM has a unique clinical and metabolic form. It is painless occasionally and malabsorption occurs after clinical hyperglycemia or DM following failure or impairment of endocrine and exocrine pancreatic function of both α and β cells [246]

11.4. Hereditary hemochromatosis

Iron overload and excessive tissues deposition of iron including the pancreas. It is an autosomal recessive genetic disorder caused by a mutation in the HFE gene located on the short arm of chromosome 6. Approximately 50% of patients diagnosed with hemochromatosis will have either type 1 or T2DM [248].

11.5. Cystic fibrosis

Diabetes Mellitus is the most common morbidity in patients with cystic fibrosis (CF). It occurs in about 20% of adolescent and 40-50% of adults with this disease. CF primarily caused by insulin insufficiency. However, there is a role for IR in acute and chronic stages of this disease due to fluctuation level of insulin. DM has a unique distinct entity in patient with CF because it has mixed features of TIDM and T2DM [249].

Other causes of damage of the pancreas are toxins like alcohol, surgical resection of the pancreas and pancreatic cancer.

11.6. Smoking

There are several studies suggestive of smoking is a risk factor for T2DM, it is an independent and modifiable risk. The early weight gain following smoking cessation is far more beneficial compared with the long term effect of smoking. This weight gain could increase the risk of diabetes [250-252]. Smoking deteriorates glucose metabolism and it is considered a possible a risk factor for development of IR and subsequently T2DM [253]. Smoking is also through a body mass index independent mechanism increasing the risk of T2DM [254, 255]. Pancreatic damage by toxic agents cause insufficient insulin secretion and development of the disease. Tobacco is one of the toxic agent to the human body and organ damage; on the pancreas it is also considered a risk factor of pancreatic cancer and chronic pancreatitis [256].

11.7. Prematurity and birth weight

Hofman PL in 2004 reported an association between low birth weight, commonly a reflection of an adverse in utero environment, and the subsequent development of diseases such as T2DM and hypertension in later life is now generally accepted as is an association between an adverse perinatal environment and a permanent reduction in IS [257, 258].This concept was changed in other report by the evidence has accumulated that small for gestational age children have long-term adult health consequences including obesity, T2DM, hypertension, coronary artery disease and stroke. This increased risk of later adult disease is likely a consequence of an early, persistent reduction in IS [259]. Reduced fetal growth is associated with increased risk of diabetes and suggested a specific association with thinness at birth [260]. Prevalence of T2DM and IGT depended on the synergic effect of thin body size at birth and obesity during adulthood [261]. IGT and T2DM are early signs and indications of growth retardation in early life. The raise in plasma levels of 32-33 split proinsulin is closely related to growth retardation and reflects the β-cells dysfunction [262]. A review and analysis of 14 studies low birth weight (<2,500 g), as compared with a birth weight of >/=2,500 g, was associated with increased risk of T2DM. The risk is the same in high birth weight (>4,000 g), as compared with a birth weight of (</=4,000 g) [263]. The two strongest predictor factors for development of T2DM in adult life are low birth weight and abdominal obesity. The risk of T2DM in Chinese adults is inversely correlated to birth weight. Subjects with high risk of developing hypertension and abdominal obesity are those with the lowest or highest birth weight [264].

12. Conclusion

The evolution of T2DM requires the presence of defects in both insulin secretion and insulin action, and both of these defects can have a genetic and an acquired component. There are many discovered complex alterations in adipose tissue secretion of cytokines, adipokines, and chemokines and immune cell composition observed in adipose tissue-related pathologies such

as obesity and IR. The later is a nearly universal finding in patients with established disease. There are many recognized genes involved in β-cell development, function and regulation. These could lead to disorders in insulin secretion, IR and glucose sensing. Physicians should be aware about the potential drugs contribute to the development of hyperglycemia and diabetes. Ladies at high risk of GDM should be identified and screened for diabetes before conception and to be followed after delivery. Early identification and diagnosis of many medical conditions and other risk factors could induce hyperglycemia or precipitate a pre-existing condition of DM.

The above demonstrated a wide range of research in this area that should be encouraged to improve our understanding of the disease. T2DM is a complex interaction between genetics, cytokines, immune cells and tissues during inflammatory responses with obesity, insulin function, IR and β-cells failure. Subsequently this could help in discovery new drugs to treat T2DM that could interfere or stop any stage of these mechanisms at molecular or genetic level.

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