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DEPARTMENT OF PHARMACY

Association of Insulin Resistance with Lipid Metabolism in Type 2 diabetic patients in the Middle Euphrates Area

Graduation research

The students

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1.Abstract

Background: Insulin resistance, identified as an impaired biologic response to insulin stimulation of target tissues, primarily involves liver, muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state.

Methods: A case–control study was designed to find the association between insulin resistance and lipid metabolism in T2DM in Iraqi population. The study consisted of 100 T2DM patients and 100 healthy control individuals. Baseline characteristics included body mass index, fasting blood sugar (FBS), lipid profile and fasting insulin. Glucose, cholesterol, triglycerides, direct HDL and direct LDL was measured by spectrophotometric method.

Results: (89%) out of 103 type 2 diabetic patients were insulin resistant when they were evaluated by the HOMA method. However, 5 (9%) out of 57 healthy individuals were observed to be insulin resistant when they were analyzed similarly. Significant increases ($P < 0.05$) of insulin, HOMA and BMI levels with significant decrease ($P < 0.05$) of HDL-cholesterol level were observed in patients.

Conclusion*:* Most of type 2 diabetic patients are presented with insulin resistance. The dyslipidemia induced by insulin resistance and type 2 diabetes (diabetic dyslipidemia). VLDL-C and LDL-C have major role in the etiology of insulin resistance in type 2 diabetic patients.

Key word: Diabetes mellitus, type 2 diabetes, Insulin resistance, lipid profile, dyslipidemia.

1. Introduction

1.1. Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both (1). Diabetes mellitus is a major worldwide health problem predisposing to markedly increased cardiovascular mortality and serious morbidity and mortality related to development of nephropathy, neuropathy, and retinopathy (2). Diabetes

has reached epidemic proportions in industrialized societies and become a major problem in public health, with an estimated 537 million people affected by the year 2021. Type 2 diabetes is by far the most common, affecting 90 to 95% of the U.S. diabetes population (3).

Changes in human behavior and lifestyle over the last century had resulted in a dramatic increase in the incidence of diabetes worldwide (4). It is interesting that the proportion of diabetes is higher in women than in men (3).

1.1.1. Classification of diabetes mellitus

Diabetes mellitus is classified by WHO as in the following (6):

1- Type 1 diabetes, previously called insulin-dependent diabetes mellitus or Juvenile – onset diabetes, accounts for 5%-10% of all cases of diabetes.

Studies indicate that there are two subgroups of type 1 diabetes. By far the most common form is type 1A, caused by autoimmune destruction of beta cells; type 1B is also associated with severe insulin deficiency, but there is no evidence of autoimmunity.

2- Type 2 diabetes, approximately 80% of patients have the so-called type-2 diabetes, previously called non-insulin-dependent diabetes mellitus or adult- onset diabetes.

3- Gestational diabetes.

4- Other specific types of diabetes: The approximately 10% of remaining cases are due to specific causes (5).

1.1.2. Complications of diabetes mellitus

Vascular disease is a common complication of diabetes mellitus, macrovascular disease is due to abnormalities of large vessels which may

present as coronary artery, cerebrovascular or peripheral vascular insufficiency, the condition is probably related to alteration in lipid metabolism and associated hypertension. Patients with type 2 diabetes mellitus have a markedly increased risk of cardiovascular complications, where insulin resistance is a major determinant of this increased risk and is a potential therapeutic target (6).

Microvascular disease is due to abnormalities of small blood vessels particularly affects the retina (diabetic retinopathy) and the kidney (nephropathy); both may be related to inadequate glucose control (7). Under diabetic conditions, reactive oxygen species (ROS) are increased in various tissues and are involved in the development of diabetic complications (8).

1.2. Type 2 diabetes mellitus:

Type 2 diabetes (T2D) is occurred due to insulin insensitivity combined with a failure of insulin secretion to overcome this by hypersecretion, resulting in relative insulin deficiency. There is a strong genetic predisposition (9). Type 2 Diabetes caused by insulin resistance (IR) in the adipose tissue and liver and skeletal muscle, increased glucose production in the liver, over production of free fatty acids by fat cells and relative insulin deficiency (10)

In the early stage of disease, glucose tolerance can be maintained at the expense of increased insulin secretion, so that insulin resistant individuals are characterized by compensatory hyperinsulinemia. Whenever the hypersecretion of insulin by pancreatic β-cells declines, clinical diabetes develops consequently (11). Pathogenesis does not involve viruses or autoimmune antibodies (12).

1.3. Metabolic syndrome:

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes, it affects one in five people, and prevalence increases with age. Some studies estimate the prevalence in the USA to be up to 25% of the population (13). Metabolic syndrome is also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome, and CHAOS (Australia). Metabolic syndrome, according to the American Heart Association, is defined as the presence of any three of the following conditions: (14)

Central obesity: waist: hip ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m2.

Raised triglycerides: > 150 mg/dL (1.7 mmol/L).

Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females.

Raised fasting plasma glucose: FPG>100 mg/dL (5.6 mmol/L), or Previously diagnosed type 2 diabetes.

Raised blood pressure: systolic BP > 130 or diastolic BP >85 mm Hg.

1.4 Insulin resistance:

Insulin resistance (IR) is a common pathologic state in which target cells fail to respond to ordinary levels of circulating insulin. It results in inability of insulin to provide normal glucose and lipid homeostasis. Hence, higher than normal concentrations of insulin are needed in order to maintain normoglycaemia (15). The subnormal biological response could be due to the inability of plasma insulin to bind to its receptor or the presence of a post-receptor binding defect (16). IR is associated with a

number of diseases including obesity, metabolic syndrome, type 2 diabetes mellitus, lipodystrophies, polycystic ovary syndrome and chronic infection. The overall prevalence of IR is reported to be 10–25% (17).

The etiology of IR includes genetic factors resulting in syndromic forms of IR, and environmental factors: food intake, reduced physical activity, aging, smoking or administration of drugs, including thiazide diuretics, beta adrenergic antagonists, glucocorticoids, which can cause or contribute to IR (18). The most important factor is obesity which is usually of combined polygenetic and environmental origin (18,19).

1.4.1 Mechanisms of insulin resistance:

1.4.1.1 Dysregulation of FFA release:

It is well established that increased availability and utilization of FFA play a critical role in the development of IR (20). The released FFA, according to the lipid supply hypothesis (Randle hypothesis), act as the predominant substrate in intermediary metabolism. Increased NADH/NAD+ and Acetyl-CoA /CoA ratios could be the reason for decreased glucose uptake which means IR (21). FFA impairs insulin signaling in insulin responsive tissues, especially in muscle, liver and adipose tissue.

1.4.1.2 Modifications of Insulin Receptor Pathway:

The decreased biological response to insulin could potentially be due to impairments in the insulin receptor signal transduction pathways. This can ultimately affect the glucose uptake by the cells and result in elevated plasma glucose (22).

In the receptor signal transduction pathway, the activated insulin receptor phosphorylates intracellular substrates such as insulin receptor

substrate (IRS) proteins through tyrosine phosphorylation. Phosphorylated IRS proteins interact with phosphatidylinositol kinase (eg, phosphoinositide 3-kinase in muscle PI-3 kinase) (23). A downstream effect of this interaction is the activation of the Akt- 2/PKBβ pathway.

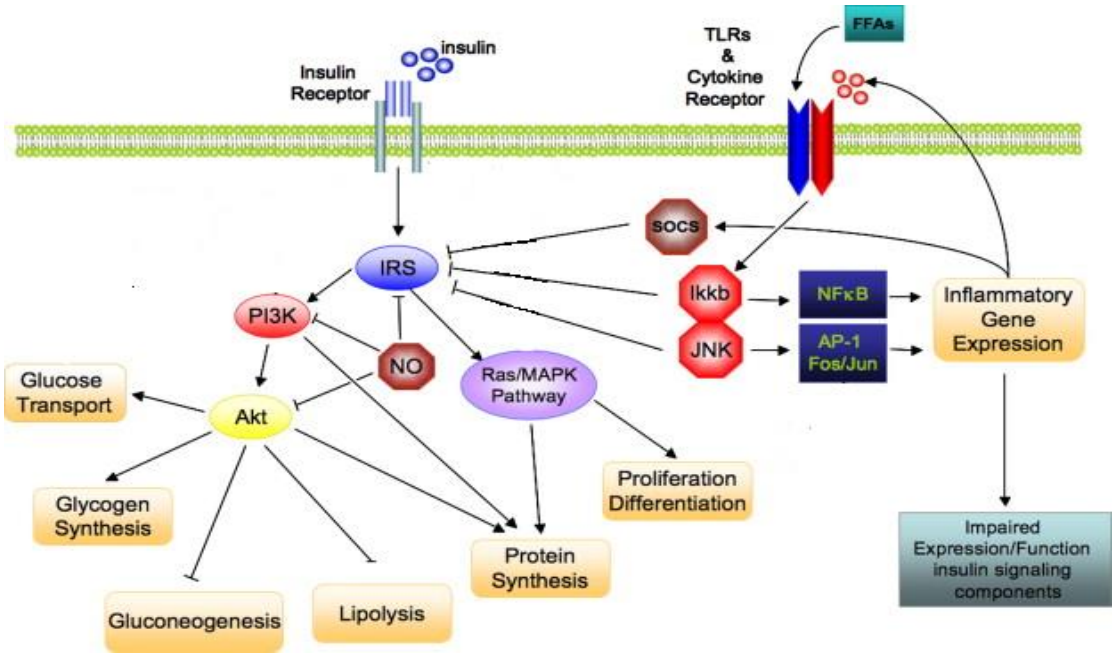

Fig 1.1: Direct interaction of insulin signaling and inflammatory pathways (24)

1.4.1.3 The role of obesity-induced proinflammatory cytokines in insulin resistance:

There are two types of adipose tissue: the brown adipose tissue (BAT) and the white adipose tissue (WAT). BAT was thought to exist mainly in the neonatal period, having largely disappeared within the first years after birth. However, several reports suggest that adults retain metabolically active BAT depots that can be cold-induced and respond to sympathetic nervous system activation and it's specialized in the production of heat and lipid oxidation (25), while WAT functions as insulation, an exemplary store of excess energy as triglycerides.

2. Materials and Methods

2.1. Patients and Control group

2.1.1. Patients

The study was conducted on 100 type 2 diabetic patients (58 males and 42 females) attending at diabetes mellitus center at Al-Sader medical city in Najaf province and Al-Hassan Mujtaba hospital at Karbala province from December 2024 till November 2024.

Patients suffered from the following cases were not included and excluded from the current study :

- Patients with renal dysfunction .
- Coexistent illness i.e. infections .
- Proliferative retinopathy.
- Chronic inflammatory diseases: (rheumatoid arthritis, sinusitis, hay fever, psoriasis, SLE).
- Patients on insulin therapy.

Diabetes mellitus was diagnosed by physicians. The patients ages were range between (40-75) years.

2.1.2. Control group

A group of 100 healthy subjects (63 males and 47 females) were included as a control group. The ages of the apparently healthy individuals were range from 40-60 years. They were collected from my family, medical staff and relatives who were free from signs and symptoms of any chronic diseases like diabetes, hypertension and others.

2.1.3. Collection of samples

Venous fasting blood samples (5-6 ml) were collected from the patients and healthy volunteers after an overnight fasting. The samples were put in tubes containing no anticoagulant. Disposable syringes and needles were used for blood collection. After allowing the blood to clot at

37°C for about 15 min, blood samples were centrifuged for 15 min. The sera were separated in a disposable tube and stored at -18 °C.

2.2. Baseline characteristics

Baseline characteristics included body mass index, fasting blood sugar (FBS), lipid profile and fasting insulin. Glucose, cholesterol, triglycerides, direct HDL and direct LDL was measured by spectrophotometric method using Randox Daytona plus (Randox Laboratories Ltd., Crumlin, UK). Insulin was measured by electrochemiluminescence method using Cobas Roche e411 auto analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

2.3. Estimation of insulin resistance in type 2 diabetic patients

Insulin resistance was evaluated by four methods as follows:

- Fasting insulin concentration (in microunits per milliliter) (**FI**).
- Homeostasis model assessment (**HOMA**):

  HOMA = [glucose (in mmole/L) * insulin (in microU/mL)] / 22.5.
- Quantitative insulin sensitivity checks index (**QUICKI**):

  QUICKI = 1/ [log glucose (in mg/dL) + log insulin (in microU/L)].
- McAuley's index (**McA**):

  McA = exp [2.63 - 0.28 ln (insulin [in microU/mL]) - 0.31 ln (triglycerides [in mmole/L])].

Patients were considered as insulin resistant when:

- **McA** ≤5.8, HOMA ≥2.5 and QUICKI ≤0.33.
- Fasting insulin was considered to assess IR and FI level ≥12mU/l was considered as insulin resistant among both non-diabetic and diabetic populations (26,27)

Biostatistical Analysis

1. The results were expressed as Mean ± SD.
2. Student's t-test was used to verify the association of inflammatory response markers in the patients relative to the control group.
3. Significant variation was considered when the P value was less than 0.05.

3. Results

3.1 Characterization features of the parameters:

The characteristics of the participants are shown in Table 3.1. It includes the data of both diabetic patients and the control group.

Table 3.1: Clinical and biochemical characteristics of the study groups.

Parameter	Patients		Control		P value
	Mean ± SD	Range	Mean ± SD	Range	
No.	100		100		-------
Sex M/F	58 / 42		63 / 47		-------
Age (y)	53.4 ± 7.8	40 – 70	49.3 ± 4.6	45 – 65	0.04
Weight(kg)	82.1±13.5	54 – 117	75.1 ±11.6	47 – 96	0.03
Height(m)	1.7 ± 0.1	1.5 – 1.9	1.7 ± 0.1	1.5 – 1.8	0.78
BMI(kg/m^2)	30.1 ± 4.4	18.7 41.8	27.2 ± 3.5	18.4 - 33	<0.01
Duration of the disease (y)	2.9 ± 2.1	0.08 – 10	-------	--------	---------
Fasting blood glucose(mmol/L)	9.9 ± 2.9	7.1– 20.2	4.8 ± 0.68	3.2 – 5.9	<0.001
TG(mmol/L)	1.8 ± 0.9	0.5 – 4.3	0.9 ± 0.5	0.4 – 2.8	<0.001
Cholesterol (mmol/L)	5.04 ± 0.92	3.81-6.91	4.20 ± 0.72	2.66-5.39	< 0.001
insulin: µIU/ml	15.82±7.79	5.47– 44.36	8.24 ±2.98	1.56– 15.27	<0.001

3.1.4 Levels of Serum Glucose, Insulin and Lipid profile in Type 2 Diabetic Patients and Control Group

Fasting glucose, insulin, total cholesterol, TG, VLDL-cholesterol and LDL-cholesterol levels were found to be elevated significantly ($p < 0.001$) in type 2 diabetic patients when compared to those of the control group. However, HDL-cholesterol was observed to be lowered significantly ($p < 0.05$) during comparable evaluation (Figure 3-1, Figure 3-2 and Table 3-2).

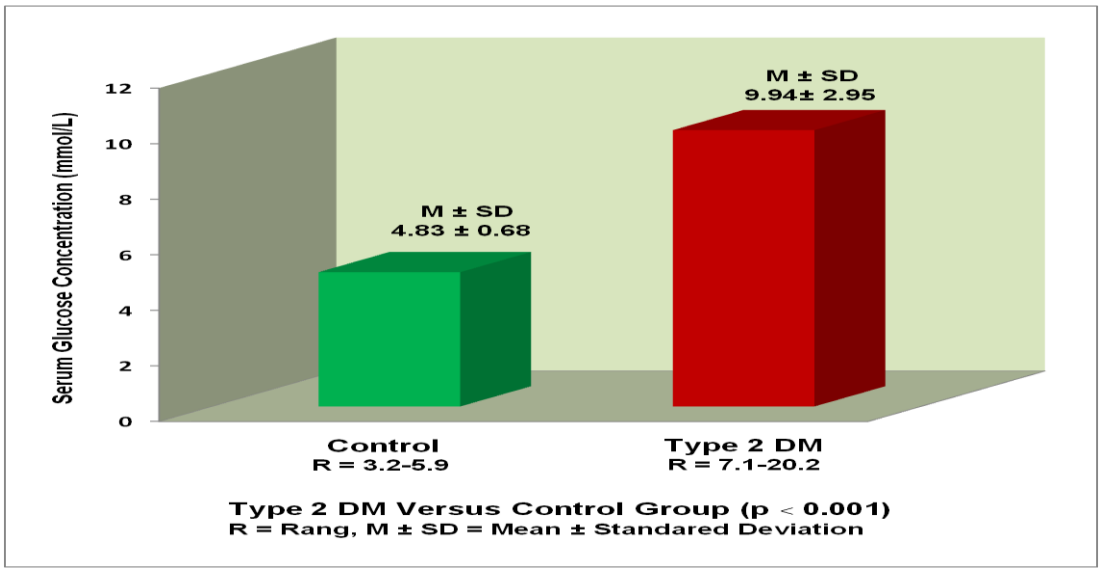

Figure 3-1: Mean Fasting Glucose Concentration in Sera of Type 2 Diabetic Patients and the Control Group

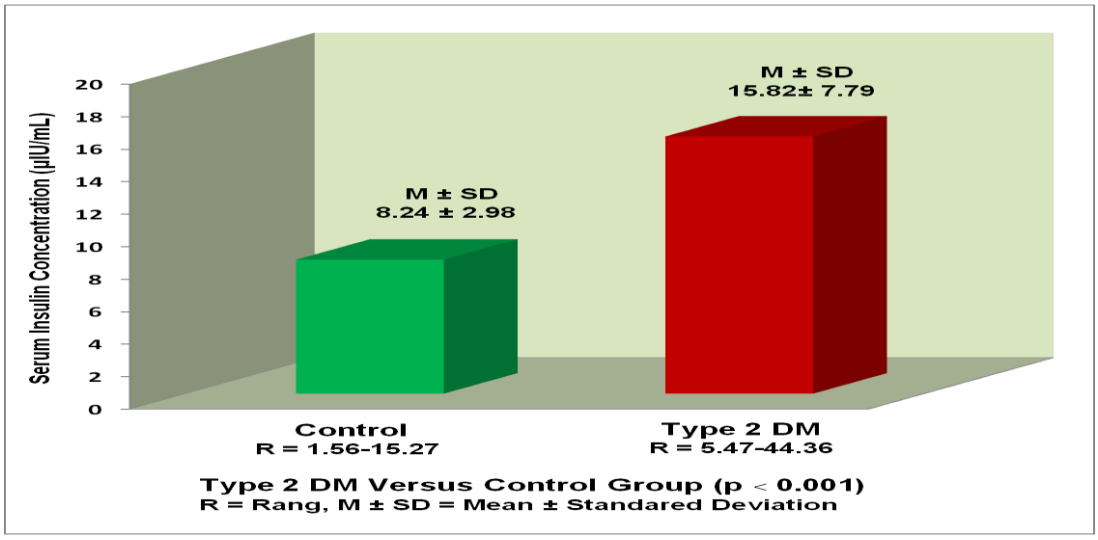

Figure 3-2: Mean Fasting Insulin Concentration in Sera of Type 2 Diabetic Patients and the Control Group.

Table 3-2: Mean Serum Total Cholesterol, HDL-Cholesterol, TGs, VLDL-Cholesterol and LDL-Cholesterol Concentration in Type 2 Diabetic Patients and the Control Group

Lipid Profile (mmol/L)	Groups	Mean ± SD	Range	P-value
Total Cholesterol	Control	4.20 ± 0.72	2.66-5.39	< 0.001
	Patient	5.04 ± 0.92	3.81-6.91	
HDL Cholesterol	Control	1.04 ± 0.26	0.58-1.79	< 0.05
	Patient	0.96 ± 0.22	0.52-1.54	
Triglycerides	Control	1.25 ± 0.52	0.49-2.27	< 0.001
	Patient	2.05 ± 0.94	0.56-3.97	
VLDL Cholesterol	Control	0.56±0.23	0.22-1.02	< 0.001
	Patient	0.92 ± 0.42	0.25-1.78	
LDL Cholesterol	Control	2.59 ± 0.77	1.16-4.19	< 0.001
	Patient	3.15 ± 1.01	1.15-5.39	

3.2 ***Evaluation of insulin resistance and sensitivity in type 2 diabetic patients and the control group:***

Insulin resistance was evaluated by using four methods: homeostasis model assessments (HOMA), quantitative insulin sensitivity checks index (QUICKI), McAuley (McA) and fasting insulin (FI). Insulin resistance was evaluated by using the criteria in section 2.2.3. The values of the four insulin resistance indices, i.e. HOMA, QUICKI, McA and FI were tabulated in Table 3-3.

The results of present study exhibited significant increases ($p < 0.001$) of insulin resistance indices of the four methods in type 2 diabetic patients when compared with the control group.

As shown in Table 3-4, 92 (89.32%), 90 (87.38%), 58 (56.31%) and 64 (62.14%) of the 103 type 2 diabetic patients were demonstrated to be insulin resistant when they were evaluated by HOMA, QUICKI, McA and FI method respectively. However, 5 (8.77%), 5 (8.77%), 3 (5.26%) and 7 (12.28%) of the 57 control group were observed to be insulin resistant when they were studied similarly.

The comparison of the four methods of estimation of insulin resistance revealed that the highest number of type 2 diabetic patients with insulin resistance was obtained with the use of HOMA index, while the lowest number of type 2 diabetic patients with insulin resistance was indicated with the MCA index as shown in Figure 3-3.

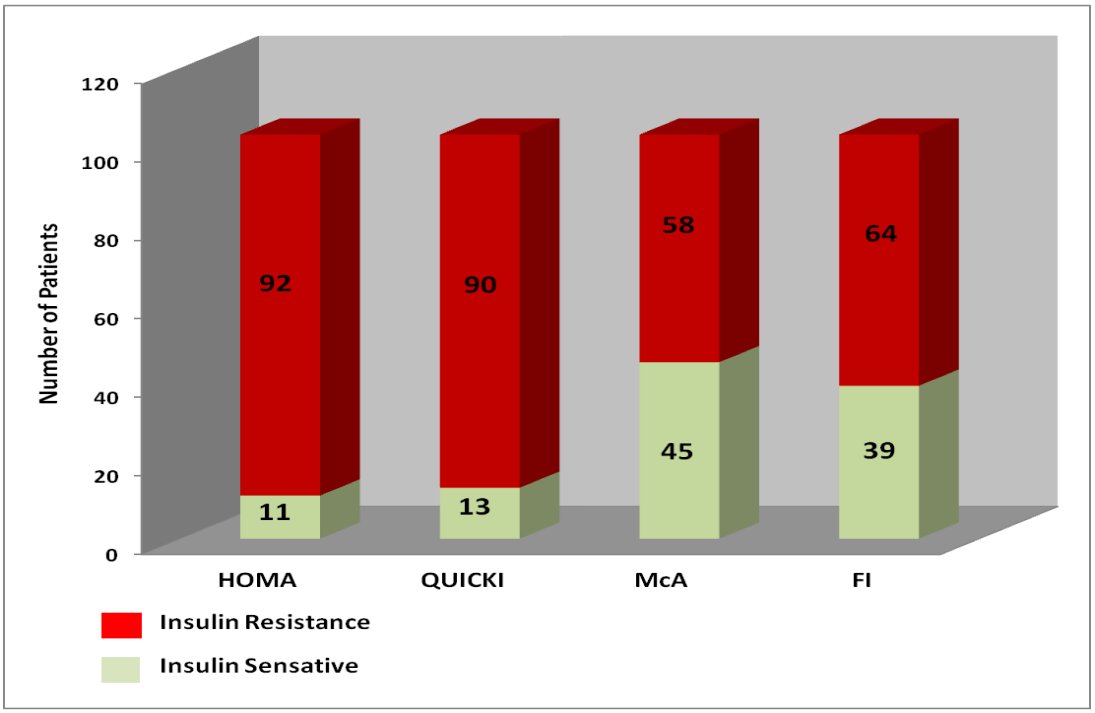

Figure 3-3: Insulin Resistance Among Type 2 Diabetes Mellitus by Four methods. HOMA (homeostasis model assessment), QUICKI (quantitative insulin sensitivity check index), MCA (McAuley's Index) and FI (fasting insulin concentration)

Table 3.3: Data of the four methods used to evaluate insulin resistance in patients and the control group.

Index	Groups	Mean ± SD	Range	p value
HOMA	Patient	7.12 ± 4.29	2.16 - 28.45	< 0.001
	Control	1.80 ± 0.68	0.33 - 3.37	
QUICKI	Patient	0.29 ± 0.02	0.24 - 0.34	< 0.001
	Control	0.35 ± 0.02	0.31 - 0.47	
MCA	Patient	5.44 ± 0.93	3.62 - 7.65	< 0.001
	Control	7.09 ± 1.11	5.45 - 11.17	
FI	Patient	15.82 ± 7.79	5.47 - 44.36	< 0.001
	Control	8.24 ± 2.98	1.56 - 15.27	

Table 3-4: The Incidence of Insulin Resistance and Sensitivity in Type 2 Diabetic Patients and the Control Group

Index	Insulin resistance subject		Insulin sensitivity subject	
	Patients	Control	Patient	Control
HOMA	92 (89.32%)	5 (8.77%)	11 (10.68%)	52 (91.23%)
QUICKI	90 (87.38%)	5 (8.77%)	13 (12.62%)	52 (91.23%)
MCA	58 (56.31%)	3 (5.26%)	45 (43.69%)	54 (94.74%)
FI	64 (62.14%)	7 (12.28%)	39 (37.86%)	50 (87.72%)

4. discussion

There are different mechanisms responsible for changes of lipid levels in DM. The defect in insulin action and/or secretion and elevated plasma levels of the counter regulatory hormones are responsible for accelerated lipolysis and impaired lipids synthesis that lead to increase plasma concentration of cholesterol, TGs and FFAs (28,29)

The faulty of glucose utilization in diabetes, resulting in hyperglycemia and mobilization of FAs from adipose tissue for energy purpose and the excess of FAs are accumulated in the liver and then converted to TGs (30). An increase in VLDL occurred in DM due to increase availability of glucose for VLDL synthesis and decrease in lipoprotein lipase activity leading to decrease the clearance of VLDL from peripheral circulation (31,32).

Lipoprotein lipase is required for chylomicrons and VLDL metabolism. This enzyme is induced by insulin and transported to the luminal surface of capillary endothelium where it is in direct contact with the blood. Lipoprotein lipase hydrolyzes the FAs from TGs that carried by chylomicrons and VLDL (33,34).

In diabetes, the active lipolysis increases cholesterol synthesis leading to cholesterol accumulation in the walls of blood arteries (35). These results indicated a high risk for heart diseases in those patients due to the atherosclerotic events of hypercholesterolemia (36).

The increase in LDL-cholesterol and oxidized LDL in diabetes stimulate the immune system that a harmful molecule has appeared in excessive quantities (37). They cause inflammation and promote further injury to the areas they target. Monocytes and other factors form the fatty substance, plaque (38). Lipid abnormalities are common in diabetics and frequently seen in type 2 diabetics. Dyslipidaemia make diabetics prone to develop coronary heart disease and other complications of atherosclerosis (39).

The results of the present study are in agreement with those of Sasmita *et al.* (40) who pointed out significant increases in fasting glucose, total cholesterol, TGs, VLDL-cholesterol and LDL-cholesterol concentration in type 2 diabetic patients when compared with the control group and significant decrease in HDL-cholesterol concentration in type 2 diabetic patients when compared with the control group.

The evaluation of insulin resistance is a promising approach in the management of diabetes mellitus. Several methods are used for such evaluation. The euglycaemic insulin clamp method, intravenous glucose tolerance test (IVGTT) and minimal model approximation of the

metabolism of glucose (MMAMG) are standard methods for the measurement of insulin resistance in researches (41,42). However, they are impractical in clinical practice and are difficult to be carried out in population research studies (43,44). Methods-based on the frequently sampled IVGTT are invasive and time consuming, and they are not appropriate for general population screening. However, they confirm that the best method was dependent on glucose status. The Galvin and the HOMA methods were the most useful among all glucose levels. Moreover, the HOMA index, has been validated with the hyperinsulinemic-euglycaemic clamp technique by ***Bonora et al***. (45) who found a highly significant correlation. Therefore, HOMA is considered a valid method to assess peripheral insulin sensitivity in epidemiologic studies. In some reports, MCA was demonstrated to be the most precise rational for prediction of insulin sensitivity (46,47).

According to the results of the present investigation, the HOMA method was implicated to select diabetics of insulin resistance. Two factors have strongly led us for HOMA implication.

The first is the wide use of HOMA in the previous work mentioned in literatures (48,49). The second is about 85% of the enrolled patients were overweight or obese. Thus, the data of the HOMA method was highly suggestive to be used for selection of insulin resistant type 2 diabetic, so 56 out of 100 patients were categorized as insulin resistant and used in the present investigation.

The results of the current study are in agreement with those of ***Ulfris and Lukshmy*** (43,50). In regards to the data of HOMA methods, however, inconsistence was also observed in comparison with those of ***Hettihewa , McAuley, and Laakso*** (51,43,52). The most satisfactory reasons for the

difference may be the patient's status and the number of the enrolled diabetics.

The dyslipidemia induced by insulin resistance and type 2 diabetes (diabetic dyslipidemia) (53) is characterized by the lipid triad: (a) high levels of plasma triglycerides, (b) low levels of HDL, and (c) the appearance of small dense low-density lipoproteins (sdLDL), as well as an excessive postprandial lipemia (53,54). Hypertriglyceridemia increases the incidence of CVD by 32% in men and 76% in women (55, 56). A study conducted in 10,038 people with normal blood pressure or pre-hypertension demonstrated dyslipidemia as a strong predictor of development of type 2 diabetes (57). Frequently, diabetic dyslipidemia precedes type 2 diabetes by several years, suggesting that Ormazabal *et al. Cardiovasc Diabetol (2018)* the abnormal lipid metabolism is an early event in the development of CVD in type 2 diabetes (58).

In this study, there are differences between diabetic and non-diabetic patients in the level of blood glucose. A significant difference was observed (p=0.001). High levels of blood glucose of diabetic patients due to resistance to insulin, same results were found (59). The fasting blood glucose level in the diabetic group is also elevated, and this indicated that there is poor control of DM. In fact, diabetes mellitus is characterized by hyperglycemia together with biochemical alterations of glucose (60) (**Firdous and Khan, 2007).**

The result of this study showed significant increased levels of total cholesterol (p=0.001) in diabetic patients compared to non-diabetic subjects, this increase it may be due to an increase in the plasma concentration of VLD L and LDL, which may be caused by increasing hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation (61)**.**

5. ***Conclusions*:**

The present study concludes that:

1. Most of type 2 diabetic patients are presented with insulin resistance.
2. The dyslipidemia induced by insulin resistance and type 2 diabetes (diabetic dyslipidemia).
3. VLDL-C and LDL-C have major role in the etiology of insulin resistance in type 2 diabetic patients.

6. ***Recommendations***

1. A large sample size to get a sufficient power for our study.
2. Analysis of genetic expression like single nucleotides polymorphisms (SNPs) of insulin receptor, insulin receptors ubstrate-1 and β3-adrenergic receptor gene to determine which one is more common in our population.
3. Evaluation of gene expression to determine the effect of SNPs on the various phenotypic properties.

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