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Diabetes Mellitus and Metabolic Disorder

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Abstract: ***The prevalence of Diabetes Mellitus (DM) has increased in recent decades. This study was designed to determine the occurrence of retinopathy, neuropathy, nephropathy, hypertension, and hyperlipidemia, as well as their interdependence in newly diagnosed diabetic patients. In this study, 200 consecutive newly diagnosed patients were evaluated, and screening tests for retinopathy, neuropathy, nephropathy, hypertension, and hyperlipidemia were undertaken. The frequency of positive screening tests for hyperlipidemia, hypertension, neuropathy, nephropathy, and retinopathy was found to be 73.5%, 58.5%, 52%, 10%, and 6%, respectively. A significant proportion of newly diagnosed diabetic patients exhibit signs of these chronic complications.***

Keywords: Diabetes, retinopathy, neuropathy, nephropathy, hypertension

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion and/or insulin action, which results in hyperglycemia with disturbances of carbohydrate, fat and protein metabolism [1]. The incidence of DM has increased dramatically in recent decades, predominantly because of changes in life style, an increase in the prevalence of obesity and longevity. Current projections estimate that the number of people with DM will increase by 50.0% by 2010, and will nearly double by 2025 [2, 3]. Type 2 diabetes is a very common disease, characterized by an asymptomatic phase between the actual onset of diabetic hyperglycemia and clinical diagnosis. This phase has been estimated to last at least 4–7 years, and 30–50% cases of type 2 diabetic patients remained undiagnosed. This leads to the development of chronic complications of diabetes, which remain the chief problems in diabetic care, and which cause a lack of fitness to work, disability, and premature death [4, 5].

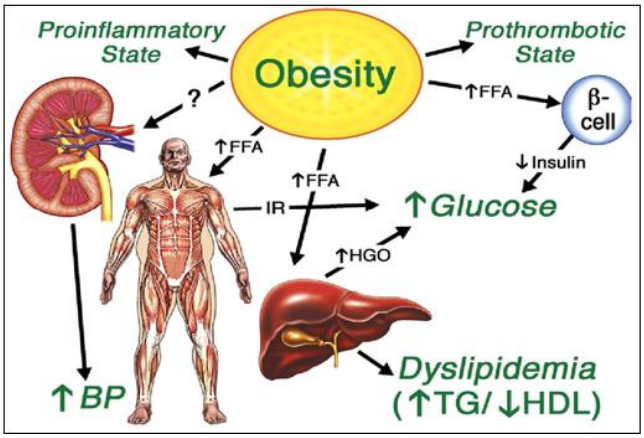

Figure: Metabolic Disorder

The literature traditionally divides the diverse spectrum of vasculopathy associated with diabetes into two main subtypes: firstly, the diabetes - specific microvascular complications of retinopathy, nephropathy and neuropathy; and secondly. Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes, and raised blood glucose causes around 20% of cardiovascular deaths (*1).* Between 2000 and 2019, there was a 3% increase in age - standardized mortality rates from diabetes. In lower - middle - income countries, the mortality rate due to diabetes increased 13%.

By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22% globally between 2000 and 2019.

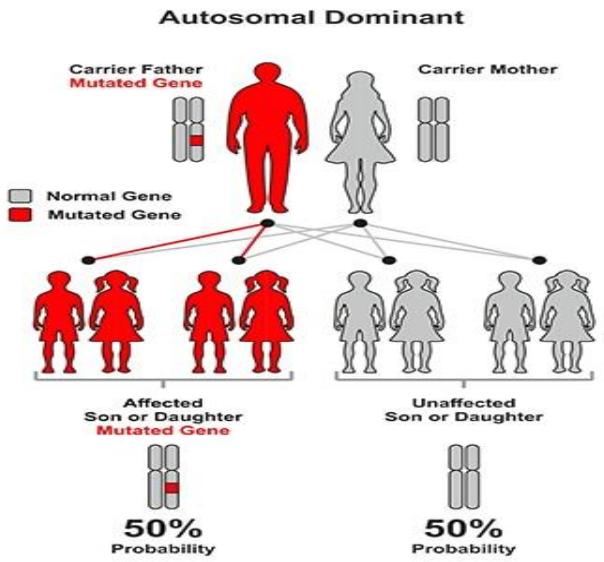

Figure 2: Diabetes mellitus Genetically

Symptoms of diabetes may occur suddenly. In type 2 diabetes, the symptoms can be mild and may take many years to be noticed.

Symptoms of diabetes include:
- Feeling very thirsty
- Needing to urinate more often than usual
- Blurred vision
- Feeling tired
- Losing weight unintentionally

Over time, diabetes can damage blood vessels in the heart, eyes, kidneys and nerves.

People with diabetes have a higher risk of health problems including heart attack, stroke and kidney failure.

Diabetes can cause permanent vision loss by damaging blood vessels in the eyes.

Many people with diabetes develop problems with their feet from nerve damage and poor blood flow. This can cause foot ulcers and may lead to amputation.

Type 1 diabetes: -
Type 1 diabetes (previously known as insulin - dependent, juvenile or childhood - onset) is characterized by deficient insulin production and requires daily administration of insulin. In 2017 there were 9 million people with type 1 diabetes; the majority of them live in high - income countries. Neither its cause nor the means to prevent it are known.

Type 2 diabetes: -
Type 2 diabetes affects how your body uses sugar (glucose) for energy. It stops the body from using insulin properly, which can lead to high levels of blood sugar if not treated.

Over time, type 2 diabetes can cause serious damage to the body, especially nerves and blood vessels.

Type 2 diabetes is often preventable. Factors that contribute to developing type 2 diabetes include being overweight, not getting enough exercise, and genetics.

Early diagnosis is important to prevent the worst effects of type 2 diabetes. The best way to detect diabetes early is to get regular check - ups and blood tests with a healthcare provider.

Symptoms of type 2 diabetes can be mild. They may take several years to be noticed. Symptoms may be similar to those of type 1 diabetes but are often less marked. As a result, the disease may be diagnosed several years after onset, after complications have already arisen.

More than 95% of people with diabetes have type 2 diabetes. Type 2 diabetes was formerly called non - insulin dependent, or adult onset. Until recently, this type of diabetes was seen only in adults but it is now also occurring increasingly frequently in children.

Gestational diabetes: -
Gestational diabetes is hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes. Gestational diabetes occurs during pregnancy.

Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future.

Gestational diabetes is diagnosed through prenatal screening, rather than through reported symptoms.

Impaired glucose tolerance and impaired fasting glycaemia: -
Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable.

Prevention: -
Lifestyle changes are the best way to prevent or delay the onset of type 2 diabetes.

To help prevent type 2 diabetes and its complications, people should:
- Reach and keep a health body weight
- Stay physically active with at least 30 minutes of moderate exercise each day
- Eat a healthy diet and avoid sugar and saturated fat
- Not smoke tobacco.

Diagnosis and treatment: -
Early diagnosis can be accomplished through relatively inexpensive testing of blood glucose. People with type 1 diabetes need insulin injections for survival.

One of the most important ways to treat diabetes is to keep a healthy lifestyle.

Some people with type 2 diabetes will need to take medicines to help manage their blood sugar levels. These can include insulin injections or other medicines. Some examples include:

- Metformin
- Sulfonylureas
- Sodium - glucose co - transporters type 2 (SGLT - 2) inhibitors.

Along with medicines to lower blood sugar, people with diabetes often need medications to lower their blood pressure and stains to reduce the risk of complications.

Additional medical care may be needed to treat the effects of diabetes:

- foot care to treat ulcers
- screening and treatment for kidney disease
- eye exams to screen for retinopathy (which causes blindness).

2. Materials and Method

In this cross sectional study, 200 consecutive newly diagnosed patients referred to the Institute of Endocrinology and Metabolism affiliated to Iran University of Medical Sciences (IUMS) from October to March 2006, were enrolled. The study was approved by the ethics committee of IUMS. The patients were informed about the study, and written consent was obtained from them.

The frequency of nephropathy, retinopathy, neuropathy, hyperlipidemia and hypertension were evaluated in these patients. The diagnosis of diabetes is confirmed by fasting plasma glucose, measured from a Venus sample after an overnight fast. Patients having ketonuria upon presentation were excluded.

WHO aims to stimulate and support the adoption of effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low - and middle - income countries. To this end, WHO:

- provides scientific guidelines for the prevention of major non - communicable diseases including diabetes;
- develops norms and standards for diabetes diagnosis and care.
- builds awareness on the global epidemic of diabetes, marking World Diabetes Day (14 November).
- conducts surveillance of diabetes and its risk factors.

Nephropathy

In this study, both urine albumin and creatinine were measured. Albuminuria is defined as a urinary albumin–creatinine ratio (ACR) of ≥ 30 mg/g. Microalbuminuria is characterized by an ACR of 30 to 300 mg/g, while macroalbuminuria is defined as an ACR > 300 mg/g. Renal failure is defined according to the laboratory cut - off values, with creatinine levels greater than 1.0 mg/dL for women and greater than 1.2 mg/dL for men.

To assess the presence of diabetic retinopathy, a fundus examination was performed by an ophthalmologist following mydriasis of both eyes using tropicamide and phenylephrine eye drops. Retinopathy was classified into two categories: proliferative and nonproliferative.

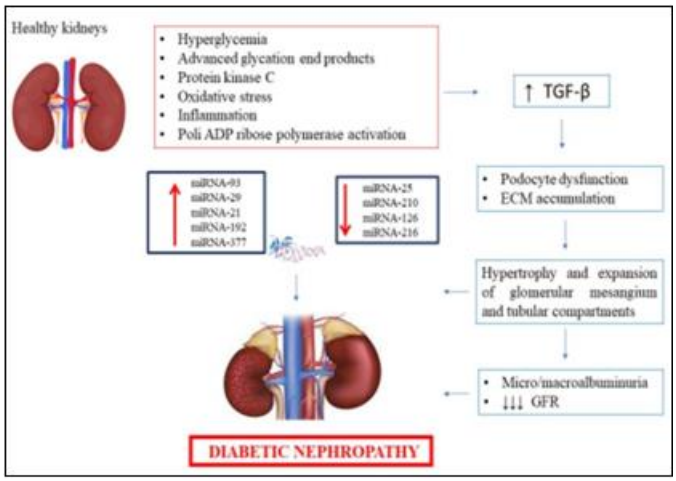

Figure 3: Diabetis Nephropathy

Neuropathy:

Patients completed a questionnaire about their symptoms, which included sensations such as pins and needles, abnormal cold or warm sensations in their feet, sharp pain, aching pain, or irritation in their feet or legs caused by bedclothes at night. A modified neuropathy disability score (NDS) was used to diagnose and quantify the severity of diabetic neuropathy during the clinical examination.

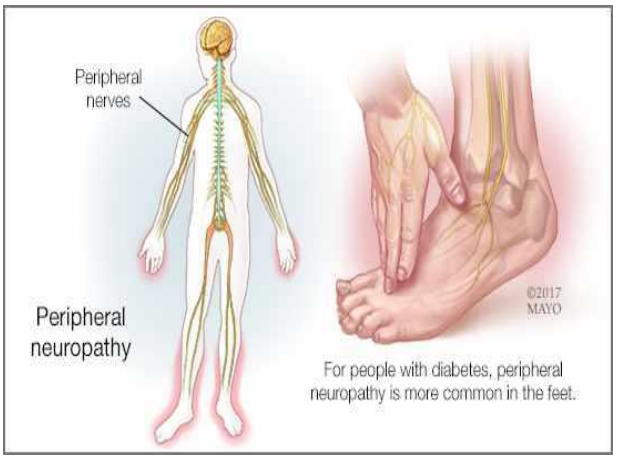

Figure 3: Peripheral Neuropathy

Lipids:

Blood samples were taken from patients after a 12 - hour fast. Total cholesterol and triglycerides were measured, with dyslipidemia defined as cholesterol levels greater than 200 mg/dL or triglyceride levels greater than 150 mg/dL.

1) **Insulin Deficiency and Lipolysis: -**

- **Insulin's Role:** Insulin is crucial in regulating lipid metabolism. It promotes the storage of fat in adipose tissue by inhibiting lipolysis (the breakdown of fats).
- **In T1D:** Due to the autoimmune destruction of pancreatic beta cells, insulin production is minimal or absent. This leads to unrestrained lipolysis, increasing free fatty acids (FFAs) in the bloodstream.

2) **Increased Free Fatty Acids (FFAs): -**

- **Consequence of Unrestrained Lipolysis:** Elevated FFAs provide substrates for hepatic ketogenesis, leading to the production of ketone bodies, which can result in diabetic ketoacidosis (DKA) if not managed properly.

- **Impact on Organs:** High levels of FFAs can contribute to insulin resistance in muscle and liver tissues, further complicating glucose metabolism.

3) Altered Lipoprotein Metabolism: -

- **VLDL and LDL:** Insulin deficiency leads to increased production and decreased clearance of very low - density lipoprotein (VLDL) and low - density lipoprotein (LDL) particles. These lipoproteins are more atherogenic (promoting the formation of fatty deposits in the arteries).
- **HDL:** High - density lipoprotein (HDL) levels may also be altered, typically reduced, which diminishes its protective cardiovascular role.

4) Ketone Bodies and Diabetic Ketoacidosis (DKA): -

- **Ketogenesis:** In the liver, increased FFAs are converted into ketone bodies (acetoacetate, beta - hydroxybutyrate, and acetone) for energy use when glucose is not available.
- **DKA Risk:** Without insulin, the balance tips towards excessive ketone production, leading to DKA, a life - threatening condition characterized by high blood sugar, ketonemia, and metabolic acidosis.

5) Long - term Complications: -

- **Cardiovascular Disease:** Altered lipid profiles (higher LDL and lower HDL) increase the risk of atherosclerosis and cardiovascular diseases.
- **Peripheral Neuropathy and Retinopathy:** Poorly managed lipid metabolism contributes to microvascular complications, affecting nerves and retinal blood vessels.

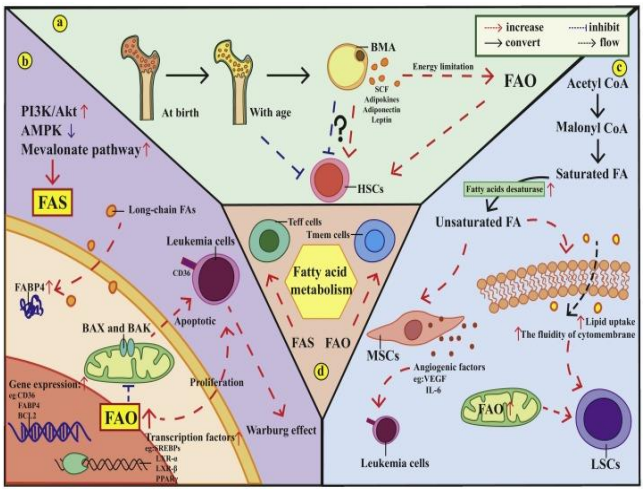

Figure 3: Type - 1 diabetes lipid metabolism

Hypertension

Blood pressure was measured in the right arm, supported on a table at heart level, using an appropriately sized cuff for the patient's arm girth. BP was measured three times within a one - week interval, and the average of these recordings was considered as their blood pressure. Individuals with a systolic BP greater than 139, a diastolic BP greater than 89, or those taking antihypertensive medication were considered to have hypertension.

Hypertension (high blood pressure) is a common comorbidity in people with diabetes mellitus. Managing hypertension is crucial for individuals with diabetes due to the increased risk of cardiovascular complications. Here are key points about the relationship between hypertension and diabetes:

Why Hypertension is Common in Diabetes: -

1) **Insulin Resistance**: Many people with type 2 diabetes have insulin resistance, which can lead to higher insulin levels. High insulin levels can increase blood pressure.
2) **Kidney Damage**: Diabetes can damage the kidneys (diabetic nephropathy), which can lead to increased blood pressure.
3) **Obesity**: Obesity is common in type 2 diabetes and is a risk factor for hypertension.
4) **Dyslipidemia**: Abnormal levels of lipids in the blood, common in diabetes, can contribute to hypertension.

Complications of Hypertension in Diabetes:

1) **Cardiovascular Disease**: Hypertension and diabetes both independently increase the risk of heart disease and stroke.
2) **Kidney Disease**: High blood pressure can worsen diabetic nephropathy, leading to chronic kidney disease.
3) **Retinopathy**: Hypertension can exacerbate diabetic retinopathy, increasing the risk of vision loss.
4) **Neuropathy**: High blood pressure can contribute to the development and progression of diabetic neuropathy.

Management Strategies

a) **Lifestyle Modifications**:

- **Diet**: Adopt a diet low in sodium and rich in fruits, vegetables, and whole grains (e. g., DASH diet).
- **Exercise**: Regular physical activity helps control both blood pressure and blood glucose levels.
- **Weight Management**: Maintaining a healthy weight can reduce the risk of hypertension.
- **Limiting Alcohol**: Reducing alcohol intake can help manage blood pressure.

b) Medication

- **ACE Inhibitors/ARBs**: Often used as first - line treatments as they protect the kidneys.
- **Diuretics**: Help reduce blood pressure by removing excess fluid from the body.
- **Beta - Blockers**: Used less frequently due to potential effects on blood glucose control but can be used in certain situations.
- **Calcium Channel Blockers**: Effective in lowering blood pressure and can be used in combination with other medications.

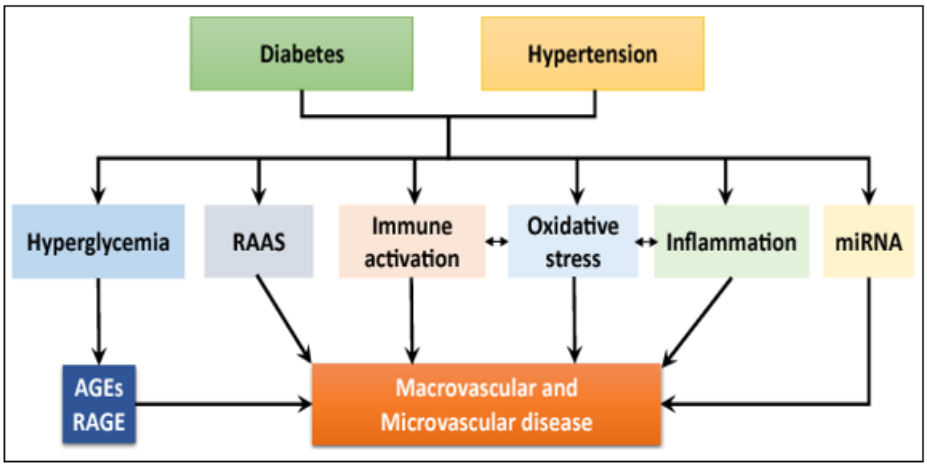

Figure 4: Hypertension is Common in Diabetes

3. Result

Among 200 newly diagnosed diabetic patients, 52% were men and 48% were women. The mean age at presentation was 52.39 ± 10.03 years. The prevalence of nephropathy was 10%, including 13 patients (65%) with microalbuminuria, 4 patients (20%) with macroalbuminuria, and 3 patients (15%) with renal failure. Retinopathy was recorded in 12 patients (6%); of these, 7 patients (58.3%) had proliferative retinopathy and 5 patients (41.6%) had non - proliferative retinopathy. Symptomatic neuropathy was found in 104 patients (52%). Among the patients with cardiovascular problems, 147 patients (73.5%) had hyperlipidemia, 37 (25.2%) had hypercholesterolemia, 49 (33.3%) had hypertriglyceridemia, and 61 patients (41.5%) had both hypercholesterolemia and hypertriglyceridemia. The prevalence of hypertension was 58.5%.

1) Age and hypertension ($p < 0.001$): The average age of hypertensive patients was 6.2 years higher than that of non - hypertensive patients.
2) Age and the form of nephropathy ($p < 0.01$): There was no statistically significant difference between age and the prevalence of nephropathy, but renal failure was more common in older patients. The mean age of patients with renal failure was 71.33 ± 14.43 years, whereas the mean age of patients with macroalbuminuria and microalbuminuria was 55.5 ± 10.5 years and 42 ± 11.1 years, respectively.
3) Retinopathy and hypertension ($p < 0.003$): The prevalence of retinopathy increased significantly with the presence of hypertension, with 33.3% of patients with retinopathy also being hypertensive.
4) Retinopathy and neuropathy ($p < 0.01$): 77.7% of patients with proliferative retinopathy had neuropathy.
5) Retinopathy and nephropathy ($p < 0.01$): The prevalence of nephropathy was 86% among patients with retinopathy, and its probability increased with the severity of retinopathy.

4. Discussion

Diabetes Mellitus (DM) is a multifactorial disease associated with various microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (ischemic heart disease, cerebrovascular disease, and peripheral vascular diseases) complications [11]. This metabolic disease is one of the most common endocrine disorders, affecting almost 6% of the world's population [12]. The prevalence of DM in Iran was estimated at 5.5% in a population - based study conducted by Azimi - nezhad et al. [13].

Type 2 DM is often undiagnosed for many years. The gap between the onset of the disease and clinical diagnosis leads to the development of chronic complications, which are the leading causes of premature mortality among diabetic patients [14].

In this study, one of the first of its kind in Iran, we assessed the prevalence of microvascular and macrovascular complications of DM in 200 newly diagnosed diabetic patients. Nephropathy was reported in 10%, neuropathy in 52%, retinopathy in 6%, hypertension in 58.5%, and hyperlipidemia in 73.5% of the patients.

Other studies have assessed the prevalence of these chronic complications. Harrzallah F et al. [15] found neuropathy in 24%, nephropathy in 13%, retinopathy in 8%, and hypertension in 22% of diabetic patients. In another study conducted by Weerasuriya [16] in Sri Lankan diabetic patients, neuropathy was present in 25.1%, nephropathy in 29%, retinopathy in 15%, and hypertension in 23%. Considering the prevalence of these chronic complications at the time of diagnosis in different studies, appropriate screening procedures for diabetic patients are strongly recommended.

Microvascular and macrovascular complications frequently coexist. It is well recognized that vascular complications in one tissue are often accompanied by evidence of pathology in other vascular territories [6]. Several studies [7, 8, 17] demonstrate a concordance between chronic complications of DM. This study found nephropathy in 86% of diabetic patients with retinopathy. Osterby et al. [17] also found a strong concordance between retinopathy and the structural parameters of diabetic nephropathy.

Our study showed that the prevalence of retinopathy increased with hypertension, as 33.5% of patients with retinopathy also had hypertension. This data aligns with the findings of Matthews et al. [18], which showed that high blood pressure is detrimental to each aspect of diabetic retinopathy, and that strict blood pressure control reduces

the risk of clinical complications from diabetic eye disease. Hideharu and Hidetoshi [19] similarly concluded that hypertension is a risk factor for the progression of diabetic retinopathy, mainly because hyperglycemia in diabetic patients impairs the regulation of retinal perfusion, leading to increased susceptibility to injury by systemic hypertension.

In this study, 77.7% of diabetic patients with proliferative retinopathy had neuropathy. Similarly, in the study by Zander et al. [20], proliferative retinopathy was correlated with somatic and autonomic neuropathy in diabetic patients.

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