Plasma Magnesium status in Type 2 Diabetic Patients with and without diabetic neuropathy

Thesis
Submitted for Fulfillment of Master Degree in Internal Medicine

By

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قالوا:
سبلانك فإن علم لنا إلا ما علمتنا إنه أنت العلي العلي الكريم
صدق الله العظيم
سورة البقرة الآية: 32
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<tr>
<td>ADA</td>
<td>American Diabetes association</td>
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<tr>
<td>AGES</td>
<td>Advanced glycated end products</td>
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<td>ACEI</td>
<td>Angiotensien converting enzyme inhibitor</td>
</tr>
<tr>
<td>ARBs</td>
<td>Angiotensien II receptor blockers</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CaSR</td>
<td>Calcium sensing receptor</td>
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<tr>
<td>CFRD</td>
<td>Cystic fibrosis related Diabetes</td>
</tr>
<tr>
<td>CSME</td>
<td>Clinical significant macular edema</td>
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<tr>
<td>CVD</td>
<td>Cardio vascular disease</td>
</tr>
<tr>
<td>C1qthf9</td>
<td>C1q and tumor necrosis factor related protein 9</td>
</tr>
<tr>
<td>DCCT</td>
<td>Diabetes control and complication trial</td>
</tr>
<tr>
<td>DCT</td>
<td>Distal convoluted tubules</td>
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<tr>
<td>DKA</td>
<td>Diabetic ketoacidosis</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DPP-4</td>
<td>Dipeptyl peptidase -4</td>
</tr>
<tr>
<td>DR</td>
<td>Diabetic retinopathy</td>
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<tr>
<td>DSME</td>
<td>Diabetes self-management education</td>
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<tr>
<td>DSMS</td>
<td>Diabetes self-management support</td>
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<tr>
<td>FBS</td>
<td>Fasting blood sugar</td>
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<tr>
<td>FHHNC</td>
<td>Familial hypomagnesemia hypercalciuria and nephrocalcinosis</td>
</tr>
<tr>
<td>GAD-65</td>
<td>Glutamic acid decarboxylase-65</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational Diabetes mellitus</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GLP-1</td>
<td>Glucagon like peptide -1</td>
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<tr>
<td>HAPO</td>
<td>Hyperglycemic adverse outcome</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immune deficiency virus</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocytic antigen</td>
</tr>
<tr>
<td>HNF</td>
<td>Hepatocyte nuclear factor</td>
</tr>
<tr>
<td>HSH</td>
<td>Hypomagnesemia with secondary hypocalcemia</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
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<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<tr>
<td>IPF</td>
<td>Insulin promotor factor</td>
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<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
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<tr>
<td>Mg</td>
<td>Magnesium</td>
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<td>MNT</td>
<td>Medical nutrition therapy</td>
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<td>MODY</td>
<td>Maturity onset of diabetes of young</td>
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<tr>
<td>NDDG</td>
<td>National Diabetes data group</td>
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<tr>
<td>NPDR</td>
<td>Non proliferative Diabetic retinopathy</td>
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<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PDR</td>
<td>proliferative Diabetic retinopathy</td>
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<tr>
<td>PG</td>
<td>Plasma glucose</td>
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<tr>
<td>PPBP</td>
<td>Pro-platelet basic protein</td>
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<tr>
<td>PTH</td>
<td>Para thyroid hormone</td>
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<tr>
<td>RDA</td>
<td>Recommended daily requirement</td>
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<tr>
<td>SGLT2</td>
<td>Sodium–glucose cotransporter 2</td>
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<tr>
<td>SU</td>
<td>Sulphonylureas</td>
</tr>
<tr>
<td>TAL</td>
<td>Thick ascending loop of Henle</td>
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<tr>
<td>TRPM6</td>
<td>Transient receptor potential melastatin 6</td>
</tr>
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<td>TRPM7</td>
<td>Transient receptor potential melastatin 7</td>
</tr>
<tr>
<td>TZDs</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>UKPD</td>
<td>U.K prospective Diabetes study</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>WHO</td>
<td>World health organization</td>
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<td>ZnT8</td>
<td>Zinc transporter 8</td>
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Introduction

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in Insulin secretion, insulin action or both the effect of diabetes mellitus include long term damage, dysfunction and failure of various organs, eyes, kidneys, nerves and heart and blood vessels. *(Bennett et al., 2005)*

Diabetic peripheral neuropathy (DPN) is a diabetes mellitus (DM) induced disorder of the peripheral nervous system *(Deli et al., 2014)* and is characterized by the pain and loss of sensation due to symmetrical degeneration of distal peripheral nerves. The symptoms will deteriorate with the progression, which may result in diabetic ulcers or even no traumatic amputation.

Statistics revealed that the incidence of DPN was as high as 30%, 60%, and 90% at 5, 10, and 20 years after diagnosis of DM, and foot injury had occurred in 50% of DPN patients when they were asymptomatic. *(Boulton et al., 2005)*

The incidence of neuropathy is now estimated to be about 8% in new cases of DM, and neuropathy will be a lifelong disease in more than 50% of DM patients, which is about 4 times the figure (12.3%) in DM patients in 2001. *(Tesfaye et al., 2012)*

Recently there has been an emerging interest regarding the important roles played by magnesium in various cell processes in the body. *(Hans et al., 2002)*
Magnesium is an essential element and has a fundamental role in carbohydrate metabolism in general and in Insulin action in particular. Magnesium is a cofactor in both glucose transport mechanism of the cell membranes and for various intracellular enzymes involved in the carbohydrate oxidation. The concentration of magnesium in serum of healthy people is constant However 25 to 39% of diabetic people have low concentrations of serum magnesium. Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes as well as on the evolution of complications such as retinopathy, arterial atherosclerosis and nephropathy. (Grafton et al., 1992)

Studies have shown that magnesium levels are lower in patients with diabetes compared with nondiabetic controls. (Limaye et al., 2011)

The association of hypomagnesaemia with poor glycemic control and also with various long-term complications of diabetes mellitus have been reported. (Pham et al., 2007)
Aim of the work

The aim of the work is to study the plasma Magnesium status and its relation to diabetic neuropathy in patients with Type 2 Diabetes mellitus.
Diabetes mellitus

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance, as a result of lack of insulin, defective insulin action, or both (Sicree et al., 2006).

BIOCHEMICAL BACKGROUND OF DIABETES MELLITUS

A regular energy source is a prerequisite for every cell to function in the human body. Glucose is the body’s primary energy source, which circulates in the blood as a mobilizable fuel source for cells (Piero et al., 2006) Insulin is a pancreatic hormone responsible for blood glucose level regulation. The hormone binds to its receptor sites on peripheral side of the cell membranes. It affords entry of glucose into respiring cells and tissues via requisite channels. Insulin stimulates catabolism on glucose into pyruvate through glycolysis. It also upregulates glycogenesis from excessive cytosolic glucose and lipogenesis from excessive cytosolic acetyl-COA. These metabolic events are antagonistic to metabolic events triggered by the hormone glucagon. When glucose levels are at or below threshold, glucose stays in the blood instead of entering the cells (Belinda, 2004).

The body attempts to arrest hyperglycemia, by drawing water out of the cells and into the bloodstream. The excess sugar is excreted in the urine. This is why diabetics present with constant thirst, drinking large amounts of water, and polyuria as the cells try to get rid of the extra glucose. This subsequently leads to glucosuria (Piero, 2006).

As hyperglycemia prolongs, the body cells are devoid of glucose due to the lack of insulin. This forces the cells to seek alternative mobilizable energy sources. In this regard, the cells turn to fatty acids stored in adipose tissue. The fats are not fuel sources for the red blood
cells, kidney cortex and the brain. The red blood cells lack mitochondria in which beta-oxidation pathway rests. The fatty acids cannot pass the blood-brain barrier. To avail energy to such cells and tissues, the acetyl-CoA arising from catabolism of fatty acids is diverted to ketogenesis to generate ketone bodies, which can serve as alternative fuel sources for such cells and tissues. These ketone bodies are also passed in the urine, thereby leading to ketonuria, which characterizes diabetes mellitus. Build up of ketone bodies in the blood produces ketosis. Ketone bodies are acidic in nature and therefore, their build up in blood lowers blood pH, leading to acidosis. A combination of ketosis and acidosis lead to a condition called ketoacidosis. If left untreated, ketoacidosis leads to coma and death (Belinda, 2004).

**Classification of Diabetes Mellitus:**

If any characteristic can define the new intentions for DM classification, it is the intention to consolidate etiological views concerning DM. The old and confusing terms of insulin-dependent (IDDM) or non-insulin-dependent (NIDDM) which were proposed by WHO in 1980 and 1985 have disappeared and the terms of new classification system identifies four types of diabetes mellitus:

1. **Type 1 diabetes** (due to b-cell destruction, usually leading to absolute insulin deficiency).

2. **Type 2 diabetes** (due to a progressive insulin secretory defect on the background of insulin resistance).

3. **Gestational diabetes mellitus** (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes).
4- **Specific types** of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation) *(ADA, 2014)*.

1) **Type 1 Diabetes:**

   - **Immune-Mediated Diabetes:**

     this form previously called “insulin- dependent diabetes” or “juvenile-onset diabetes” accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic b-cells. Autoimmune markers include: islet cell autoantibodies, autoantibodies to insu- lin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phospha- tases IA-2 and IA-2b, and autoantibodies to zinc transporter 8 (ZnT8). Type 1 di- abetes is defined by the presence of one or more of these autoimmune markers. The disease has strong HLA associations with linkage to the DQA and DQB genes. These HLA-DR/DQ alleles can be either predisposing or protective. *(Dabelea et al., 2014)*.

     The rate of B-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Children and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient B- cell function to prevent ketoacidosis for many years, such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-
peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. Autoimmune destruction of B-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis. These patients are also prone to other autoimmune disorders such as Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, vitiligo, celiac disease, autoimmune hepatitis, myasthenia gravis, and pernicious anemia. (*Sorensen, 2013*).

- **Idiopathic Diabetes:**

  Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for B-cell autoimmunity. (*Ziegler et al., 2013*).

2) **Type 2 Diabetes:**

This form previously referred to as “non-insulin-dependent diabetes” or “adult-onset diabetes,” accounts for 90–95% of all diabetes. Type 2 diabetes encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. At least initially and often throughout their lifetime, these individuals may not need insulin treatment to survive. There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction
of B-cells does not occur and patients do not have any of the other known causes of diabetes. Most, but not all, patients with type 2 diabetes are obese. Obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.\cite{Araneb et al., 2014}.

Ketoacidosis seldom occurs spontaneously in type 2 diabetes when seen it usually arises in association with the stress of another illness such as infection. Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice the classic diabetes symptoms. Nevertheless, such patients are at an increased risk of developing macrovascular and microvascular complications.\cite{Hsu et al., 2013}.

Whereas patients with type 2 diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their B-cell function been normal. Thus insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM, in those with hypertension or dyslipidemia, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood.\cite{Griffin et al., 2011}.
• **Certain medications:**

  Such as glucocorticoids, thiazide diuretics, and atypical anti-psychotics are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis (Erickson *et al.*, 2012).

**3) Gestational diabetes mellitus:**

  For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

  The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, resulting in an increase in the number of pregnant women with undiagnosed type 2 diabetes. Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes at their initial prenatal visit, using standard diagnostic criteria. Women with diabetes in the first trimester would be classified as having type 2 diabetes. GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes. *(Lawrence *et al.*, 2008).*

**4) Monogenic Diabetes Syndromes:**

  Monogenic defects that cause B-cell dysfunction such as neonatal diabetes and MODY represent a small fraction of patients with diabetes (5%). These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).

• **Neonatal Diabetes:**

  Diabetes diagnosed in the first 6 months of life has been shown not to be typical autoimmune type 1 diabetes. This so-called neonatal diabetes
can either be transient or permanent. The most common genetic defect causing transient disease is a defect on ZAC/HYAMI imprinting, whereas permanent neonatal diabetes is most commonly a defect in the gene encoding the Kir6.2 subunit of the B-cell K\textsubscript{ATP} channel. Diagnosing the latter has implications, since such children can be well managed with sulfonylureas.

- **MODY:**

  Maturity-Onset Diabetes of the Young MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor, referred to as hepatocyte nuclear factor (HNF)-1a. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the B-cell. The less common forms of MODY result from mutations in other transcription factors, including (HNF-4a, HNF-1b, insulin promoter factor (IPF)-1, andNeuroD1). *(Shield et al., 2009)*.

5) **Cystic Fibrosis–Related Diabetes:**

  CFRD is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults. Diabetes in this population is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure. Insulin insufficiency related to partial fibrotic destruction of the islet mass is the primary defect in CFRD. Genetically,
determined function of the remaining B-cells and insulin resistance associated with infection and inflammation may also play a role. While screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, there appears to be no benefit with respect to weight, height, BMI, or lung function compared with those with normal glucose tolerance <10 years of age. The use of continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD, but this likely needs more evidence. *(Kern et al., 2013)*

**Diagnosis of Diabetes mellitus:**

**Diagnostic tests for diabetes:**

Diabetes may be diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT).

**Table (1):** Criteria for the diagnosis of diabetes.

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<thead>
<tr>
<th>A1C ≥ 6.5%. The test should be performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L). In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.</td>
</tr>
</tbody>
</table>
The same tests are used to both screen and diagnose diabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios, in seemingly low-risk individuals who happen to have glucose testing, in symptomatic patients, and in higher-risk individuals whom the provider tests because of a suspicion of diabetes. The same tests will also detect individuals with prediabetes. *(The international Expert Committee, 2009)*.

**A1C:**

The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care (POC) A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of POC assays for diagnostic purposes may be problematic and is not recommended.

The A1C has several advantages to the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness. These advantages must be balanced by greater cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals.

It is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes.

**Age:**

The epidemiological studies that formed the framework for recommending A1C to diagnose diabetes only included adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should
be used to diagnose diabetes in children and adolescents (Nowicka, 2011).

**Race/Ethnicity:**

A1C levels may vary with patients race/ ethnicity. For example, African, Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and postglucose load glucose levels. A recent epidemiological study found that, when matched for FPG to African Americans (with and without diabetes) had higher A1C levels than non-Hispanic whites, but also had higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher. (Selvin, 2011).

**Hemoglobinopathies/Anemias:**

Interpreting A1C levels in the presence of certain hemoglobinopathies and anemia may be problematic. For patients with an abnormal hemoglobin but normal red cell turnover such as those with the sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. In conditions associated with increased red cell turnover such as pregnancy (second and third trimesters), recent blood loss or transfusion, erythropoietin therapy, or hemolysis only blood glucose criteria should be used to diagnose diabetes.

- **Fasting and 2-Hour Plasma Glucose:**

In addition to the A1C test, the FPG and 2-h PG may also be used to diagnose diabetes. The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of \( \geq 6.5\% \) identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of \( \geq 126 \text{ mg/dL (7.0 mmol/L)} \) (Murri et al., 2012).
Numerous studies have confirmed that compared with these A1C and FPG cut points, the 2-h PG value diagnoses more people with diabetes. Of note the lower sensitivity of A1C at the designated cut point may be offset by the test’s ease of use and facilitation of more widespread testing.

Unless there is a clear clinical diagnosis (e.g., a patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL) it is recommended that the same test be repeated immediately using a new blood sample for confirmation because there will be a greater like- lihood of concurrence. For example, if the A1C is 7.0% and a repeat result is 6.8% the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5%), but not FPG (≥126 mg/dL [7.0 mmol/L], that person should nevertheless be considered to have diabetes. (Picon et al., 2012).

Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is least likely for A1C, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples are collected at room temperature and not centrifuged promptly. Barring laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional should follow the patient closely and repeat the test in 3–6 months. (Genuths et al., 2003).
Criteria for testing for diabetes or prediabetes in asymptomatic adults:

1- Testing should be considered in all adults who are overweight (BMI \( \geq 25 \text{ kg/m}^2 \) or \( \geq 23 \text{ kg/m}^2 \) in Asian Americans) and have additional risk factors as:
   - Physical inactivity.
   - First-degree relative with diabetes.
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander).
   - Women who delivered a baby weighing 9 lb or were diagnosed with GDM.
   - Hypertension (\( \geq 140/90 \text{ mmHg} \) or on therapy for hypertension).
   - HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level \( \geq 250 \text{ mg/dL} \).
   - Women with polycystic ovary syndrome.
   - A1C \( \geq 5.7\% \), IGT, or IFG on previous testing.
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans).
   - History of CVD.

2- For all patients, particularly those who are overweight or obese, testing should begin at age 45 years.

3- If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status (Ackermann et al., 2011).
**Prediabetes:**

Is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and indicates an increased risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes and CVD. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

**Diagnosis:**

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus defined IFG as FPG levels (100 upto 125) mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels (140 upto 199) mg/dL (7.8–11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L). Hence, it is reasonable to consider an A1C range of (5.7 upto 6.4%) as identifying individuals with prediabetes (*Genuth, 2003*).

**Diagnoses of specific types of DM:**

**Diagnosis of Gestational diabetes mellitus:**

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large-scale 25,000 pregnant women, multinational cohort study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk.
These results have led to careful reconsideration of the diagnostic criteria for GDM. GDM diagnosis can be accomplished with either of two strategies:

1- “One-step” 75-g OGTT or

2- “Two-step” approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk leading some experts to debate and disagree on optimal strategies for the diagnosis of GDM. (Metzger et al., 2011).

**Screening for and diagnosis of GDM:**

- **One-step strategy:**

  Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

  The OGTT should be performed in the morning after an overnight fast of at least 8 h.

  The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

  - Fasting: 92 mg/dL (5.1 mmol/L).
  - 1 h: 180 mg/dL (10.0 mmol/L).
  - 2 h: 153 mg/dL (8.5 mmol/L).

- **Two-step strategy:**

  **Step 1:** Perform a 50-g GLT (nonfasting) with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.
If the plasma glucose level measured 1 h after the load is >140 mg/dL (7.8 mmol/L), proceed to a 100-g OGTT.

**Step 2:** The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

**Table (2):** Two-step strategy for Screening and diagnosis of GDM.

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Carpenter/Coustan</th>
<th>NDDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fasting</td>
<td>95 mg/dL (5.3 mmol/L)</td>
<td>105 mg/dL (5.8 mmol/L)</td>
</tr>
<tr>
<td>- 1 h</td>
<td>180 mg/dL (10.0 mmol/L)</td>
<td>190 mg/dL (10.6 mmol/L)</td>
</tr>
<tr>
<td>- 2 h</td>
<td>155 mg/dL (8.6 mmol/L)</td>
<td>165 mg/dL (9.2 mmol/L)</td>
</tr>
<tr>
<td>- 3 h</td>
<td>140 mg/dL (7.8 mmol/L)</td>
<td>145 mg/dL (8.0 mmol/L)</td>
</tr>
</tbody>
</table>

NDDG, National Diabetes Data Group.

*The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).*(Duran et al., 2014).

**Diagnosis of MODY:**

Readily available commercial genetic testing now enables a true genetic diagnosis. It is important to correctly diagnose one of the monogenic forms of diabetes because these children may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal treatment regimens and delays in diagnosing other family members *(Hatterssley et al., 2009)*
The diagnosis of monogenic diabetes should be considered in children with the following findings:

a) Diabetes diagnosed within the first 6 months of life.

b) Strong family history of diabetes but without typical feature of type 2 diabetes (non-obese, low-risk ethnic group).

c) Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and non-obese.

d) Diabetes with negative autoantibodies and without signs of obesity or insulin resistance.
Figure (1): Anti hyperglycemic therapy in type 2 diabetes.
Microvascular and Macrovascular Complications of Diabetes

Diabetes is a group of chronic diseases characterized by hyperglycemia. Modern medical care uses a vast array of lifestyle and pharmaceutical interventions aimed at preventing and controlling hyperglycemia. In addition to ensuring the adequate delivery of glucose to the tissues of the body, treatment of diabetes attempts to decrease the likelihood that the tissues of the body are harmed by hyperglycemia. overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). (Michael et al., 2008).

Microvascular Complications of Diabetes:

Diabetic neuropathy:

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.

The incidence of diabetic neuropathy is the highest among diabetic complications, and diabetic neuropathy develops early after the onset of diabetes.

The risk factors of diabetic neuropathy are hyperglycemia and its persistence

Hypertension, dyslipidemia , obesity, and cigarette smoking are also included in the risk factors (Hinder et al.,2012)
Pathological mechanism of diabetic neuropathy

The pathological mechanism of diabetic neuropathy cannot be explained with a single cause, and various hypotheses have been proposed (Table 2. These are roughly divided into metabolic, vascular, and neuroregeneration disorder hypotheses. (Yasuda et al., 2003)

Potential pathogenesis of diabetic neuropathy:

- Activation of polyol pathway
- Down-regulation of intracellular myoinositol
- Dysfunction of protein kinase C
- Down-regulation of intracellular cyclic AMP
- Inhibition of Na+/K+/ATPase
- Degradation of nitric oxide
- Advance of protein glycation
- Increase of free radical
- Disorder of polyunsaturated fatty acid synthesis
- Disorder of prostaglandin synthesis
- Action attenuation of a nerve growth factor
- Nerve blood flow degradation, nerve vascular resistance enhancement

Impairment of polyol pathway:

Altered peripheral nerve polyol metabolism has been implicated as a central factor in the pathogenesis of diabetic neuropathy. Aldose reductase converts glucose to sorbitol (such as polyol) using NADPH as a coenzyme. Sorbitol is further converted to fructose by sorbitol dehydrogenase using nicotinamide adenine dinucleotide (NAD+) as a coenzyme, constituting the bypass polyol pathway of glucose metabolism.
In hyperglycemia accompanying diabetes, the cellular glucose level rises independently from insulin, resulting in enhancement of aldose reductase activity, which elevates the intracellular sorbitol level and, subsequently, the intracellular osmotic pressure. This condition induces functional and structural abnormalities in tissue and cell (Yabe-Nishimura, 1998)

![Polyol Pathway](image)

**Figure (2)**: The polyol pathway consists of two-step metabolic pathway.

**Activation of protein kinase C:**

Hyperglycemia promotes the synthesis of an endogenous protein kinase C activator, diacylglycerol.

Actually, excess activation of β2-type protein kinase C in cardiovascular tissue in an animal diabetes model has been reported. Enhanced vascular protein kinase C is involved in permeability, the contractile force, and the differentiation and proliferation of cells.

Excess protein kinase C activation induces ischemia in peripheral nerves through increased vascular permeability and thickening of the basement membrane and causes neuropathy. (Geraldes, 2010)

**Increase in oxidative stress:**

Hyperglycemia enhances NADPH oxidase expression and the endothelial nitric oxide synthase uncoupling reaction in vascular endothelial cells, through which superoxide

is excessively produced. Nitric oxide is essential for endothelial
cell function.

Excess superoxide decreases NO by binding to it, and this binding reaction promotes the secondary synthesis of ROS, such as peroxynitrite and hydroxyl radicals. ROS have strong cytotoxicity, and an increase in ROS induces neurosis (Vincent et al., 2004)

Other factors:

Bone marrow-derived proinsulin-and tumor necrosis factor-α (TNFα)-producing cells appear in a diabetic state. These cells enter the dorsal root ganglions and peripheral nerves (axon and Schwann cells) and induce cell fusion.

Fused cells impair Ca2+ homeostasis and induce apoptosis. The appearance of these abnormal cells is resolved by insulin treatment.

It has also been clarified that the abnormality of intracellular signal transmission systems in nerve tissues including that of insulin signals is closely involved in abnormal peripheral nerve function.

The peripheral neuropathy developmental mechanism may be a new target of neuropathy treatment, other than blood glucose control. (Terashima et al., 2012)

Classification of diabetic neuropathy. (Llewelyn, 2003)

Generalised neuropathies:

- **Symmetric distal polyneuropathy** (with or without autonomic neuropathy): also referred to as chronic sensorimotor neuropathy or diabetic sensorimotor polyneuropathy. This is the most commonly encountered type of neuropathy in people with diabetes.

- **Hyperglycaemic neuropathy**: also referred to as acute sensory neuropathy. This is characterised by a symmetrical polyneuropathy of acute or sub-acute
onset, with severe sensory symptoms, which may involve pain (of various types), paraesthesia or numbness. It is rare, but usually occurs following an episode of glycaemic instability, such as the initiation of insulin or rapid correction of long-term hyperglycaemia. Symptoms are often most prominent in bed at night. This form of neuropathy usually resolves within twelve months.

- **Acute painful sensory neuropathy** variants, e.g. insulin neuritis

**Focal and multifocal neuropathies:**

- **Cranial neuropathies:** e.g. sixth nerve palsy and less often a third nerve palsy, with full recovery usually within three to six months

- **Focal limb neuropathies:** secondary to compression or entrapment, e.g. carpal tunnel syndrome or ulnar neuropathy

- **Thoracolumbar radiculoneuropathy:** generally unilateral pain and hyperaesthesiae involving a focal area on the chest or abdomen with an abrupt onset and spontaneous recovery over a few months (seen in people with both type 1 and type 2 diabetes)

- **Lumbosacral radiculoplexus neuropathy:** also referred to as diabetic amyotrophy, femoral neuropathy or Bruns-Garland syndrome. This form of neuropathy primarily affects the motor nerves of the proximal muscles of the legs. Usually seen in patients who have type 2 diabetes, are older and are male. Characterised by severe aching or burning pain that affects the lower back, buttocks and thighs, that is often worse at night.

**Clinical features of diabetic neuropathy:**

The manifestation of subjective symptoms of diabetic neuropathy is the earliest among complications of diabetic patients, and the incidence is the highest. Its pathology starts with numbness and sensory disturbance of
the four limbs, and manifests various clinical pictures, such as autonomic neuropathy and mononeuropathy (Rutkove, 2009)

Sensory symptoms accompanying diabetic neuropathy, such as pain and numbness, distress patients, and subsequent hypoesthesia leads to the primary cause of lower limb amputation due to diabetic gangrene.

In diabetic neuropathy, sensory neuropathy is dominant, but subjective sensory symptoms generally do not extend to the proximity from the ankle joint in many cases, and its onset is associated with numbness and pain of the toes and sole. The fingers are asymptomatic in this stage, showing “tabi (socks with the big toe separated)-type” sensory symptoms, and this pattern is frequently noted in routine medical practice. In the late stage, “glove-socks-type” sensory abnormality manifests. Diabetic neuropathy cases with the expansion of sensory symptoms to the precordium and parietal region have been reported.

This neurologic manifestation pattern is derived from the advancement pattern of axon degeneration, and it occurs because the nerves in the lower limbs are longer than those in the upper limbs. Since diabetic neuropathy progresses slowly, the divergence between the upper and lower limb symptoms may continue for a relatively long time. Regarding sensory disturbance, in diabetic neuropathy in which positive symptoms of the feet, such as numbness and pain, develop in the early to middle stage and negative symptoms, such as hypoesthesia, develop in the terminal stage.

Generally, an abnormal autonomic nerve function appears from the early stage and then autonomic nerve symptoms may manifest, but the manifestation of motor neuropathy is late. Diverse symptoms of autonomic neuropathy markedly reduce the Quality of Life (QOL) of patients.
**Clinical features of diabetic neuropathy:**

- Constipation, diarrhea, gastric hypokinesia (dull feeling in the stomach)
- Dizziness (orthostatic hypotension)
- Silent myocardial infarction: Myocardial infarction or angina without chest pain
- Dysuria
- Erectile dysfunction
- Non-symptomatic hypoglycemia

Since diabetic neuropathy progresses slowly, the divergence between the upper and lower limb symptoms may continue for a relatively long time. Regarding sensory disturbance, in diabetic neuropathy in which positive symptoms of the feet, such as numbness and pain, develop in the early to middle stage and negative symptoms, such as hypoesthesia, develop in the terminal stage, generally, an abnormal autonomic nerve function appears from the early stage and then autonomic nerve symptoms may manifest, but the manifestation of motor neuropathy is late (Table c).

**Table (3): Severity grade of diabetic neuropathy. (Tesfaye et al., 2010)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No neuropathy</td>
</tr>
<tr>
<td>N1</td>
<td>Asymptomatic neuropathy</td>
</tr>
<tr>
<td>N1a</td>
<td>Abnormal of examination without neuropathy symptom</td>
</tr>
<tr>
<td>N1b</td>
<td>Abnormal of examination with neurologic signs without neuropathy symptom</td>
</tr>
<tr>
<td>N2</td>
<td>Symptomatic neuropathy</td>
</tr>
<tr>
<td>N2a</td>
<td>Abnormal of examination with neurologic signs with neuropathy symptom</td>
</tr>
<tr>
<td>N2b</td>
<td>N2a plus weakness of ankle dorsiflexion</td>
</tr>
<tr>
<td>N3</td>
<td>Disabling neuropathy</td>
</tr>
</tbody>
</table>
Diagnosis of diabetic neuropathy:

Diabetic neuropathy can be diagnosed when the patient has been diagnosed with diabetes and other diseases causing polyneuropathy have been ruled out.

Diseases required to be differentiated are shown in Table 7. There are no diabetic neuropathy-specific symptoms or tests, and no diagnostic criteria with international consensus have been established. Diabetic neuropathy has to be comprehensively diagnosed based on various neurologic manifestations and test results.

The symptom characteristic of diabetic neuropathy is bilateral symmetric polyneuropathy with dominance on the distal side, and it more frequently develops from the lower limbs, particularly from the feet and crura, than from the upper limbs. (Rathur et al., 2005)

Table (4). Diagnosis of diabetic neuropathy

<table>
<thead>
<tr>
<th>1. Ongoing diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. There is no disorder to cause neurological symptom besides diabetes mellitus</td>
</tr>
<tr>
<td>3. Symmetric symptom (spontaneous pain, paresthesia, hypaesthesia, anesthesia)</td>
</tr>
<tr>
<td>4. Attenuation of reflexes in the ankle or knee</td>
</tr>
<tr>
<td>5. Pallesthesia</td>
</tr>
<tr>
<td>6. Abnormal of electrophysiological neurologic function tests</td>
</tr>
<tr>
<td>7. Symptoms of autonomic neuropathy</td>
</tr>
</tbody>
</table>

The peripheral neuropathy signs important to objectively diagnose the disease stage of diabetic neuropathy are summarized below:

- **Reduction/loss of Achilles tendon reflex:**

  Since this symptom is frequently observed even in patients showing no symptoms, it is very important to identify diabetic neuropathy in the asymptomatic stage.
A test in a kneeling posture (Babinski position), in which loss of the reflex can be readily observed, is recommended.

Many cases of diabetic neuropathy show bilateral abnormality and apparent laterality is a sign of lumbar vertebral disease.\textit{(Shehab et al., 2012)}

- **Pallesthesia:**

  The impairment of vibration perception threshold is used to early diagnosis of peripheral neuropathy.

  An aluminum 128-Hz tuning folk is standard for the examination of pallesthesia. Since the vibration of a tuning folk exponentially attenuates, the time required to reach the threshold is almost constant when it is hit with a force stronger than a specific level. The base of a vibrating tuning fork was placed on the hallux of the patient. The examiner asks the patients first if the vibration is perceived. Next, the patient should inform the examiner when the vibration stops.

  The diagnosis of diabetic neuropathy is to be suspected if the vibration duration sensation is less than 10 seconds\textit{(Manivannan et al., 2009)}

- **Peripheral nerve conduction velocity test:**

  In this test, peripheral nerves are stimulated with electricity through the skin, and the nerve conduction velocity and waveform are analyzed based on the reactions to diagnose and treat diseases.

  When neuropathy occurs, the nerve conduction velocity decreases.\textit{(Kong et al., 2008)}

- **Monofilament:**

  Activity of nerves perceiving tactile and pressure sensations is investigated by attaching a monofilament to the foot. Perception
decreases in diabetic neuropathy patients. (Perkins et al., 2010)

- **Coefficient of respiratory heart rate variability:**

  This is an autonomic nerve function test. Variation in the pulse with deep breaths compared to that on rest is investigated using electrocardiography. Normally, pulse variation increases on deep breathing, but this variation decreases when autonomic nerves are impaired. (Astrup et al., 2006)

**Diabetic retinopathy:**

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for ~ 10,000 new cases of blindness every year in the United States alone. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K Prospective Diabetes Study (UKPDS), and most patients with type 1 diabetes develop evidence of retinopathy within 20 years of diagnosis, retinopathy begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes. (Fongs et al., 2004).

**Mechanism of diabetic retinopathy:**

a) Cells are thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs). In animal models, these substances have also been associated with formation of microaneurysms and pericyte loss. evaluations of AGE inhibitors are underway. (Fongs et al., 2004).

b) Oxidative stress may also play an important role in cellular injury from hyperglycemia. High glucose levels can stimulate free radical
production and reactive oxygen species formation. Animal studies have suggested that treatment with antioxidants, such as vitamin E, may attenuate some vascular dysfunction associated with diabetes, but treatment with antioxidants has not yet been shown to alter the development or progression of retinopathy or other microvascular complications of diabetes. (Fongs et al., 2004).

c) Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway. This pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. In animal models, sugar alcohol accumulation has been linked to microaneurysm formation, thickening of basement membranes, and loss of pericytes. Treatment studies with aldose reductase inhibitors, however, have been disappointing. (Gabby et al., 2004).

d) Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy (Aiello et al., 2004).
Diabetic retinopathy:

Diabetic retinopathy is generally classified as either background or proliferative. It is important to have a general understanding of the features of each to interpret eye examination reports and advise patients of disease progression and prognosis.

1) Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as “dots” and therefore are frequently referred to as “dot hemorrhages.” Hard exudates are caused by lipid deposition that typically occurs at the margins of hemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear.

2) as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. The appearance is one of grayish retinal areas. Retinal edema may require intervention because it is sometimes associated with visual deterioration. (Watkins et al., 2003).

3) Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina (“cotton wool spots”) can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial. (Watkins et al., 2003).
**Diabetic nephropathy:**

Diabetic nephropathy is the leading cause of renal failure in the United States. It is defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or “microalbuminuria.”

Microalbuminuria is defined as albumin excretion of 30–299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type 1 and type 2 diabetes.

As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes. *(Gross et al., 2005).*

The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies), and other changes. The underlying mechanism of injury may also involve some or all of the same mechanisms as diabetic retinopathy.*(Adler et al., 2003).*

Screening for diabetic nephropathy or microalbuminuria may be accomplished by either a 24-hour urine collection or a spot urine measurement of microalbumin. Measurement of the microalbumin-to-creatinine ratio may help account for concentration or dilution of urine, and spot measurements are more convenient for patients than 24-hour urine collections. It is important to note that falsely elevated urine protein levels may be produced by conditions such as urinary tract infections exercise, and hematuria.*(Steven RJ 2003).*

Initial treatment of diabetic nephropathy, as of other complications of diabetes, is prevention. Several studies have demonstrated
renoprotective effects of treatment with ACE inhibitors and angiotensin receptor blockers (ARBs), which appear to be present independent of their blood pressure lowering effects, possibly because of decreasing intraglomerular pressure. Both ACE inhibitors and ARBs have been shown to decrease the risk of progression to macroalbuminuria in patients with microalbuminuria by as much as 60–70%. These drugs are recom- mended as the first-line pharmacological treatment of microalbuminuria, even in patients without hypertension. *(Rossing K 2003).*

Similarly, patients with macroalbuminuria benefit from control of hypertension. Hypertension control in patients with macroalbuminuria from diabetic kidney disease slows decline in glomerular filtration rate (GFR). Treatment with ACE inhibitors or ARBs has been shown to further decrease the risk of progression of kidney disease, also independent of the blood pressure–lowering effect.

Combination treatment with an ACE inhibitor and an ARB has been shown to have additional renoprotective effects. It should be noted that patients treated with these drugs (especially in combination) may experience an initial increase in creatinine and must be monitored for hyperkalemia. Considerable increase in creatinine after initiation of these agents should prompt an evaluation for renal artery stenosis. *(Gross et al., 2005).*

**Macrovascular Complications of Diabetes:**

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of
arteries, Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction.\(^{(Boyle, 2007)}\).

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes.\(^{(Beckman, 2002)}\).

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes. In fact, CVD accounts for the greatest component of health care expenditures in people with diabetes.\(^{(Paterson et al., 2007)}\).

Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also
act to promote CVD. Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischemic disease, stroke, and death. Among people with type 2 diabetes, women may be at higher risk for coronary heart disease than men. The presence of microvascular disease is also a predictor of coronary heart events. (Avogaro et al., 2007).

Diabetes is also a strong independent predictor of risk of stroke and cerebro-vascular disease, as in coronary artery disease. Patients with type 2 diabetes have a much higher risk of stroke, with an increased risk of 150–400%. Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes.

There has not been a large, long-term, controlled study showing decreases in macrovascular disease event rates from improved glycemic control in type 2 diabetes. Modification of other elements of the metabolic syndrome, however, has been shown to very significantly decrease the risk of cardiovascular events in numerous studies. Blood pressure lowering in patients with type 2 diabetes has been associated with decreased cardiovascular events and mortality. (Beckman et al., 2002).

The UKPDS was among the first and most prominent study demonstrating a reduction in macrovascular disease with treatment of hypertension in type 2 diabetes. There is additional benefit to lowering blood pressure with ACE inhibitors or ARBs. Blockade of the renin-angiotensin system using either an ACE inhibitor or an ARB reduced cardiovascular endpoints more than other antihypertensive agents. It should be noted that use of ACE inhibitors and ARBs also may help slow progression of diabetic microvascular kidney disease. Multiple drug therapy, however, is generally required to control hypertension in patients with type 2 diabetes. (Lindholm et al., 2002).
Another target of therapy is blood lipid concentration. Numerous studies have shown decreased risk in macrovascular disease in patients with diabetes who are treated with lipid-lowering agents, especially statins. These drugs are effective for both primary and secondary prevention of CVD, but patients with diabetes and preexisting CVD may receive the highest benefit from treatment. It should be noted these beneficial effects of lipid and blood pressure lowering are relatively well proven and likely also extend to patients with type 1 diabetes. In addition to statin therapy, fibric acid derivates have beneficial effects. They raise HDL levels and lower triglyceride concentrations and have been shown to decrease the risk of MI in patients with diabetes. (Athan et al., 2005).
Role of Cellular Magnesium in Human Diseases

Magnesium (Mg2+) is integral to cellular and systemic human physiology and its ability to function. Yet, this mineral is often overlooked in deference to other cations such as calcium or iron. As the fourth most abundant element in the human body, magnesium accounts for ~25 grams, most of which is stored within bones (50%) and soft tissues (47%). *(Payandeh et al., 2013)*

**Daily magnesium intake:**

The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/kg/day, lower than the previous recommendation of 6-10 mg/kg/day. The daily requirement is higher in pregnancy, lactation and following debilitating illness. Recent dietary surveys show that the average intake in many western countries is less than the RDA. *(Saris et al., 2000)*

Magnesium intake depends on the magnesium concentration in drinking water and food composition. Magnesium is plentiful in green leafy vegetables such as spinach and broccoli (which are rich in magnesium-containing chlorophyll), cereal, grain, nuts, banana, and le- gumes. Fruits, meats, chocolates, and fish have intermediate values, and dairy products are poor in magnesium. The average magnesium intake of a normal adult is approximately 12 mmol/day. In addition to this, approximately 2 mmol/day of magnesium is secreted into the intestinal tract in bile and pancreatic and intestinal juices. From this pool 6 mmol (about 30%) is absorbed giving a net absorption of 4 mmol/day. *(Saris, 2000).*
Whole body magnesium homeostasis:

Magnesium is an essential intracellular cation. Nearly 99% of the total body magnesium is located in bone or the intracellular space. Magnesium is a critical cation and cofactor in numerous intracellular processes. It is a cofactor for adenosine triphosphate, an important membrane stabilizing agent, required for the structural integrity of numerous intracellular proteins and nucleic acids, a substrate or cofactor for important enzymes such as adenosine triphosphatase, guanosine triphosphatase, phospholipase C, adenylate cyclase, and guanylate cyclase, a required cofactor for the activity of over 300 other enzymes, a regulator of ion channels, an important intracellular signaling molecule, and a modulator of oxidative phosphorylation. Finally, magnesium is intimately involved in nerve conduction, muscle contraction, potassium transport, and calcium channels. Because turnover of magnesium in bone is so low, the short-term body requirements are met by a balance of gastrointestinal absorption and renal excretion. Therefore, the kidney occupies a central role in magnesium balance. Factors that modulate and affect renal magnesium excretion can have profound effects on magnesium balance. In turn, magnesium balance affects numerous intracellular and systemic processes. (Rouffignac et al., 1993).

Intestinal absorption of magnesium:

About 30-40% of the dietary magnesium content is absorbed, mainly in the jejunum and ileum. Fractional intestinal absorption of magnesium is inversely related to intake, 65% at low intake and 11% at high intake. Most of the absorption occurs in the jejunum, ileum, and colon. At normal intake, absorption is primarily passive. During low magnesium intake a saturable component of magnesium absorption can be demonstrated. Factors
controlling magnesium absorption are not well understood. Studies suggest a role for parathyroid hormone (PTH) in regulating magnesium absorption. Intestinal magnesium absorptive efficiency is stimulated by 1,25-dihydroxyvitamin D (1,25(OH)2D) and can reach 70% during magnesium deprivation, but the role of vitamin D and its active metabolite 1,25(OH)2D is controversial. (Swaminathan et al., 2003).

**Magnesium reabsorption in the kidney:**

The kidney plays a major role in magnesium homeostasis and the maintenance of plasma magnesium concentration. Urinary magnesium excretion normally matches net intestinal absorption and is ~4 mmol/d (100 mg/ day). Regulation of serum magnesium concentration is achieved mainly by control of renal magnesium reabsorption. Under normal circumstances, when 80% of the total plasma magnesium is ultrafiltrable, 84 mmol of magnesium is filtered daily and 95% of this reabsorbed, leaving about 3-5 mmol to appear in the urine. Under normal circumstances, approximately only 20% of filtered magnesium is reabsorbed in the proximal tubule, whereas 60% is reclaimed in the cortical thick ascending limb (TAL) of loop of Henle and the remaining 5-10% in the distal convoluted tubule (DCT). (Yu AS, 2001).

Magnesium transport in the proximal tubule appears to be primarily a uni-directional passive process depending on sodium/water reabsorption and the luminal magnesium concentration. Magnesium transport in the TAL is directly related to sodium chloride reabsorption and the positive luminal voltage in the segment. (Rouffignac et al., 1994).

In the TAL, approximately 25% of the filtered sodium chloride is re-absorbed through the active transcellular transport (sodium chloride-potassium transport) and passive para-cellular diffusion. This creates a
favorable luminal positive potential at the TAL where most of the magnesium is reabsorbed. Magnesium reabsorption in the TAL occurs via a paracellular route that requires both a lumen-positive potential, created by NaCl reabsorption, and the tight- junction protein, claudin-16/paracellin-1.(Konard et al., 2003).

The mutations in claudin-16/paracellin-1 are responsible for familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC). Magnesium reabsorption in the TAL is increased by PTH but inhibited by hypercalcemia, both of which activate the calcium sensing receptor (CaSR) in this nephron segment. Magnesium re- absorption in the DCT is active and transcellular .(Bringhurst et al., 2008).

The active transcellular transport of magnesium in the DCT was similarly enhanced by the realization that defects in transient receptor potential melastatin 6 (TRPM6) cause hypomagnesemia with secondary hypocalcemia (HSH). This channel regulates the apical entry of magnesium into epithelia and alters whole-body magnesium homeostasis by controlling urinary excretion. TRPM6 is regulated at the transcriptional level by acid-base status, 17β-estradiol, and both FK506 and cyclosporine. The molecular identity of the protein responsible for the baso- lateral exit of magnesium from the epithelial cell remains unidentified (Alexaander et al., 2008).

Factors affecting tubular reabsorption of magnesium:

- Plasma magnesium concentration/magnesium status Glomerular filtration rate.
- Volume status.
- Hormones.
- Parathyroid hormone, Calcitonin, Antidiuretic hormone, Insulin.
• Phosphate depletion.
• Acid base status.
• Hypercalcemia.
• Diuretics.
• Miscellaneous factors. \((\text{Noronha, et al., 2002})\).

The plasma magnesium concentration is a major determinant of urinary magnesium excretion. Hypomagnesemia is associated with an increase in magnesium excretion due to an increase in the filtered load and reduced reabsorption in TAL.

**Assessment of magnesium status:**

At present, there is no simple, rapid, and accurate laboratory test to indicate the total body magnesium status. The most commonly used method for assessing magnesium status is the serum magnesium concentration. The total serum magnesium concentration is not the best `z` method to evaluate magnesium status as changes in serum protein concentrations may affect the total concentration without necessarily affecting the ionized fraction or total body magnesium status. The correlation between serum total magnesium and total body magnesium status is poor.\((\text{Du Bose et al., 2002})\).

Measurement of ultrafiltrable magnesium may be more meaningful than the total magnesium as it is likely to reflect ionized magnesium concentration, but methods are not available for routine use. In the last few years, ion selective electrodes for magnesium have been developed and several commercial analyzers are now available for the measurement of ionized magnesium concentration. Measurement of ionized magnesium has been found to be useful in several clinical situations. In summary, no single method is satisfactory to assess magnesium status. The simplest, most
useful, and readily available tests are the measurement of serum total magnesium and the magnesium tolerance test. Ionized magnesium measurement may become more readily available with the development of reliable analyzers. *(Saris et al., 2000)*

**Hypomagnesemia and magnesium deficiency:**

Magnesium plays a role in the structure of bones and teeth, acts as a cofactor for more than 300 enzymes in the body, including binding to ATP for kinase reactions, and affects permeability of excitable membranes and neuromuscular transmission as well as nervous tissue electrical potential) *(Roach, 2003)*

Magnesium is crucial for controlling ECF volume, Na+/K+-ATPase and cellular uptake of solutes, as a driving force for secondary active transport, and neuromuscular transmission *(Roach et al., 2003).*

Certain groups are at higher risk for magnesium deficiencies, due to underlying medical conditions or insufficient consumption. Such populations include patients with gastrointestinal diseases, type II diabetes, older adults, and alcoholics. People with Crohn’s disease and celiac disease encounter longitudinal magnesium depletion in their gastrointestinal tract, while small intestinal bypass can lead to malabsorption, which further aggravates magnesium loss *(Nadler, 2000)*

The terms hypomagnesemia and magnesium deficiency are commonly used interchangeably. However, total body magnesium depletion can be present with normal serum magnesium concentrations and there can be significant hypomagnesemia without total body deficit. Hypomagnesemia is frequently undetected. Measurement of serum magnesium concentration in 1,000 samples received for electrolyte determination showed that only 10% of the hypomagnesaemic patients
had magnesium requested. Thus, it has been suggested that magnesium should be determined routinely in all acutely ill patients especially in those with conditions, diseases, or treatment that may predispose to magnesium deficiency. (*Ghamdi et al., 1994*).

**Etiology and pathogenesis of hypomagnesemia:**

Hypomagnesemia may result from one or more of the following mechanisms: redistribution, reduced intake, reduced intestinal absorption, increased gastrointestinal loss, and increased renal loss.

1) **Hypomagnesemia due to redistribution:**

Hypomagnesemia due to the shift of magnesium from extracellular fluid into cells or bone is seen in refeeding of starved patients (refeeding syndrome), during treatment of metabolic acidosis, and in hungry bone syndrome which is seen after parathyroidectomy or in patients with diffuse osteoblastic metastases. (*Swaminathan et al., 2003*).

2) **Gastrointestinal causes:**

Magnesium deficiency entirely due to reduced dietary intake in otherwise healthy subjects is very uncommon. Hypomagnesemia may be seen in patients who are maintained on magnesium-free intravenous fluids or total parenteral nutrition, especially in those patients who have a marginal or reduced serum magnesium to start off with. An inherited disorder of isolated magnesium malabsorption associated with hypocalcemia, tetany, and seizures has been described in infants as well as in older individuals. Children with this condition usually present at 4-5 weeks of age with generalized convulsions associated with protein losing enteropathy, hypoalbuminaemia, and anasarca. The disorder is caused by a mutation in the TRPM6 gene which codes for an ion channel, resulting in defective carrier mediated transport in the small intestine. (*Konrad, 2003*).
3) Renal causes:

Proximal tubular magnesium reabsorption is proportional to sodium reabsorption, and a reduction in sodium reabsorption during long-term intravenous fluid therapy may result in magnesium deficiency.

a-Renal disease:

Hypomagnesemia is occasionally observed in chronic renal failure due to an obligatory renal magnesium loss. It is also seen during the diuretic phase of acute renal failure, in post-obstructive diuresis and after renal trans-plantation, (Yu ASL, 2000).

b-Inherited disorders:

Several different congenital disorders of renal tubular reabsorption of magnesium have been described but there is no consensus on their classification. The classification, features and molecular defects in some of the syndromes.

c-Drugs:

A variety of drugs including antibiotics and chemo-therapeutic agents cause magnesium wasting. Loop diuretics inhibit magnesium transport in TAL and cause magnesium depletion, especially during long-term use. Short-term administration of thiazide diuretics which act on the DCT, where less that 5% of magnesium is absorbed, does not produce magnesium wasting. However, long term administration may produce substantial magnesium depletion due to secondary hyperaldosteronism, increased sodium load, and interaction with calcium metabolism. (Ellison, 2008).
Hypomagnesemia is a frequent complication of cisplatin treatment and may be acute or chronic. Cisplatin, for example, frequently causes magnesium wasting with hypocalciuria and hypokalemia, resembling Gitelman syndrome, a disease caused by defective electroneutral Na–Cl cotransporter in the DCT. Cisplatin increases the trans- epithelial voltage in the DCT, consistent with a ‘Gitelman-like’ effect. The incidence of hypomagnesemia increases with cumulative dose. In the acute phase, poor dietary intake and the use of diuretics are contributing factors. (*Panichpisal et al., 2006*).

**Clinical Features of Hypomagnesemia:**

Many patients with hypomagnesemia and magnesium deficiency remain asymptomatic. As magnesium deficiency is usually secondary to other disease processes or drugs, the features of the primary disease process may complicate or mask magnesium deficiency. Signs and symptoms of magnesium deficiency are usually not seen until serum magnesium decreases to 0.5 mmol/L or lower. Manifestations may depend more on the rate of development of magnesium deficiency and/or on the total body deficit rather than the actual serum magnesium concentration. (*Yu AS, 2000*).

**Hypomagnesemia and the cardiovascular system:**

Low magnesium intake has been linked to high blood pressure, arterial plaque build-up, calcification of soft tissues, cholesterol, and hardening of arteries. Additionally, inflammation from magnesium deficiency can also lead to increased production of reactive oxygen species, which can contribute to elevating blood pressure. In humans, specific magnesium-selective electrodes hooked up to patients with hypertension, ischemic heart disease, stroke, and atherosclerosis revealed
a significant decrease of serum/plasma ionized, but not total, magnesium, while in rat and rabbit models, dietary magnesium deficiency caused vascular remodeling associated with hypertension and atherosclerosis (Altura et al., 2010).

Carotid Intima Media Thickness (IMT), an index of atherosclerosis and associated with an increased risk for CVD, is improved in heart disease patients that were given magnesium supplementation. Additionally, the serum magnesium levels were found to inversely correlate with carotid IMT in HD patients. Hypomagnesaemia has also been linked to the development of atrial fibrillation following cardiac surgery. Intravenous magnesium supplementation can improve rate control in atrial fibrillation and help maintain sinus rhythm, while hypomagnesaemia increases the dose of digoxin required for rate control and lowers the threshold for digoxin-related arrhythmias (Khan et al., 2013)

**Hypomagnesemia and the neurological system:**

magnesium plays a key role in the activation of nervous system sympathetic activity. Magnesium deficiency has been shown to impair the affinity of serotonin and angiotensin II for their receptors in coronary vascular muscle, as well as affect depolarization-induced contractions by interfering with potassium in a competitive manner (Altura et al, 1982)

**Clinical manifestation:**

- mood disorders; anxiety & depression,
- neurodegenerative diseases, Parkinson’s disease,
- Convulsions.
- Muscle weakness, fasciculations, tremors.
- Vertigo, Nystagmus.
- Athetoid movements & choreiform movements
**Hypomagnesemia and the renal system:**

Numerous studies indicate that magnesium may play a protective role in vascular calcification via one of the following mechanisms:

1) magnesium inhibits formation of apatite crystals and forms smaller deposits that are more soluble;
2) magnesium functions as a calcium antagonist, which prevents calcium from entering cells.
3) magnesium restores balance between the expression of calcification promoters and inhibitors;
4) magnesium acts on CaSR and activates it, acting as calcimimetics that inhibit VSMC calcification (*M de Francisco, 2013*).

Deficient magnesium levels, while prevalent, are often undetected. This increases the risk for other diseases, including diabetes mellitus type 2, low bone mass, osteoporosis, vascular calcification and CKD.

**Hypomagnesemia and the respiratory system:**

Asthma is a pathological condition characterized by inflammation and narrowing of the respiratory airways. Therapeutically, the narrowing of the respiratory airways is resolved by inducing rapid bronchodilation, usually through the usage of β2-adrenergic receptor agonists (*Rowe et al., 2000*).

Magnesium can induce bronchial smooth muscle cell relaxation by inhibiting cytosolic calcium increase in the cells, or by inhibiting the release of histamine from mast cells or the release of acetylcholine from cholinergic nerve endings or by increasing the bronchodilator effect of β2-adrenergic agonist through changes in receptor affinity. Additionally, administration of magnesium sulfate has a stabilizing effect on the atria, attenuating the tachycardia that is usually observed following β2-adrenergic agonist intake (*Sellers, 2013*).
Hypomagnesemia and the skeletal/muscular systems:

Tight magnesium control is essential for healthy bone growth. In the bones, over half of the whole body’s magnesium store is found (60%), with an additional 30-40% contained in skeletal muscles and soft tissues, and just 1% in the extracellular fluid. A depletion of magnesium can lead to endothelial dysfunction, which affects bone health, as well as inflammation, lending to the release of more inflammatory cytokines and subsequent bone remodeling and osteopenia. Because magnesium also has mitogenic effects on osteoblasts, magnesium deficiency inhibits growth in cells and causes larger and more mineralized hydroxyapatite crystals to form. For these reasons, osteoporosis, where bones become brittle and weak and bone formation is limited, may develop, and microfractures of the trabeculae become detectable, while tibial cortical thickness markedly decreases (Rude et al., 2003).

A depletion of magnesium also promotes high levels of free radical production, which are shown to induce structural damage in skeletal muscle tissue of magnesium-deficient rats, mainly in sarcoplasmic reticulum and mitochondria.

Magnesium deficiency indirectly affects bone structure and functioning by altering PTH and 1,25 (OH)2-Vitamin D levels, which ultimately leads to hypocalcemia. Lower levels of magnesium impair PTH secretion since magnesium is required as a cofactor for PTH signaling. The decreased secretion of PTH will eventually result in low serum concentrations of 1,25 (OH)2-Vitamin D levels.

A study in 2007 on magnesium, zinc, and copper levels in postmenopausal women that were normal, osteopenic, or osteoporotic revealed that magnesium levels were significantly lower in osteoporotic women as compared to the levels measured in normal women. (Mutlu et al., 2007)
Hypomagnesemia and immunological responses:

Magnesium deficiency acts as a stressor effect that makes the body more susceptible to physiological stress, with consequent activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and sympathetic nervous system. This activation can increase oxidative stress or lead to elevation of NFkB, which would promote translation of molecules involved in cell metabolism and apoptosis. NFkB signaling is one of the two mechanisms believed to trigger the increase in inflammatory cytokines in magnesium deficiency through the activation of a calcium-channel normally blocked by magnesium. Release of the inhibition under magnesium-deficient conditions increases calcium entry and, ultimately, promotes production of reaction oxygen species, with consequent membrane oxidation and NFkB activation. This inflammatory response in magnesium deficiency can extend to the liver and other tissues. Increasing extracellular magnesium concentration, on the other hand, decreases inflammatory effects \((\text{Rayssiguier et al. ,2010})\)

Prophylaxis of hypomagnesemia:

In patients likely to develop magnesium deficiency, prophylactic measures should be taken to prevent the development or progression of hypomagnesemia and magnesium deficiency. High-risk patients such as chronic alcoholics, patients receiving total parenteral nutrition, long term diuretic therapy or other drugs causing magnesium loss, and those with chronic diarrheal and steatorrheal states should have serum magnesium monitored regularly and, if necessary, supplemented with magnesium.

Patients on parenteral nutrition should receive prophylactic doses of 4-8 mmol/day of magnesium. Higher doses may be required in malnourished patients and in those with ongoing magnesium loss.\((\text{Swaminathan et al., 2003})\).
**Treatment of hypomagnesemia:**

Mild, asymptomatic hypomagnesemia may be treated with oral magnesium salts [MgCl₂, MgO, Mg(OH)₂] in divided doses totaling 20-30 mmol/d (40-60 mEq/d). Diarrhea may occur with larger doses. Assessment of renal function before replacement therapy is important, and magnesium therapy in patients with any renal failure should be undertaken cautiously. During intravenous replacement therapy it is important to monitor serum concentrations of magnesium, potassium, and other major cations as well as deep tendon reflexes. If there is deterioration in renal function, the dose of magnesium should be halved and serum magnesium monitored more frequently. *(Krane et al., 2008).*

If hypermagnesemia or signs of magnesium intoxication (hypotension, bradycardia or depression of tendon reflexes) develop, therapy should be stopped. More severe hypomagnesemia should be treated parenterally, preferably with MgCl₂, which can be administered safely through a continuous infusion of 50 mmol/d (100 mEq Mg²⁺/d) if renal function is normal. MgSO₄ may be given IV instead of MgCl₂, although the sulfate anions may bind calcium in serum and urine and aggravate hypocalcemia.

Serum magnesium should be monitored at intervals of 12-24 hours during therapy, which may continue for several days because of impaired renal conservation of magnesium (only 50-70% of the daily IV magnesium dose is retained) and delayed repletion of intracellular deficits, which may be as high as 1-1.5 mmol/kg (2-3 mEq/kg). *(Brinkhurst et al., 2008).*
Magnesium Intake and Insulin/Glucose Homeostasis

Magnesium may play a role in glucose homeostasis, insulin action in peripheral tissues, and pancreatic insulin secretion. Although the exact mechanisms are not well-understood, several mechanisms have been proposed. First, magnesium functions as a cofactor for several enzymes critical for glucose metabolism utilizing high-energy phosphate bonds. Diminished levels of magnesium were observed to decrease tyrosine kinase activity at insulin receptors and to increase intracellular calcium levels, leading to an impairment in insulin signaling. Thus, intracellular magnesium levels have been hypothesized to be important for maintaining insulin sensitivity in skeletal muscle or adipose tissue. Additionally, intracellular magnesium levels may also influence glucose-stimulated insulin secretion in pancreatic B-cells through altered cellular ion metabolism oxidative stress, endothelial function, and the proinflammatory response. (Barbagallo et al., 2003).

Epidemiologic evidence provides further support for an important role of magnesium in insulin sensitivity. Some cross-sectional studies have shown an inverse association between plasma or erythrocyte magnesium levels and fasting insulin levels in both diabetic patients and apparently healthy individuals. Several epidemiologic studies have also found an association between dietary magnesium intake and insulin homeostasis. Several short-term metabolic studies and small randomized trials have also specifically examined the efficacy of magnesium supplementation in improving insulin sensitivity among nondiabetic individuals, although evidence remains inconclusive. Specifically, two randomized double-blind placebo-controlled trials found that magnesium supplementation improved both insulin secretion and insulin action among nondiabetic participants. We also observed down regulation of
several genes related to metabolic and inflammatory pathways including C1q and tumor necrosis factor related protein 9 (C1qthf9) and pro-platelet basic protein (chemokine (C-X-C) motif) ligand (PPBP). Our results from urine proteomic profiling showed a number of proteins significantly altered expression in response to Mg treatment. These findings indicate that among overweight or obese individuals Mg supplementation for four weeks may improve insulin and glucose homeostasis and may lead to systemic changes in gene and protein expression that warrant further investigation in larger trials (Chacko et al., 2011).

In earlier clinical studies, hypomagnesemia was shown to be frequent among patients with diabetes, especially those with poor metabolic control. Several cross-sectional studies have documented an inverse association between plasma or erythrocyte magnesium levels and fasting insulin levels in both diabetic patients and apparently healthy individuals. Other cross-sectional studies have also shown an inverse association between serum or plasma concentrations of magnesium and prevalence of type 2 diabetes, suggesting a potential role of magnesium status in the pathogenesis of type 2 diabetes. However, the evidence from cross-sectional studies cannot imply any causal relation between hypomagnesemia and type 2 diabetes (Rosolova et al., 2000).

**Potential modifying effects of genetic variant on association of magnesium intake with type 2 diabetes:**

To enhance our understanding of the epidemiology of magnesium-type 2 diabetes relation, it has become increasingly important to consider molecular and genetic variations in the homeostatic regulation of magnesium metabolism and their roles in the etiology of type 2 diabetes.
Magnesium homeostasis in the human body is tightly regulated and may involve the as-yet unidentified mechanism underlying the balance between intestinal absorption and renal excretion. Growing evidence suggests that many genes are involved in magnesium uptake, distribution, and metabolism in the human body. Of them, ion channel transient receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7) play a central role in magnesium homeostasis, which is critical for maintaining glucose and insulin metabolism. TRPM6 is a magnesium-permeable channel protein primarily expressed in intestinal epithelia and kidney tubules that may play an important role in intestinal and renal magnesium handling (Schlingmann et al., 2004).

Several loss-of-function mutations in TRPM6 have been identified among patients with autosomal recessive familial hypomagnesemia with secondary hypocalcemia, TRPM7 is ubiquitously expressed in various tissues or cell lines, and may be part of a magnesium sensing and/or uptake mechanism underlying cellular magnesium homeostasis. Low serum magnesium levels caused by TRPM6 mutations among HSH patients can be ameliorated by oral supplementation of high doses of magnesium, indicating a potential gene-diet interaction on magnesium homeostasis. However, it is unclear whether common genetic variation in TRPM6 and TRPM7 contributes to risk of type 2 diabetes. It will suggest that common genetic variation in the TRPM6 locus known to harbor severe mutations causing monogenic magnesium deficiency confers a modest susceptibility to the risk of type 2 diabetes in a small subgroup of the general population (Groenestege et al., 2006).
Figure (3): Relationship between low plasma magnesium level and type2 diabetes mellitus.
**Subjects and Methods**

This study was conducted on 110 subjects including 100 type 2 diabetic patient and 10 non diabetic subjects admitted to the Department of Internal Medicine, Benha University Hospital within the period between june 2015 to june 2016.

**Selection of patients:**

**Inclusion Criteria**

- Patients with type 2 diabetes mellitus aged between 30 to 70 years with or without clinically evident diabetic neuropathy.

**Exclusion Criteria:**

- Renal failure.
- Acute myocardial infarction.
- patients on diuretics, aminoglycosides and other drugs causing magnesium supplements and magnesium containing antacids.
- pregnant and lactating women.

**FOR the study, subjective population were divided into:**

- **group (I):** (10) patients without diabetes mellitus used as control.
- **group (II):** (74) patients of type 2 diabetes mellitus with clinically evident diabetic neuropathy.
- **group (III):** (26) patients of type 2 diabetes mellitus without clinically evident diabetic neuropathy.

**Method of Collection of Data:**

*For All patients, after giving their informed consent, they were subjected to the following:*
1) **Detailed medical history:**

Patients age, sex, duration of diabetes mellitus, Details regarding presenting complaints, Past history of any Other diseases, History of comorbid diseases like hypertension, Ischemic heart disease. Family history of Diabetes and Hypertension taken and Detailed general.

2) **Complete clinical examination:**

physical examination conducted and detailed systemic examination was carried out in all patients with stress on prephral and cranial nerve examination.

3) **Fundoscopic examination:** was done for all patients to asses diabetic retinopathy

4) **Laboratory investigations including:**

- RBS; assessed by quantitative determination of glucose by glucose oxidase method.
- Serum magnesium Levels; assed by xylidyl Blue, colorimetric Endpoint method.
- HbA1C; assessed by Ion exchange HPLC method.
- Urine analysis, assessed by urine reagent diagnostic test strips
- 24 hrs. urinary albumin assessed by TCA 5% (tricloroacetic acid) method and estimated GFR to asses evident diabetic nephropathy.

The normal serum magnesium level is ranging from 1.8 mg /DL to 2.9 mg /dL. Serurn magnesium levels < 1.5 mg / DL is considered as low magnesium level in this study.

Data had been collected and statistical analyzed.
**Subjects and Methods**

**Data management:**

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 16 to obtain.

**Descriptive data:**

Descriptive statistics were calculated for the data in the form of:

1- Mean and standard deviation ($\pm SD$) for quantitative data.

2- Frequency and distribution for qualitative data.

**Analytical statistics:**

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:-

1- **Student's $t$-test**: Used to compare mean of two groups of quantitative data.

\[
 t = \frac{X_1 - X_2}{SD_{1}^2 + SD_{2}^2} \sqrt{n_1 + n_2}
\]

2- **ANOVA test (F value)**: Used to compare mean of more than two groups of quantitative data.

3- Inter-group comparison of categorical data was performed by using fisher exact test (FET).

4- **Correlation coefficient**: to find relationships between variables.

A $P$ value $<$0.05 was considered statistically significant (*) while $>0.05$ statistically insignificant $P$ value $<$0.01 was considered highly significant (***) in all analyses.
Results

This study was conducted on 110 subjects, 10 of them are non-diabetics and 100 of them are type 2 diabetic patients with and without clinically evident diabetic neuropathy who fulfilled the inclusion criteria and divided into 3 groups:

- **group (I):** (10) patients without diabetes mellitus used as control.
- **group (II):** (74) patients of type 2 diabetes mellitus with clinically evident diabetic neuropathy.
- **group (III):** (26) patients of type 2 diabetes mellitus without clinically evident diabetic neuropathy.

**Table (5):** Demographic features of studied groups

<table>
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<th>Group 2 mean ±SD</th>
<th>Group 3 mean ±SD</th>
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<td>12(46.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was statistically significant difference between the three groups as regard mean Age.

**Figure (4):** Comparison between the studied groups in type 2 diabetes mellitus regarding mean age.
Table (6): Comparison between the studied groups regarding duration.

<table>
<thead>
<tr>
<th></th>
<th>Group1 mean ±SD</th>
<th>Group 2 mean ±SD</th>
<th>Group 3 mean ±SD</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>-</td>
<td>12.19±5.61</td>
<td>7.42±6.63</td>
<td>t=3.55</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

There was statistically significant difference between the three groups as regard duration of diabetes, the longer duration with group II

Figure (5): Comparison between the studied groups in type 2 diabetes mellitus regarding mean duration.
Table (7): Comparison between the studied groups RBS.

<table>
<thead>
<tr>
<th></th>
<th>Group1 mean ±SD</th>
<th>Group 2 mean ±SD</th>
<th>Group 3 mean ±SD</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBS</td>
<td>102.6±23.41</td>
<td>270.96±80.52</td>
<td>180.85±61.04</td>
<td>32.51</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

There was statistically significant difference between the three groups as regard RBS, the high level of RBS with group II.

Figure (6): Comparison between the studied groups in type 2 diabetes mellitus regarding mean RBS.
**Results**

**Table (8):** Comparison between the studied groups HbA1c.

<table>
<thead>
<tr>
<th></th>
<th>Group1 mean ±SD</th>
<th>Group 2 mean ±SD</th>
<th>Group 3 mean ±SD</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>4.12±0.20</td>
<td>8.39±1.35&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.7±0.97&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>64.13</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

There was statistically significant difference between the three groups as regard HbA1c, the high level of HbA1c with group II

**Figure (7):** Comparison between the studied groups in type 2 diabetes mellitus regarding mean HBA1C.
Results

Table (9): Comparison between the studied groups regarding Mg level.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 mean ±SD</th>
<th>Group 2 mean ±SD</th>
<th>Group 3 mean ±SD</th>
<th>F test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Mg</td>
<td>2.12±0.15</td>
<td>1.47±0.30a</td>
<td>1.93±0.26b</td>
<td>22.77</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

There was statistically significant difference between the three groups as regard S Mg, the high level of S Mg with group I.

![Bar Chart](image.png)

Figure (8): Comparison between the studied groups in type 2 diabetes mellitus regarding mean S Mg.
Results

Table (10): Comparison between the studied groups regarding diabetic retinopathy (assessed by fundoscopic examination).

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>FET</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0(0.0)</td>
<td>62(83.8)</td>
<td>2(7.7)</td>
<td>65.38</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>No</td>
<td>10(100)</td>
<td>12(16.2)</td>
<td>24(92.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The average percentage of diabetic retinopathy among 3 groups was 0%, 83.8% and 7.7% respectively.

There was statistically significant difference between the three groups (P < 0.01) regarding diabetic retinopathy.

![Graph](image)

Figure (9): Comparison between the studied groups regarding diabetic retinopathy.
Results

Table (11): Comparison between the studied groups regarding diabetic nephropathy (assessed by Urine analysis, 24 hrs urinary albumin and GFR)

<table>
<thead>
<tr>
<th>Nephropathy</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>FET</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0(0.0)</td>
<td>37(50.0)</td>
<td>0(0.0)</td>
<td>31.78</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>No</td>
<td>10(100)</td>
<td>37(50.0)</td>
<td>26(100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The average percentage of diabetic nephropathy among 3 groups was 0%, 50% and 0% respectively.

There was statistically significant difference between the three groups (P < 0.01) regarding diabetic nephropathy.

Figure (10): Comparison between the studied groups regarding diabetic nephropathy.
Table (12): Comparison between the studied groups regarding Clinically evident neuropathy.

<table>
<thead>
<tr>
<th></th>
<th>Group1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>FET</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically evident neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0(0.0)</td>
<td>74(100)</td>
<td>0(0.0)</td>
<td>128.2</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>No</td>
<td>10(100)</td>
<td>0(0.0)</td>
<td>26(100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The average percentage of Clinically evident diabetic neuropathy among 3 groups was 0%, 74%, and 0% respectively.

There was statistically significant difference between the three groups (P < 0.01) regarding Clinically evident neuropathy.

Figure (11): Comparison between the studied groups regarding clinically evident diabetic neuropathy.
Results

Figure (12): Scatter diagram showing correlation between S Mg & duration of type 2 diabetes showing significant difference between S Mg & duration of type 2 diabetes.

Figure (13): Scatter diagram showing correlation between RBS & S Mg showing significant difference between RBS & MG.

Figure (14): Scatter diagram showing correlation between s Mg & HbA1c showing significant difference between S Mg & HbA1c.
Discussion

Magnesium (Mg), is one of the most abundant intracellular cation with an essential role in fundamental biological reactions. Magnesium activates more than 300 enzymes in the body and is a critical cofactor of many enzymes in carbohydrate metabolism. Cellular magnesium deficiency can alter the activity of membrane bound sodium-potassium ATPase. (Grofton et al., 1992).

Diabetes mellitus (DM), characterized by metabolic disorders related to high levels of serum glucose, is probably the most common disease associated with Mg depletion in intra and extra cellular compartments. (Delva et al., 2002).

Hypomagnesemia has been related, as a cause, to insulin resistance, also being a consequence of hyperglycemia, and when it is chronic, it leads to the development of macro and microvascular complications of diabetes, that worsens the deficiency of Mg.

Hypomagnesemia, defined by low serum Mg concentrations, has been reported to occur in 13.5% to 47.7% of non hospitalized patients with type 2 diabetes compared with 2.5% to 15% among normal subject. (Walti et al., 2003).

In diabetes, there is a direct relationship between serum magnesium level and cellular glucose disposal that is independent of insulin secretion. This change in glucose disposal has been shown to be related to increased sensitivity of the tissues to insulin in presence of adequate magnesium levels. It is observed that low serum magnesium concentration and poor magnesium status are common in type 2 diabetes. (Rosolova et al., 2000).
Preventing hypomagnesemia in diabetic patients by supplementing magnesium may be helpful in increasing insulin sensitivity and delaying the development of late diabetic complication. *(Rayssiguier et al., 2010)*

The aim of this study is to study the plasma Magnesium status and its relation to diabetic neuropathy in patients with Type 2 Diabetes mellitus.

The current study enrolled 100 type2 diabetic patients and 10 non diabetic patients attending to Banha university hospital, internal medicine department. The patients were classified into 3 categories, non diabetic patient without neuropathy, diabetic patient with neuropathy, diabetic patient without neuropathy respectively. Serum magnesium, random blood glucose and glycated hemoglobin were determined. Among the 110 patients there were 10 patient (non diabetic) without neuropathy (group I), 74 patients of type 2 diabetes mellitus with diabetic neuropathy (group II) and 26 patients of type 2 diabetes mellitus without diabetic neuropathy (groupIII). There is a significant statistical differences (P-value <0.01) between diabetic neuropathy (group II) and control group(group I) and group II in serum magnesium, random blood glucose, glycated hemoglobin and duration of diabetes. The average range of serum Magnesium level among 3 groups was, 2.12±0.15, 1.47±0.30 and 1.93±0.26 respectively, There is significant difference among 3 group(P< 0.05), low level of serum magnesium with group II (diabetic patient with neuropathy) and high level with group I( non-diabetic patient without neuropathy).

Serum magnesium level decreased in patients with diabetic neuropathy with lowest level being observed in patients with neuropathy associated with diabetic retinopathy and nephropathy.
The results of the current study were agreed with (Ramachandra et al., 2013); Study of serum magnesium level in diabetic patients with microvascular complications including diabetic neuropathy, retinopathy and nephropathy reveal that the serum magnesium levels were significantly lower in patients with microvascular complications compared to diabetics without complications.

The comparative study was done on 50 diabetic subjects (25 without microvascular complications, 25 with microvascular complications). Serum magnesium was compared between the two groups. Both groups were subjected to estimation of biochemical parameters, statistically observed. In this study, it was found that diabetics with microvascular complications had significantly lower levels of serum magnesium (1.46 ± 0.32) compared to diabetics without microvascular complications (1.92 ± 0.25).

The results of the current study were agreed also with (Prasad et al., 2014):

Study of serum magnesium levels in type 2 Diabetes Mellitus. This study demonstrated that low Mg2+ status is common in Type 2 diabetes mellitus patients when compared to non-diabetic controls. It may be prudent in clinical practice to periodically monitor plasma Mg2+ concentration in diabetic patients. If plasma Mg2+ is low, an intervention to increase dietary intake of magnesium may be beneficial. This study was done in randomly chosen 100 Type 2 diabetic patients, and 100 non-diabetic age/sex matched controls. Age group 30 to 70 years attending diabetic clinic. All patients and controls underwent thorough clinical examination and required laboratory investigation.
Discussion

Statistically observe that 33% of diabetic patients had low serum magnesium levels (Mg2+level≤1.5mg/dL) and 5% of controls had low serum magnesium levels (Mg2+level≤1.5mg/dL). Significant association between serum magnesium level and neuropathy, retinopathy and nephropathy. The mean serum magnesium level was 1.69±0.31 mg/dL and 2.04±0.28 mg/dL in diabetics and controls respectively (0.000 S, p < 0.05)

The results of the current study were agreed also with (Arundhati et al.,2012);study of the relation of hypomagnesemia to glycemic control and various long-term complications of diabetes mellitus.150 type 2 diabetic patients were studied for uncontrolled hyperglycemia and/or various diabetic complications.

The study revealed that the incidence of retinopathy, microalbuminuria, macroalbuminuria, foot ulceration, and neuropathy was present in 64%, 47%, 17.64%, 58.8%, and 82.35%, respectively, of the patients with hypomagnesemia. serum magnesium was in a less concentration in the patients with diabetic polyneuropathy. Magnesium supplementation improved the nerve conduction

The results of the current study were agreed also with (Mirza et al.,2012):to study serum magnesium as a marker of diabetic complication .60 patients of type 2 diabetes mellitus between 40– 70 years, which were divided into following groups

Group I: Included 30 patients of type 2 diabetes without complications.

Group II: Included 30 patients of type 2 diabetes with proven complications, like retinopathy and neuropathy.

In this study it was observed that the mean serum magnesium level was statistically significantly low (P<0.001) in Diabetic patients without and with complications when compared with each other.
The study revealed that serum magnesium level in cases with diabetic complications (1.29 ± 0.31) was much lower than those without complications (1.61 ± 0.41).

The results of the current study were agreed also with (Mohamed et al., 2014); to study serum magnesium in type 2 diabetic patient 50 patients with type 2 Diabetes Mellitus were recruited from the institute’s medicine department. Fifty age and sex matched apparently healthy individuals with normal plasma glucose and with no symptoms suggestive of Diabetes mellitus were taken as controls. Both cases and controls were subjected to estimation of biochemical parameters. There is significant difference between levels of serum magnesium levels among diabetics and controls. The mean serum magnesium levels in cases and controls are 1.67 mg/dl and 2.03 mg/dl respectively (p<0.001).

The results of the present study showed that there were statistically significant differences in the level of serum magnesium among different stages of neuropathy. These differences correlate negatively with advancing stages of neuropathy i.e. the more advanced the stage of neuropathy, the lower is the serum magnesium concentration. Low Mg levels may also lead to induction of pro-inflammatory and pro-fibrogenic response and to reduction of protective enzymes against oxidative stress.
Summary

Diabetes Mellitus is a metabolic and endocrine disorder characterized by both insulin deficiency and insulin resistance. Most of the cases are diagnosed as Type 2 diabetes. Type 2 diabetes has become a leading cause of morbidity and mortality across the world. Diabetic complication are likely because of its metabolic changes. chronic complications include majorly neuropathy, nephropathy and retinopathy. *(ADA, 2014)*

Diabetic peripheral neuropathy (DPN) is a diabetes mellitus (DM) induced disorder of the peripheral nervous system *(Deli et al., 2014)* and is characterized by the pain and loss of sensation due to symmetrical degeneration of distal peripheral nerves. The symptoms will deteriorate with the progression, which may result in diabetic ulcers or even no traumatic amputation.

Statistics revealed that the incidence of DPN was as high as 30%, 60%, and 90% at 5, 10, and 20 years after diagnosis of DM, and foot injury had occurred in 50% of DPN patients when they were asymptomatic *(Boulton et al., 2005).*

Mineral ions play specific roles in our body. One of the important mineral cation is magnesium (Mg), which is a cofactor in glucose transporting mechanism of the cell membrane of nearly or more than cellular enzymatic systems. Magnesium is the second most common intracellular cation. Many studies have been shown reduced magnesium concentrations in diabetic adults. Intracellular magnesium is having an important role in insulin action regulation, insulin-mediated glucose uptake, and vascular tone. In diabetic patient’s reduced intracellular Mg concentrations results in abnormal tyrosine-kinase activity, post receptorial impairment in insulin action, and insulin resistance worsening. *(Maltezos, et al., 2004)*.
in this study 110 patient with age group 30-70 years (including 100 type 2 diabetic patient and 10 non diabetic patients) were fit in the inclusion criteria were studied.

Detailed history and clinical examination and biochemical investigations were included: Patients age ,sex, duration of diabetes mellitus , Details regarding presenting complaints, Past history of any Other diseases, History of comorbid diseases like hypertension, Ischemic heart disease.Family history of Diabetes and Hypertension taken and Detailed general physical examination conducted and detailed systemic examination was carried out in all patients. serum magnesium, RBS , KFT, glycated hemoglobin and fundus examination.

Among the 110 patients there were 10 patients non diabetic without neuropathy (group I), 74 type 2 diabetic patient with neuropathy (group II) and 26 type 2 diabetic patients without neuropathy (group III) respectively. There was significant statistical difference among the three groups(P< 0.01), regarding serum magnesium , random blood glucose and glycated hemoglobin and duration of diabetes.

The results of the current study showed that there were significant difference in the level of serum magnesium between group I (healthy controls ) and group II (diabetics with neuropathy) and group III(diabetics without neuropathy ) indicating that low plasma magnesium level leads to acceleration of development of diabetic complications , including diabetic neuropathy.
Conclusion

Hypomagnesaemia is likely among patients with type 2 diabetes mellitus. Long term complications especially neuropathy may have hypomagnesemia as a contributing factor.

Moreover, because Mg is crucial in DNA synthesis and repair. It is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis. We, therefore, conclude that serum magnesium level decreased in patients with diabetic neuropathy with lowest level being observed in patients with advanced neuropathy.

Because Mg2+ depletion reduces insulin sensitivity and may increase risk of secondary complications, Hence it is prudent that serum magnesium levels are carefully monitored in diabetic patients.
**Recommendations**

This study demonstrated that low Mg 2+ status is common in type 2 diabetes mellitus patients when compared to non diabetic controls. It may be prudent in clinical practice to periodically monitor plasma magnesium concentration in diabetic patients.

If plasma Mg 2+ is low, an intervention to increase dietary intake of magnesium which is abundant in whole grains, green leafy vegetables, legumes and nuts may be beneficial.

The efficacy of oral magnesium supplementations as adjacent therapy in improving glycemic control among diabetic patient has been suggested in some small randomized clinical trails.

Although further replication in large-scale studies is warranted, further studies will be needed linking low magnesium status in type 2 diabetes with micro and macro vascular complications of diabetes mellitus and results of magnesium intake in insulin resistance and type 2 diabetes from observational studies to intervention Trials.
References


American Diabetes Association (2014). Diagnosis and classification of diabetes mellitus. Diabetes Care ;37(Suppl. 1) s81-s90

References


References


References


الملخص العربي

يتميز مرض السكري بمجموعة غير متجانسة من الاضطرابات الأيضية التي تؤدي إلى ارتفاع السكر المزمن في الدم مع اضطراب في الكريهيدرات والدهون وانتقال البروتين الناتج عن عيب في إفرز أو عمل الإنسولين أو كليهما مما يؤثر على الجسم البشري على المدى الطويل، والعجز وفشل مختلف الأجهزة.

وبعد مرض إعتلال الأعصاب السكري الناجح عن مرض السكري من المضاعفات المتعارف عليها والتي تسبب الأحاسيس بالألم الشديد وفقدان الإحساس بسبب انحلال الأعصاب الطرفية البعيدة وقد تتدهور مع التقدم، مما يؤدي إلى ترقات أو بتر في الأطراف. ولقد كشفت الإحصاءات أن نسبة الإصابة باعتلال الأعصاب السكري كان يصل إلى 30%, و90% في 5 و 10 و 20 سنوات بعد تشخيص مرض السكري، وإصابة القدم قد وقعت في 50% من المرضى عندما كانوا بدون أعراض.

ويعتبر الماغنيسيوم أشهر الكاتيونات داخل خلايا جسم الإنسان والعامل المحفز لأشهر من 300 إنزيم مسؤول عن التمثيل الغذائي للنواتج.

يرتبط نقص الماغنيسيوم بإرتفاع سكر الدم ومقاومة الجسم لعمل الأنسولين والذي يدور يؤدي إلى مضاعفات مرض السكري ومنها الاعتلال العصبي من التدخل في عمل الإنزيمات المسؤولة عن حماية الأعصاب والخلايا العصبية ضد مضادات الأكسدة والنمو الطبيعي والموت المنظم للخلايا.

وفي هذه الدراسة تم التعامل مع ثلاث مجموعات:

- المجموعة الأولى: 10 أفراد غير مصابين بمرض السكري.
- المجموعة الثانية: 24 مريضا من مرضى السكري النوع الثاني المصابين باعتلال الاعصاب السكري.
- المجموعة الثالثة: 24 مريضا من مرضى السكري النوع الثاني غير مصابين باعتلال الاعصاب السكري.

وتتم الفحص السريري الشامل وعمل التحاليل اللازمة في صورة سكر عشوي، نسبة الماغنيسيوم بالدم، وظائف كلي، هيموجلوبين سكري، فحص قاع العين.

تتم الدراسة لكل حالات مرضى السكري من النوع الثاني مابين عمري الثلاثين والسابعين ويستثني:
· حالات الفشل الكلوي الحاد.
· المصابون باحتشاء عضلة القلب الحاد.
· المستخدمون لادوية تحتوي على الماغنسيوم أو مدرات البول.
· الحوامل والمرضى.

من خلال هذه الدراسة تم استنتاج الآتي:

· وجود علاقة عكسية بين نسبة الماغنسيوم بالدم ومضاعفات مرض السكر، ومنها إعتلال الأعصاب السكري، بمعنى نقص الماغنسيوم بالدم (وخصوصا في مرضى السكر من النوع الثاني) يصاحبه خلل بوظائف الأنسولين وظهور مضاعفات مرض السكر ومنها إعتلال الأعصاب السكري، هذا من الضروري قياس نسبة الماغنسيوم بالدم لكل مرض السكر من النوع الثاني.

· تستهدف الدراسات المستقبلية أهمية تعويض الماغنسيوم لكل مرض السكر من النوع الثاني وتأثير ذلك على تقليل مضاعفات مرضى السكر.

· حالات الفشل الكلوي الحاد.
· المصابون باحتشاء عضلة القلب الحاد.
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· تستهدف الدراسات المستقبلية أهمية تعويض الماغنسيوم لكل مرض السكر من النوع الثاني وتأثير ذلك على تقليل مضاعفات مرضى السكر.
حالة الماغنسيوم في بلازما مرضى السكري من النوع الثاني المصابين والغير مصابين بإعتلال الأعصاب السكري

رسالة

توطئة للحصول على درجة الماجستير في أمراض الباطنة

مقدمة من الطبية/ رشا محمد عبدالهادي

بكالوريوس الطب والجراحة

كلية الطب - جامعة بنها

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مدرسة الباتولوجيا الإكلينيكية والكيميائية

كلية الطب - جامعة بنها

كلية الطب

جامعة بنها

2016