

## ALTERATIONS OF LIPID LEVELS MAY INDUCE THE INSULIN RESISTANCE IN TYPE TWO DIABETES MELLITUS: A SYSTEMIC REVIEW

DIVYA JYOTHI P<sup>1</sup>, DOONDI PHANI KUMAR N<sup>2\*</sup>, VINAY MOHAN A<sup>2</sup>, RAMYA A<sup>2</sup>

<sup>1</sup>Department of Pharmacy Practice, Nirmala College of Pharmacy, Atmakur, Andhra Pradesh, India. <sup>2</sup>Department of Pharmacy Practice, Pharm D Students, Nirmala College of Pharmacy, Atmakur, Andhra Pradesh, India. Email: phani.krishna.07.97@gmail.com

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### ABSTRACT

Diabetes mellitus (DM) is not one disorder; it represents a series of metabolic conditions related to hyperglycemia and caused by defects in hormone secretion and hormone action. Exposure to chronic hyperglycemia may result in microvascular complications in the retina (diabetic retinopathy), kidney (diabetic nephropathy), neuron (diabetic-neuropathy), skin, foot, and cardiac complications (stroke, hypertension...etc.). International Diabetes Federation estimates that 1.1 million children and adolescents aged 14–19 years have type one DM. Without interventions to halt the increase in diabetes, there will be at least 629 million people living with diabetes by 2045. In the body, white adipose tissue is the leading site for the storage of excess energy produced from the food intake in large quantities, of the development of insulin resistance (IR) and type 2 DM by the over intake of fatty acid in the body. It results in the accumulation of fatty acyl co-A (FA-CoA) within the myocytes. It leads to improper signaling of the insulin and reduces the level in the myocytes and pancreas beta cells. It combines with genetically reduces the expression of peroxisome proliferator-activated receptor-gamma (PPAR- $\gamma$ ) coactivator-1, initiates the inflammation process by the activation of the tumor necrotic factor alpha and protein kinase C. These alterations lead to further increase the intramyocellular FA-CoA and triglycerides. The sequence of events may develop mitochondrial dysfunction in the sarcolemma outer layers. Finally improves IR also with increasing intramyocellular lipids. This concept might be helpful to those who are pursuing endocrinology specialization, nursing staff, pharmacists, and other medical departments.

**Keywords:** Diabetes mellitus, Hyperglycemia, Essential fatty acids, Lipid metabolism, Expression of peroxisome proliferator-activated receptor-gamma coactivator, Fatty acyl co-A, Triglycerides, Insulin resistance.

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### INTRODUCTION

Diabetes mellitus (DM) is not one disorder; it represents a series of metabolic conditions related to hyperglycemia and caused by defects in hormone secretion and hormone action. Exposure to chronic hyperglycemia may result in microvascular complications in the retina (diabetic retinopathy [DR]), kidney (diabetic nephropathy), neuron (diabetic-neuropathy), skin complications, foot complications, and causes cardiac complications (stroke, hypertension...etc.) [1]. It comes from the Greek language, which means (Gr: Passing through) [2] DM was portrayed 3000 years before the old Egyptians. The expression "diabetes" was first-authored by Aratus of Cappadocia (81-133AD). Afterward, the word mellitus (nectar sweet) was included by Thomas Willis (Britain) in 1675 after rediscovering the sweetness of pee and blood of patients (first seen by the old Indians). It was distinctly in 1776 that Dobson (Britain) right off the bat affirmed the nearness of abundance sugar in urine and blood as a reason for their sweetness. In the current time, the historical backdrop of diabetes corresponded with the development of an exploratory drug. A significant achievement in the historical context of diabetes is the foundation of the job of the liver in glycogenesis, and the idea that diabetes is because of overabundance glucose generation Claude Bernard (France) in 1857. Mering and Makowski found the role of the pancreas in the pathogenesis of diabetes (Austria) in 1889 [3].

Most of the epidemiological examinations report the general predominance of diabetes without recognizing. Despite the benefit of subtyping is the examination of the individuality of condition. Subtyping type one diabetes mellitus (T1DM) and type two diabetes mellitus (T2DM) in the populace concentrates achievable utilizing as often as possible accessible clinical data [4,5] A few investigations have revealed. The populace pervasiveness of different types of diabetes, for example, monogenic diabetes [6,7] and diabetes

because of pancreatic infection [8]. Grouping of diabetes type is especially critical for frequency. It also observes in thinner people from low- and middle-income countries such as India [8], and among people of Indian descent living in high-income nations [9,10] diabetes found in every population in the world and all regions, including rural parts of low- and middle-income countries. The number of people with diabetes is gradually rising, with the World Health Organization (WHO) estimating there were 422 million adults with diabetes worldwide in 2014. The age-adjusted prevalence in adults rose from 4.7% in 1980 to 8.5% in 2014, with the most considerable rise in low- and middle-income countries compared to high-income countries [11]. Moreover, the International Diabetes Federation estimates that 1.1 million children and adolescents aged 14–19 years have T1DM [12]. Without interventions to halt the increase in diabetes, there will be at least 629 million people living with diabetes by 2045.

### TYPES OF DIABETES

Diabetes can be incorporating into the two types.

1. Diabetes insipidus (Type I insulin non-dependent).
2. DM (Type II insulin-dependent).

### DIABETES INSIPIDUS

Type 1 diabetes (earlier called insulin-dependent or juvenile diabetes) typically diagnosed in infants and young adults, but it can occur at any age [13]. Type 1 diabetes is an immune system disease where the  $\beta$ -cells of the pancreas do not deliver adequate insulin, a hormone which enables users to (glucose) for vitality. The cells become kept from energy and glucose be abundant in the blood. DM is then trailing by perilous states of hypoglycemia (low glucose) and hyperglycemia (high glucose).

At the point when hypoglycemia creates, cells do not get enough glucose, and patients endure perplexity, loss of awareness, and trance-like state. Indeed, even passing can result when the mind is concerning glucose for a long time. Hyperglycemia and delayed nonattendance of insulin may indicate ketoacidosis, which is the aggregation of ketones in the blood when the body uses fat for vitality rather than glucose because unsaturated lipids cannot be changed over into glucose at a constant state. Ketones compose the blood acidic and close all body roles. Likewise indicates a state of extreme torpidity and in a long time declining [14-19].

### Symptoms [20]

- Polyuria
- Polydipsia
- Polyphagia
- Unexplained weight loss
- Numbness in extremities
- Dysesthesias (pain in feet)
- Recurrent or severe infections
- Loss of consciousness or severe nausea/vomiting or coma.

### Pathophysiology

T1DM is the after effect of a blend of hereditary and ecological impacts. It most ordinarily results from the immune system obliteration of insulin-delivering  $\beta$ -cells in the pancreas. Eisenbarth recommended that at least one environmental variable, for example, enteroviruses, dietary components, or poisons, may trigger the advancement of T-cell secondary autoimmunity in hereditarily helpless individuals [21]. Autoimmunity is showed by discernible antibodies to ICA512/IA-2, insulin autoantibody, and glutamic acid decarboxylase. Insulinitis with slow  $\beta$ -cell obliteration prompts pre-diabetes lastly to manifest DM. These patients are vulnerable to other immune system ailments, for example, Hashimoto's thyroiditis, celiac illness, Addison's sickness, and myasthenia gravis. Different ancestral loci in the significant histocompatibility (human leukocyte antigen) [22] locale are associated with expanded defencelessness to creating T1DM, including the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. The danger of T1DM is roughly 5% if there is an influenced first-degree relative and somewhat higher if the affected parent is the dad instead of the mother. Continuous research by universal systems is investigating approaches to avert, deferral or turn around the movement of T1DM (for example, Trial Net, TRIGR) [23].

### Screening

The American Diabetes Association (ADA), as of late, adjusted their rules to suggest screening for islet autoantibodies in high hazard people [24]. More recently, professional organizations, including the ADA, have recommended the use of the hemoglobin A1c (HbA1c) for the diagnosis of diabetes. The HbA1c test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized according to the diabetes control and complications trial (DCCT) (Table 1) [25].

### DIABETES MELLITUS/T2DM

As maturity-onset DM, there is no loss of moderate reduction in the beta-cell mass, insulin in circulation is shallow [28]. Incessant fuel surfeit is the essential pathogenic occasion that drives the improvement of type 2 diabetes in hereditarily and epigenetically powerless individuals [29,30] T2DM is most common in adults, but an increasing number of children and adolescents are also affected [31].

### Symptoms [32]

- Symptoms for years before being diagnosed
- May also experience numbness in extremities
- Pain in feet
- Blurred vision
- May have recurrent or severe infections.

### Pathophysiology

T2DM is an insulin-obstruction condition with related beta-cell brokenness. At first, there is a compensatory increment in insulin discharge, which keeps up glucose levels in a typical range. As the condition advances, beta cells change, and insulin discharge cannot keep up glucose homeostasis, delivering high glucose. A large portion of the patients with T2DM are stout or have higher muscle versus fat ratio, appropriated transcendently in the stomach district. This fatty tissue itself advances insulin obstruction through different inflammatory mechanisms, including expanded free fatty acid (FFA) discharge and adipokine malfunction. Inadequacy of physical activity, preceding gestational DM (GDM) in those with hypertension or dyslipidemia, enhances the chance of getting T2DM. Developing information proposes a job for adipokine dysregulation, irritation anomalous incretin science with diminished incretins, for example, glucagon-like peptide-1 or incretin obstruction, hyperglucagonemia, expanded renal glucose reabsorption, and variations from the norm in gut microbiota [33].

### Screening

The best test for diabetes, the fasting plasma glucose (FPG), is likewise a segment of the symptomatic test. FPG examination and the 75-g oral galactose tolerance test (OGTT) are both reasonable tests for diabetes; nevertheless, the FPG test is favored in clinical settings since it is simpler and quicker to perform, progressively helpful and worthy to patients, and more affordable. An FPG 126 mg/dl (7.0 mmol/l) is a sign for retesting, which ought to be rehashed on an alternate day to affirm a conclusion. If the FPG is <126 mg/dl (7.0 mmol/l) and there is a high doubt for diabetes, an OGTT ought to perform. A 2-h post-load, an incentive in the OGTT 200 mg/dl (11.1 mmol/l), is a positive test for diabetes and ought to affirm on an alternative day,

**Table 1: The American Diabetes Association, as of late, adjusted their rules to prescribe screening for islet autoantibodies in diagnosis guidelines[26] and from type 1 diabetes treatment and guidelines [27]**

Test	Results	Interpretation
HbA1c <sup>1</sup>	≥6.5% 5.7–6.4%	Diabetes Impaired glucose tolerance <sup>2</sup>
Fasting plasma glucose <sup>3</sup>	≤5.7% ≥126 mg/dL (7.0 mmol/L) 100–125 mg/dL	Normal Diabetes Impaired glucose tolerance <sup>2</sup>
2-h plasma glucose during an OGTT <sup>4</sup>	≤100mg/dL ≥200 mg/dL (11.1 mmol/L)	Normal Diabetes
Random plasma glucose or patients with classic symptoms of hyperglycemic crisis	≥200 mg/dL (11.1 mmol/dL) 140–199 mg/dL	Diabetes Impaired glucose tolerance <sup>1</sup>
	≤140 mg/dL	Normal

<sup>1</sup>The examination should be performed in a laboratory using a method that is NGSP approved and regulated to the DCCT assay. <sup>2</sup>IGT is like IFG but is diagnosed with an independent OGTT. Both IGT and IFG are opportunity factors for prospective diabetes and cardiovascular diseases. They are seldom joint related to as pre-diabetes. Group Health recommends avoiding the term pre-diabetes because not all patients with IGT and IFG will develop diabetes. <sup>3</sup>Fasting is defined as no calorie intake for at least 8 h. <sup>4</sup>The examination should be conducted as reported by the WHO using a glucose load-receiving the equivalent to 75 g of anhydrous glucose dissolved in water. IGT: Impaired glucose tolerance, IFG: Impaired fasting glucose, OGTT: Oral galactose tolerance test

This examination demands the use of a glucose load-receiving the equivalent of 75 g anhydrous glucose dissolved in water: 2-h PG, 2-h post-load glucose (Table 2).

**GDM**

During a healthy pregnancy, an active insulin resistance (IR) creates starting around mid-pregnancy and advances during the third trimester [35]. Hormones and adipokines discharged from the placenta, including necrotic tumor necrotic factor (TNF)-α, human placental lactogen, and human placental development hormone are potential reasons for IR in pregnancy. Likewise, expanded estrogen, progesterone, and cortisol during IR pregnancy add to an interruption of the glucose-insulin balance [36]. To make up for the fringe during pregnancy, insulin discharge increments from a lady’s pancreas.

The improvement of GDM happens when a lady’s pancreas does not emit enough insulin to stay aware of the metabolic worry of the IR. Moreover, expanded maternal fat affidavit, diminished exercise, and expanded caloric admission add to this condition of relative glucose bigotry [36]. In early pregnancy increases the insulin secretions, while insulin sensitivity is consistent, lowered, or may increase. At the mid of the pregnancy insulin sensitivity starts to decline progressively, and became worse during the rest of the pregnancy, being worst in the late third trimester and disappear, GDM usually develops in the late second trimester and disappears, instantly, post-delivery [36].

**Symptoms [37]**

- Recurrent infections
- Blurred vision
- Tiredness
- Needing to urinate frequently.

**Pathophysiology**

Especially observed in second-trimester of the pregnancy women. The significant donors are the placental hormones human placental lactogen, progesterone, cortisol, development hormone, and prolactin. These hormones cause diminished phosphorylation of insulin receptor substrate and, in this way, significant insulin opposition. Cytokines like tissue corruption factor has likewise in the pathogenesis of insulin obstruction. Coherently, the pancreas ought to make up for this interest by expanding insulin discharge. Notwithstanding, in GDM, there is a weakening of β cell work, especially the main stage of insulin discharge.

In an investigation on Latino ladies with GDM, 67% decrease of β cell capacity noted when contrasted with the ordinary pregnant control. The second stage of insulin discharge is practically identical to that in the individual with ordinary glucose resilience. The deformities in β cells have been ascribed either to immune system procedure or enzymatic imperfection like glucokinase. Autoimmunity ought to suspect in ladies who do not have ordinary qualities of the expanded danger of GDM, for example, who are lean and Caucasians. In this manner, the blend of insulin opposition and secretory deformity during pregnancy results in GDM [38-44].

**Table 2: Displays the demonstrative criteria for diabetes. Fasting is characterized as no utilization of nourishment or drinks other than water for in any event 8 h before testing [34]**

Normoglycemia	IFG or IGT	Diabetes*
FPG<100 mg/dL	FPG≥100 and <126 mg/dL (IFG)	FPG≥126 mg/dL
2-h PG+ <140 mg/dL	2-hPG+ ≥140 and <200 mg/dL (IGT)	2-h PG+ ≥200 mg/dL

\*p<0.05. Symptoms of diabetes and casual plasma glucose concentration of ≥200 mg/dL. \*In the inadequacy of unambiguous hyperglycemia, an examination of diabetes must be approved, on the following day, by measurement of FPG, 2-h PG, or random plasma glucose (if symptoms are present). The FPG test is sufficient preferred because of the efficiency of treatment, accessibility, acceptability to patients, and lower expenses. Fasting is defined as no caloric intake for at least 8 h

**Screening**

Standard OGTT is doing at 24–28 weeks after a medium-term quick (fasting plasma glucose and plasma glucose 2 h after 75 g glucose drink). A 2-h level >7.8 mmol/L (or 140 mg/dL) is demonstrative of gestational diabetes. If fasting and post-prandial blood sugars are raising in the primary trimester, this may demonstrate previous DM (which is the view as an alternate condition, with different results) [45].

**OTHER TYPES OF DM**

**Monogenic diabetes**

Since the last WHO characterization of diabetes [46], there have been significant advances in characterizing. The fundamental sub-atomic hereditary qualities that can help recognize specific subtypes of diabetes. These advances have uncovered clinical subgroups that are genetically heterogeneous and have brought about the acknowledgment new hereditary disorders. The most significant development has been that genetic determination can result. In improved treatment results for specific individuals, yet a little extent of the all outnumber of individuals with diabetes. As a result, genetic testing has received for chosen subgroups of individuals as a guide to clinical administration in certain nations.

A straightforward way to deal with a grouping of monogenic subtypes of diabetes utilizes the quality image of the changed quality pursued by the clinical disorder [47]. For example, a child diagnosed with permanent neonatal DM (PNDM) because of a transformation in KCNJ11 is marked as having KCNJ11 PNDM. If there is a clinical conclusion of PNDM; however, a quality change had not been searched for nor discovered, at that point, an individual would be ordered as PNDM as it was.

**Juvenile diabetes**

Juvenile diabetes commits to diabetes in blooming. Type 1 diabetes affects 90% of the people younger than 25 who have diabetes. It is the most common metabolic disorder in young. There is no accepted meaning of what is anticipated by a younger person in this meaning; but, most people would notice in a young person as occurring under 16–18 years of age [48]. Clinical manifestations of monogenic defects in β-cell function include maturity-onset diabetes of the young (MODY), PNDM, transient neonatal diabetes, and genetic syndromes where insulin-deficient diabetes is associated with specific clinical features [49].

**TYPE 1.5 DIABETES/LADA**

The type 1.5 diabetes is a non-official term that is occasionally used to allude to a type of type1 diabetes known as idle immune system diabetes in grown-ups (LADA). Type 1.5 diabetes is analyzed during adulthood, as is most instances of sort two diabetes. Type 1.5 diabetes additionally has a modest beginning, like sort 2 diabetes. Nevertheless, type 1.5 diabetes is an immune system illness like sort one diabetes and will practically inevitably require insulin at some point will in future [50].

**TYPE-3 DM (T3D)**

T3D is a neuroendocrine disorder that represents the progression of T2DM to Alzheimer’s disease [51] T3D contributes to the increase of a total load of Alzheimer’s patients worldwide. It also suggests that insulin-degrading enzyme could be significant who holds the capacity to shift type II DM to type III DM by altering the metabolic pathways such as regulation of beta-cell development negative regulation of P13K/AKT pathways and amyloid-beta degradation [52].

**MODY**

MODY is a form of diabetes classically characterized as having an autosomal dominant inheritance, onset before the age of 25 years in at least one family member and partly preserved pancreatic beta-cell role. The 14 capable genes are related to being MODY type 1–14, of which MODY 2 and three might be the most common forms. MODY could

adequately hold characteristics of T2DM, which is of multifactorial causation [53].

### COMPLICATIONS OF DIABETES MELLITUS

Diabetes is associated with several complications. Acute metabolic complexities associated with fatality include diabetic ketoacidosis from abnormally high blood glucose (hyperglycemia) concentration and coma as the effect of low blood glucose (hypoglycemia). The complications are wide-ranging and are expected at least in part to persistent elevation of blood glucose levels, which leads to the destruction of blood vessels. The complication is grouped under microvascular disease (due to damage to small blood vessels) and macrovascular disease (due to damage to the arteries). Microvascular complications include retinopathy, nephropathy, and neuropathy. Significant complications of macrovascular complexities incorporate accelerated cardiovascular disease (CVD) following in myocardial infarction and cerebrovascular disease manifesting as cerebrovascular strokes; other chronic complications of diabetes incorporate depression [54], dementia [55], and sexual dysfunction [56,57].

### DIABETIC NEPHROPATHY

Diabetic nephropathy represents the primary cause of end-stage renal failure in western societies [58]. The development of proteinuria clinically characterizes it with a subsequent decrease in glomerular filtration rate, which progresses over a long period, often over 10–20 years. If left untreated, the resulting uremia is fatal [59], kidney disease is also a significant risk factor for the development of macrovascular complexities such as heart attacks, strokes [60], and hypertension [61].

### DR

DR is characterized by a spectrum of lesions within the retina and is the leading cause of blindness among adults aged 20–74 years [62,63]. These incorporate changes in vascular permeability, capillary microaneurysms, capillary destruction, and excessive formation of new blood vessels. The neuronal retina is also dysfunctional with the destruction of some cells, which modifies retinal electrophysiology and appears in an inability to distinguish colors.

### DIABETES NEUROPATHY

Diabetic neuropathy is a syndrome which comprises both the somatic and autonomic divisions of the peripheral nervous system. Half of the patients with diabetes finally develop neuropathy [64], with an existing prospect of one or more lower extremity amputations considered in some states to be up to 15%. The neuropathy is a significant factor in the impaired wound healing, erectile dysfunction, and cardiovascular dysfunction seen in diabetes [65].

### CVD

There is an extended risk of CVD in diabetes, such that an individual with diabetes has a risk of myocardial infarction equivalent to that of non-diabetic individuals who have previously had a myocardial infarction [66]. CVD considers for more than half of the fatality seen in diabetic people [67] and diabetes equate to an approximately threefold increased risk of myocardial infarction compared with the general population [68]. Normally, type 2 diabetes is also called as the insulin-independent diabetes because based on their pathogenesis. It is a metabolic syndrome, and it also caused by different multifactor (Fig. 1).

### ESSENTIAL FATTY ACIDS

Dietary essential fatty acids supply the nutrients and lipids to the body. Those also play a primary function in the body for energy production, growth, cellular metabolism, and muscle activity. The specific components of fats are necessary for the proper growth and development in animals, and humans were introduced in the 1930s (Burr and Burr, 1929). These fatty acids are mainly required for hormone synthesis like estrogen; progesterone and thermogenesis

also serve as the indispensable dietary precursors for the formation of proteinoids and other eicosanoids. The eicosanoid has provided more considerable significance to the study of their role in health and disease conditions. The eicosanoids are powerful autocrine and paracrine regulators of cell and tissue functions, i.e., thrombocyte aggregation, and provocative reactions, leukocyte functions, blood pressure, bronchial constriction, uterine constriction, vasoconstriction, and vasodilation of blood vessels.

Essential fatty acids are essential for lipid metabolism. The dietary fatty acids are also affecting cholesterol metabolism throughout life in the body. The primary source of essential fatty acids in the food chain is the \*Terrestrial, marine plants, and phytoplankton. The fish and other marine animals can elongate and desaturate the parent essential fatty acids and finally forming the long-chain polyunsaturated fatty acids (LCPUFAs). (Sprecher, 1981; Willis, 1984; Simopoulos, 1991).

In animals and humans' tissues, especially the liver tissues, can further elongation and desaturating the parent essential fatty acids. In normal conditions, the PUFAs promote fatty acid oxidation of normal levels of FFAs in the blood and in the case of n-3 LCPUFAs decreases the very-low-density lipoproteins (VLDL) secretion from the liver. For this mechanism, some fatty acids promote or inhibit the process of peroxisomal proliferation by the peroxisome proliferator-activated receptor (PPAR) (Masataka *et al.*, 1997; Schoonjans *et al.*, 1996). In some of the individuals, the intake of fatty acids contains more amount of saturated fat and a double bond, or trans fatty acids affect the PPAR activity. Hence, it prevents fatty acid oxidation by preventing the biosynthesis of LCPUFAs from parent-FFAs [69].

### CIRCULATING FATTY ACIDS MEDIATE IR

It is difficult to identify the mediators, cause IR, but now one most important mediator was identified, i.e., FFAs. This hypothesis, that excess of circulating fatty acids mediate IR and strong correlation with obesity in animals and humans [70-72]. Furthermore, the deposition of fatty acids into non-adipose fat stores like muscle induces IR [73-77].

### ANOTHER HYPOTHESIS

The excess circulating FFAs activate the toll-like receptors (TLRs) mainly TLR2 and TLR4. These two receptors are also already in the adipose tissue and with macrophages. Whenever the circulating FFAs activate the TLR2 and TLR4, promote the inflammatory changes with macrophages. These inflammatory signals suppress insulin signaling in myocytes that lead to IR in myocytes [78-81]. From the research, the mutation in TLR4 prevents diet-induced obesity and IR in mice [82]. Based on two, this hypothesis confirms that the increased intake of essential fatty acids leads to IR in skeletal muscle. It leads to type 2 diabetes by combining with genetically and environmental factors (Fig. 2).

### DYSLIPIDEMIA

The quantitative and qualitative abnormalities of lipid lipoproteins in the body. This condition is characterized by the raised triglyceride levels, low high-density lipoproteins (HDL)-cholesterol levels and increases the accumulation of the VLDL, LDL, and cholesterol-enrichment lipoprotein particles [83-85].

Dyslipidemia is an essential component of the IR syndrome and types two DM. In the animal and humans, the dyslipidemia condition can occur by changes, mainly

- a. White adipose tissue
- b. Apolipoproteins.

### White adipose tissue

In humans, the adipose tissue plays an essential role as a master regulatory tissue in controlling whole-body lipid flux by maintaining both glucose and lipid homeostasis. In the body, white adipose tissue

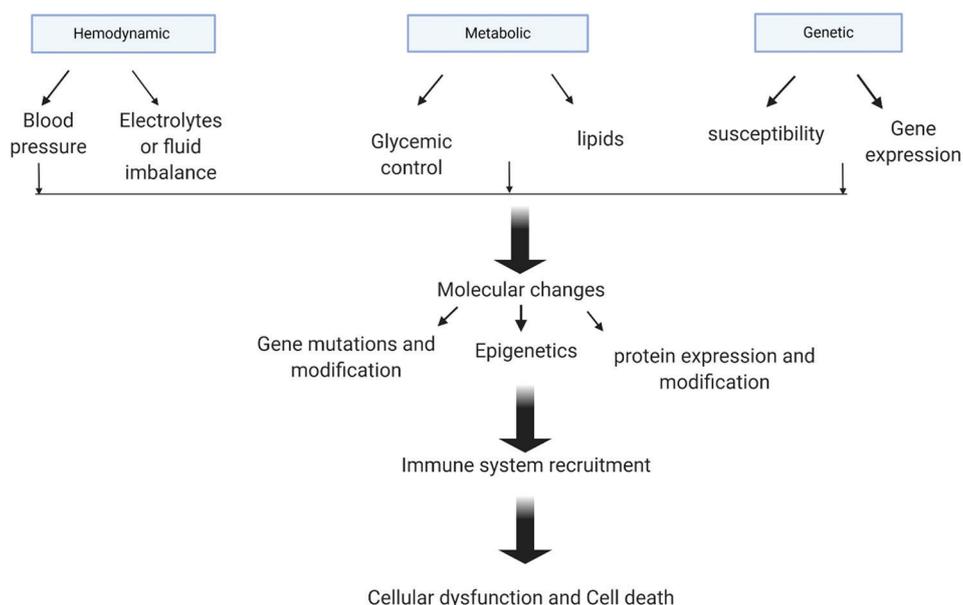


Fig. 1: Schematic overview of the significant areas contributing to diabetic complications

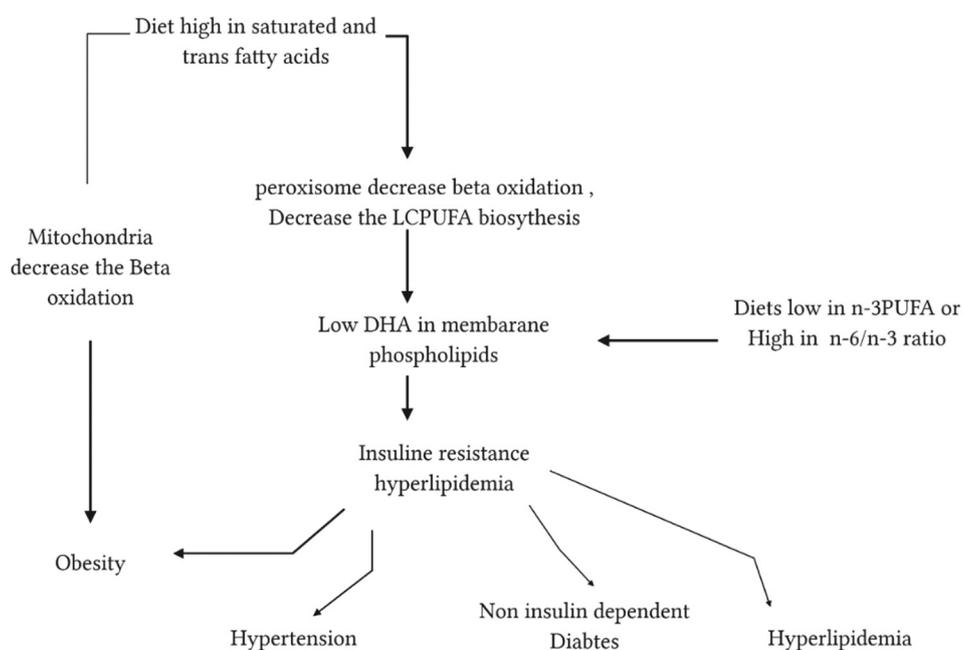


Fig. 2: The effects of excess dietary fatty acids, it is present in the body. These fatty acids decrease the beta-oxidation and long-chain polyunsaturated fatty acids) synthesis in adipose tissue, decrease the beta-oxidation in mitochondria of the sarcolemma. These alter causes obesity, hyperlipidemia, hypertension, and Type 2 diabetes mellitus. In developing countries, the population mostly takes the excess amount of vegetable oils, mainly sunflower oil, and corn oils. These oils contain an excess amount of lactic acidosis, it leads to may decrease the formation of DHA from a-linolenic acid [LNA (18:3, n-3)] since the delta-6 desaturates is inhibited by an excess substrate

is the leading site for the storage of excess energy produced from the food intake in large quantities [86,87]. In white adipocytes, the energy is concentrated as the triglycerides (TG), like in a single large lipid droplet. In fasting conditions, these TG undergo rapidly hydrolyzed by lipases (this process is called lipolysis) and produce the fatty acids are transported to other tissues to be oxidized mainly in mitochondria for energy production [88]. In healthy conditions, during the fasting states, the tissues maintain equilibrium between the release of fatty acids into the circulations from the adipose tissues to their uptake and oxidation by the peripheral tissues like skeletal muscle. In human's larger intake of the

calories, there is a change in the anatomical and physiological changes in the adipose tissue, i.e., size of adipocytes, release, and use fatty acids.

In the lean state, fatty acyl-CoA (FA-CoA) enzyme levels are within the muscle cells produce in the required quantity for rapid oxidation in mitochondria (Fig. 3a). In hyperplasia-induced obesity, as the caloric intake increases, so the adipocytes are enlarged because of the increasing amount of TG stores in humans and mice [89,90]. In the early stages, fatty acid levels can rise, but the skeletal muscle maintains high insulin sensitivity (Fig. 3b) [91-93].

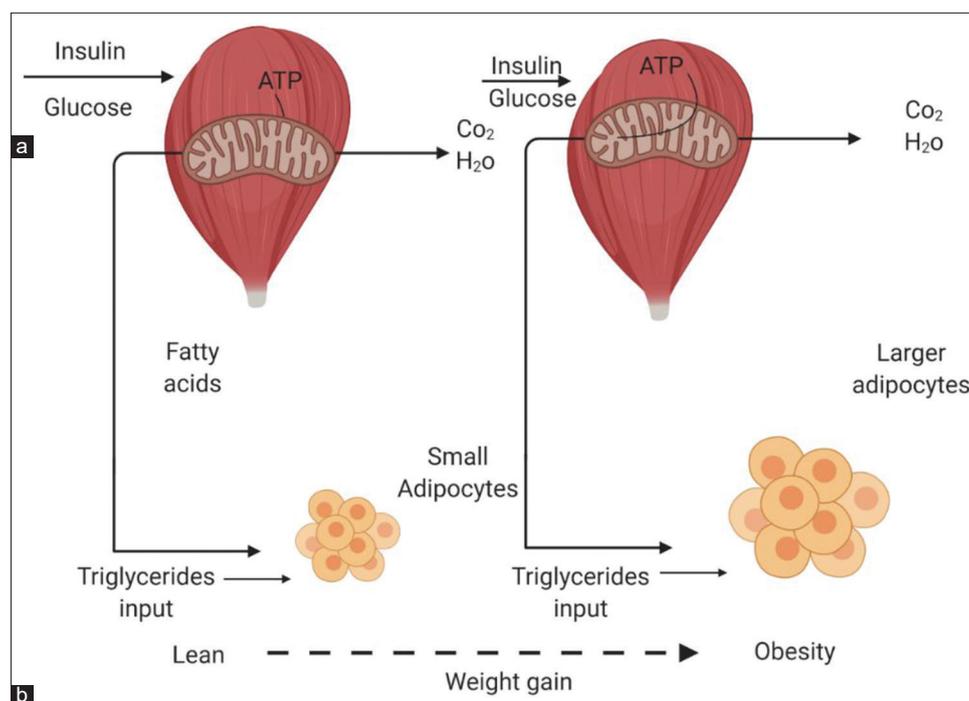


Fig. 3: (a and b) Adipose tissue triggers the insulin resistance in skeletal muscle

As the TGs a level are increase in adipose cells, it leads to acts as the endocrine cell and promotes various biological proteins and affects their metabolism and functions. In a few cases, there is an extension in fats but not adipose tissue. Hence, it promotes the elevated circulating TG and fatty acids. Finally, it leads to IR and combines with obesity causes type 2 diabetes. These altered functions have induced the synthesis of the VLDL in the liver also decreases the production of the HDL. It results in IR in the skeletal muscle and atherosclerosis disease; obesity finally types 2 diabetes in mice and humans [94-97].

#### Apolipoproteins (apoE)

The main two apolipoproteins are apoA and apoB play an important role in the lipoprotein metabolism in liver tissue. The apoE protein necessary required for the metabolism of VLDL to IDL and LDL [98]. From other cellular and animal studies, reported that an apoE plays significant roles, those are

- It also mediates the direct hepatic clearance of VLDL, HDL, and their remnants for example, LDL-R and lipoprotein receptor-related protein [98-102]. The main function is modifying the breakdown of lipoproteins that contains apoB, HDL metabolism, and TG secretion in all humans and animals [99,103-107].
- ApoE is readily exchangeable between VLDL and HDL lipoproteins and transferred from HDL to TG-rich lipoproteins [108]. The process is called lipolysis by lipoprotein and hepatic lipases but depends on cholesterol and TG clearance. The lipoprotein lipase activity is inversely correlated with IR [109]. From *in vitro* studies prove that the ApoE increases the HDL levels in the liver by promoting the cholesterol efflux from peripheral cells to the liver [110]. This apolipoprotein acts as the direct anti-atherogenic by activating antioxidant activity and inhibits the platelet aggregation through the nitric oxide pathway and also acts as the anti-inflammatory activity [111-113]. The activity of apoE decreases in the body leads to metabolic changes and IR [83-85,114].

#### OBESITY

Obesity is defined as unnecessary fat deposition in the body. The body mass index (BMI) is a popular indicator of obesity [115]. BMI is >30 kg/m square and is considered as obesity. Obesity is caused by the mainly genetically and imbalance between feeding and physical

activity. This factor plays a chief role in the pathogenesis of T2DM and CVDs. The relationship between obesity and T2DM has been known for many years, and it is the primary etiology of T1DM in 60–90% of patients [116].

However, obesity in humans is not the main factor in the diabetic state, also with other factors such as genetics and environmental factors. Obesity triggers metabolic syndrome, which can be characterised by the appearance of three out of five criteria, the criteria are abdominal (visceral obesity), increased plasma TG, decreased HDL cholesterol, elevated blood pressure, and plasma glucose levels in the body [117,118]. The metabolic syndrome is closely related to the IR in the peripheral tissues.

The inbred mouse strains research, reports the metabolic changes to occur when high-fat diet intake, which leads to obesity and causes IR. It leads to T2DM in mice and humans [119-121]. In humans being, obesity induces increases in circulating and sarcolemma fatty acids after this condition the elongation and desaturation of fatty acids in the outer layers of the sarcolemma in human skeletal muscle [117,122-124]. It develops the skeletal muscle IR (mostly depends on genetically), but it does not cause type 2 diabetes. Because the blood glycemia level can be maintained by compensatory metabolism, i.e. insulin secreted by the pancreatic beta cells. The failure of the insulin secretion from the pancreas's beta-cells leads to abnormal levels of glucose levels in the blood so in that condition develop T2DM [118,120-127].

The metabolism of amino acids occurs in the liver; the process is called gluconeogenesis. This pathway increases glucose levels, which promotes insulin secretion from the pancreas. Insulin growth factor -1 and insulin activate mTORC1 (mammalian target of rapamycin complex1 and S6K1 (ribosomal protein S6 kinase beta1) persist activation leads to serine phosphorylation of IR substrate (IRS-1 and IRS-2). It leads to IR develops. The prolongation of this condition leads to the negatively affect the function of islets, resulting in an impairing in insulin secretion leading to the onset of T2DM.

In the obesity condition, hyper aminoacidemia is the sign of increased IR. Insulin action is regulated by the branched-chain alpha-keto acid dehydrogenase complex, an enzyme complex involved in BCAA

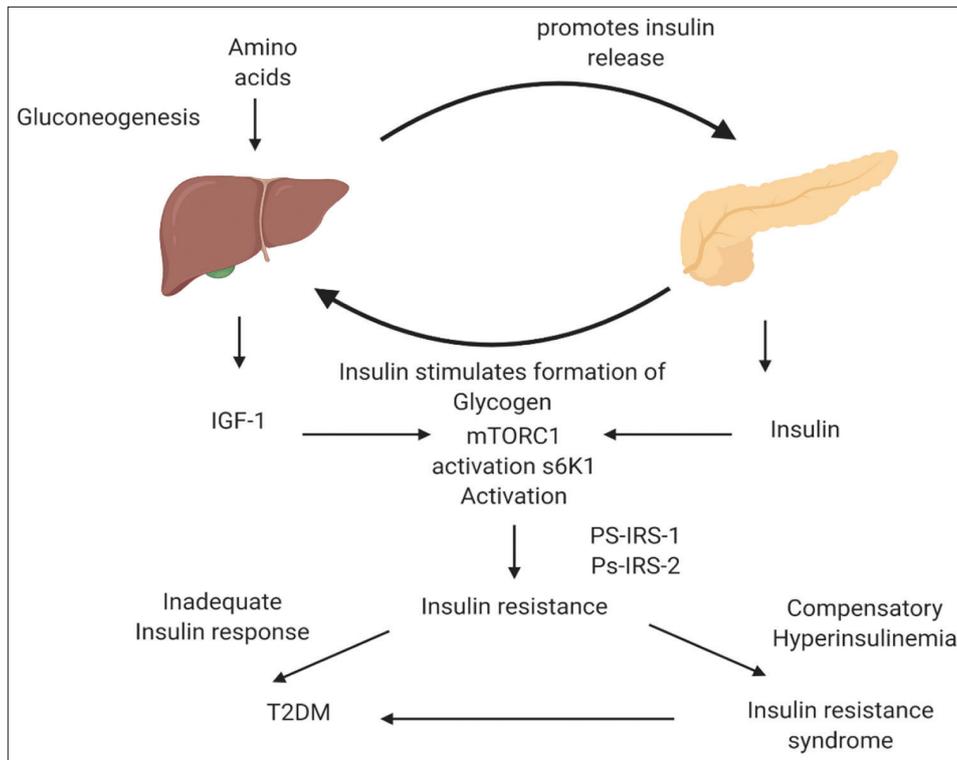


Fig. 4: Mechanism of the link between insulin resistance and T2D. IGF-1: Insulin-like growth factor; IRS: Insulin receptor substrate; mTORC1: Mammalian target of rapamycin complex 1; S6K1: Ribosomal protein S6 kinase beta1; T2D: Type 2 diabetes

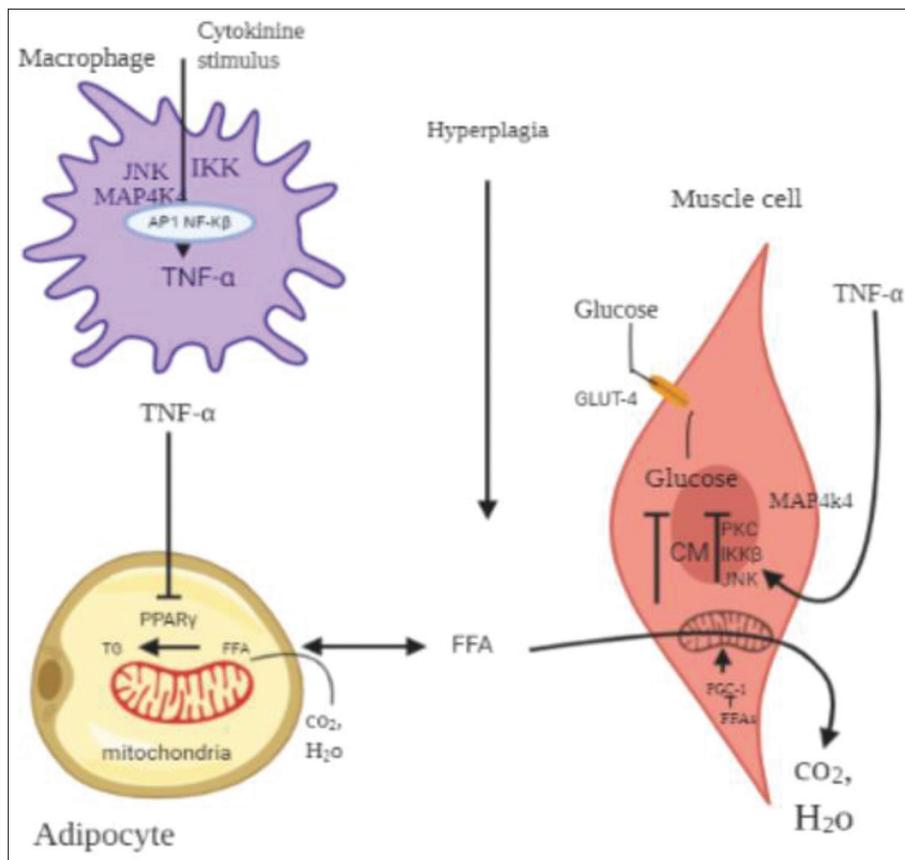
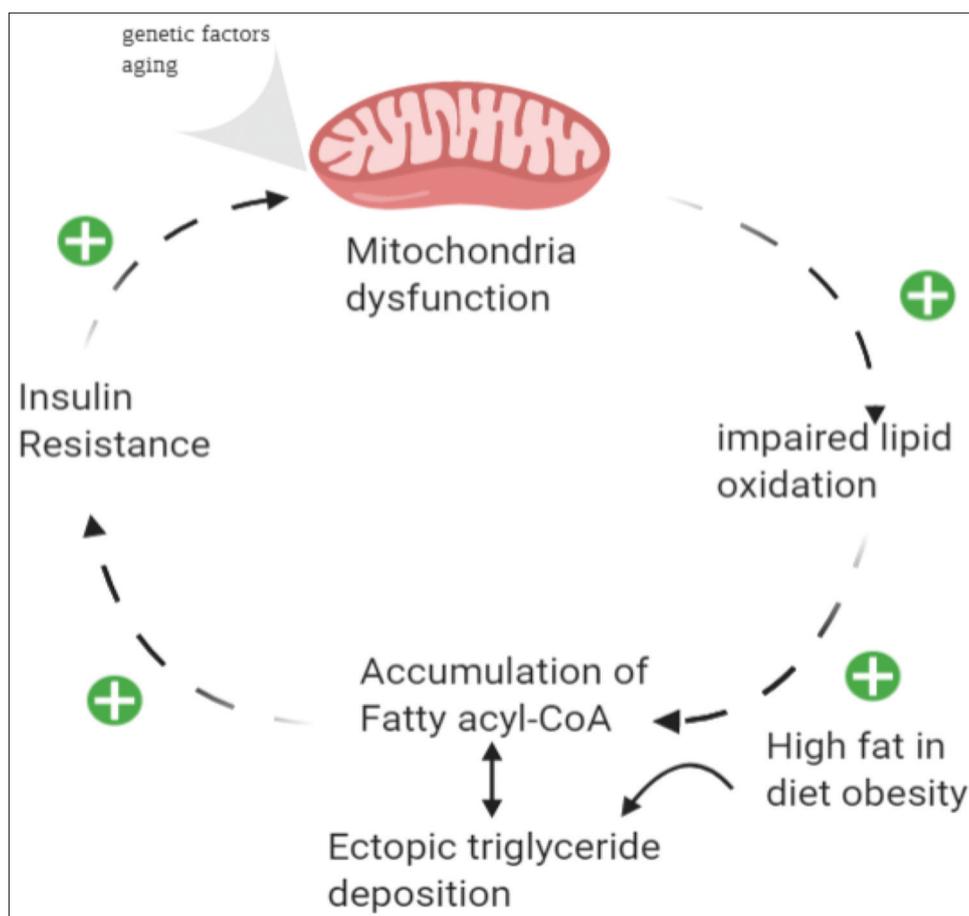


Fig. 5: The inflammation of adipose tissue and its effects. The overload of lipids in adipose tissue triggers the macrophage infiltration to produce a large amount of tumor necrotic factor-alpha through the Jun N-terminal kinase-activator protein-1 and mitogen-activated protein kinase kinase kinase kinase-4 signaling pathways. It causes mitochondrial dysfunction through the proliferative proliferator-activated receptor-gamma (PPAR-γ) coactivator. It leads to insulin resistance



**Fig. 6:** This cycle is explaining the relation of metabolic syndrome, genetic factors, and obesity in humans. Since obesity is highly associated with insulin resistance causes the “type 2 diabetes mellitus.” The insulin resistance correlated with the number and activity of the angiotensin II receptors. Hence, this condition leads to hypertension

catabolism [128,129]. In IR conditions, it has been found to reduce the enzymatic activity of branched-chain alpha-keto acid dehydrogenase complex and hence suppress BCAA catabolism. This shows the positive association between IR and circulating concentrations of BCAAs [129-135]. Besides, IR also alters several other PFAAs, including AAAs, alanine (Ala), proline (Pro), and glycine (Gly) [134] mainly Phe and Tyr. Phe and Tyr determine metabolic syndrome and CVDs (Fig. 4) [135-142].

#### INFLAMMATION

The overload of the caloric intake in adipocytes causes an inflammatory response. The inflammation could also cause IR by the direct action of TNF- $\alpha$ . The hypertrophied adipocytes are producing a large amount of the MCP-1, which functions as the chemoattractant and enhances the macrophages infiltration in the cells. It contributes to the pro-inflammatory state through the protein kinases JNK1 and MAP4K4. The development of an inflammatory state in adipose tissue associated with skeletal muscle IR (Fig. 5) [143,144].

#### PPAR- $\gamma$

The PPAR- $\gamma$  is a member of the PPAR family. It is the nuclear hormone receptor, PPAR- $\gamma$ . It is mainly involved in the fatty-acid-controlled differentiation of preadipocytes, nutritional changes in the white adipose tissue regulation of cholesterol metabolism [145,146]. The activity of PPAR- $\gamma$  mainly based on inheritance. During the over intake of food, the structural changes occur in the adipocytes form hypertrophy (large size). It leads to decreasing the activity of the PPAR- $\gamma$  on the adipocytes. The accumulation of fat in adipocytes decreases but

increases in the plasma levels, which subsequently may lead to IR in the liver, muscle, and adipose tissue (Fig. 6).

#### DISCUSSION

We know the development of IR that leads to the cause of T2DM. The sequences of development of IR is by the over intake of fatty acid in the body. As a result of the accumulation of FA-CoA within the myocytes. It leads to improper signaling of the insulin and reduces the level in the myocytes and pancreas beta cells. It combines with genetically reduces the expression of PPAR- $\gamma$  coactivator-1, initiates the inflammation process by the activation of the tumor necrotic factor- $\alpha$ , and protein kinase C. These alterations lead to further increase the intramyocellular FA-CoA and TG. The sequence of events may develop mitochondrial dysfunction in the sarcolemma outer layers finally develops IR and increasing intramyocellular lipids.

#### CONCLUSION

DM is a persistent metabolic disorder which is caused by IR and damage of the pancreas due to socioeconomic, environmental factors. A person was suffering from DM for an extended period they will get macro and microvascular complications in some time; however, we choose our diet wisely and must maintain the physical activities in our daily life as physician advice. If we cannot maintain a proper diet at least take an equal quantity of carbohydrates, fats, and proteins. Dieticians are planning a new diet for T2DM; they try to improve the patient life, and this concept might be helpful for those who are pursuing endocrinology specialization, nursing staff, pharmacists, and other medical departments.

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**AUTHORS' CONTRIBUTIONS**

All the authors have contributed for review preparation and editing of the manuscript.

**CONFLICTS OF INTEREST**

No conflicts of interest.

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