Hypophosphatemia and Type-2 Diabetes Mellitus: A Review

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Abstract
Type-2 diabetes is a global public health crisis that threatens the economies of all nations, particularly developing countries. Type-2 diabetes mellitus has been suggested to be the most common endocrine disorder associated with several metabolic disturbances including changes in serum calcium, zinc, magnesium, or phosphate. Moreover, those who have poor glycemic control and longtime diabetes mellitus are more likely to decrease the blood phosphate level. Low serum phosphate level may be associated with morbidity and mortality from cardiovascular disease in these patients. So, the findings of this study may suggest that serum phosphate is an important screening parameter in type-2 diabetic patients especially who have poor glycemic control and longtime diabetes mellitus.

Keywords: Type-2 Diabetes Mellitus, Inorganic Phosphate, Hypophosphatemia

Introduction
Diabetes Mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both1. There are two main forms of diabetes mellitus. Type-1 diabetes is due primarily to autoimmune-mediated destruction of pancreatic β-cell islets, resulting in absolute insulin deficiency2. Its frequency is low relative to type-2 diabetes, which accounts for over 90% of cases globally. Type-2 diabetes is characterized by insulin resistance and/or abnormal insulin secretion, either of which can predominate3.

Type-2 diabetes mellitus is a complex metabolic disorder of heterogeneous etiology with social, behavioral, and environmental risk factors unmasking the effects of genetic susceptibility4. Microvascular and macrovascular complications of diabetes increase as a function of the duration of hyperglycemia5.

High concentration of glucose can increase the glycation of hemoglobin, forming glycosylated hemoglobin (HbA1c)6. It is a simple and economical way to monitor and manage long term blood sugar control in diabetes mellitus and its reading gives an accurate index of the average concentration of blood sugar during the previous two to three months6. Type-2 diabetes mellitus is associated with microvascular complications, such as retinopathy, neuropathy and nephropathy or macrovascular complications, including cardiovascular, cerebrovascular, and peripheral vascular disease6.

Minerals in Type-2 DM
The human body needs about twenty different minerals to function properly which are usually classified into two main categories that are the micro- and macro-minerals depending on their required daily intake rather than their relative importance or physiological functions7. Macrominerals are typically needed at levels higher than 100 mg/day which include calcium (Ca), phosphorus (P), magnesium (Mg), sulfur (S), sodium (Na) and potassium (K). On the other hand, microminerals are needed in amounts lower than 100 mg/day and include elements such as iron (Fe), zinc (Zn), iodine (I), selenium (Se), manganese (Mn), chromium (Cr), copper (Cu), molybdenum (Mo), fluorine (F), boron (B), cobalt (Co), silicon (Si), aluminum (Al), arsenic (As), tin (Sn), lithium (Li) and nickel (Ni)8.

Macro elements have multiple roles within the body. They work together with vitamins and initiate hormone production as well as speeding up the metabolic processes. Trace elements participate in tissue and cellular and subcellular functions; these include immune regulation by humoral and cellular mechanisms, nerve conduction, muscle contractions, membrane potential regulations, mitochondrial activity, and enzyme reactions9. Trace elements interact with vitamins and macro elements to enhance their effects on the body. They are accepted as essential for human health and have diverse metabolic characteristics and functions9. Direct associations of macro and trace elements with

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diabetes mellitus have been observed in many research studies\textsuperscript{10}. It is also reported that the metabolism of several trace and macro elements alters in type-2 diabetes mellitus and these elements might have specific roles in the pathogenesis and progress of this disease and its complications\textsuperscript{11}.

**Phosphorus and Phosphate**

Phosphorus is a chemical element with the symbol ‘P’, atomic number 15, and atomic weight of 31. It constitutes about 1\% of the total body weight\textsuperscript{12}. Elemental phosphorus exists in two major forms, white phosphorus, and red phosphorus. Elemental phosphorus was first isolated as white phosphorus in 1669\textsuperscript{12}.

Phosphate contains one Phosphorus (P) atom and four Oxygen (O) atoms in which one central Phosphorus (P) atom is surrounded by four Oxygen (O) atoms in a tetrahedral shape. It forms an ionic bond between these 2 atoms. It is also known as a Phosphate ion or Orthophosphate. It is a polyatomic ion. The chemical formula of Phosphate is PO\textsubscript{4}^3- and its molecular weight is 94.97 g/mol. It is slightly soluble in water. It is present in bones, teeth, and genes in the human body\textsuperscript{13}. In a 70-kg adult has about 600 gm or approximately 20 mol of phosphorus of which about 85\% is in the skeleton and the rest is principally in soft tissue\textsuperscript{14}. Phosphate is readily available in our diet as it is present in almost all natural foods. Important dietary sources of phosphate are milk, cereal grains, fish, poultry, eggs, meat, and peanut\textsuperscript{15}.

![Figure-1: Chemical structure of Phosphate\textsuperscript{13}](image)

**Plasma Inorganic Phosphate**

Plasma contains both inorganic and organic phosphate. Most of the intracellular phosphates are organic with only a small percentage being inorganic\textsuperscript{12}. Organic phosphates are the esters of phosphoric acid. Inorganic phosphates are salts of phosphoric acid. Inorganic phosphate is the major intracellular anion\textsuperscript{12}. Inorganic phosphate in the form of hydroxyapatite (in bone) plays a major role in structural support of the body and provides phosphate for extra cellular and intracellular body fluids\textsuperscript{16}.

Intracellular phosphate is a component of nucleotide derivatives such as NADP, ATP, GTP etc., is involved in nucleic acid structure formation and in regulation of intermediary proteins, carbohydrate and fats metabolism, cell growth, gene transcription and body buffer system\textsuperscript{17}.

Though plasma contains both inorganic and organic phosphate, only inorganic phosphate is measured in the plasma. The normal plasma concentration of inorganic phosphate in adults ranges between 2.5-4.5 mg/dl or 0.75-1.45 mmol/l\textsuperscript{18}. Inorganic phosphate level varies according to several factors; for example, infants and young children, have almost double the serum inorganic phosphate level as compared to adults, due to greater need of phosphorous for rapid mineralization of the skeleton\textsuperscript{19}. Ingestion of a rich carbohydrate meal will result in a decrease in serum inorganic phosphate level by 0.3-0.5 mmol/l or 1.0-1.5 mg/dl, due to the increase in the secretion of insulin which is needed for increase cellular uptake and utilization of inorganic phosphate\textsuperscript{18}.

**Biological Functions of Phosphate**

The role of phosphate in different parts of the body are:\textsuperscript{20-22}

- **Bone mineralization**: phosphate is responsible for mineralization of the bony matrix.
- **Endochondral Ossification**: Phosphate is responsible for endochondral ossification of the bone as increased intracellular phosphate levels induce apoptosis of the terminally differentiated chondrocytes.
- **Teeth**: Phosphate is important for mineralization of all the structural components of the teeth i.e., it is an integral component of enamel, dentin, cementum, and alveolar bone.
- **Cellular Functions**: In the cell, phosphate is an important component of the lipid bilayer of cell membranes, DNA, RNA, and proteins.
- **Urinary Buffer**: The inorganic phosphate [HPO\textsubscript{4}^2-] is an important urinary buffer, as it can reversibly bind with free hydrogen ions and its pK is 6.8, is also very close to plasma pH.

![Figure-2: Biological Functions of Phosphate\textsuperscript{23}](image)
Inorganic Phosphate and ATP
Phosphorus plays a critical role in the storage, transfer, and liberation of energy in the organism as well as in the intermediate metabolism of carbohydrates, fat, and proteins. Inorganic phosphate (Pi) is a vital component of DNA and RNA and participates both in glycolysis and oxidative phosphorylation. In glycolysis, Pi is a substrate for glyceraldehyde-3-phosphate dehydrogenase and stimulates the activities of hexokinase and phosphofructokinase. Mitochondria are the power plants of our bodies, and their primary function is to manufacture adenosine triphosphate (ATP), which provides 90-95% of all cellular energy mainly by oxidative phosphorylation.

Definition and Features of Hypophosphatemia
Hypophosphatemia is defined as serum phosphate levels of less than 2.5 mg/dL. Hypophosphatemia’s physiological consequences are likely to differ between patient groups. Its clinical presentation can vary according to its onset, severity, and patient’s age. Mild hypophosphatemia (2 to <2.5 mg/dl) is usually asymptomatic. In moderate to severe cases the most important clinical symptoms of hypophosphatemia are bone pain, altered mental status, fatigue with muscle weakness or numbness, platelet dysfunction, metabolic acidosis and cardiac dysfunction. In very severe cases without treatment can lead to rhabdomyolysis or softening of the bones, seizures, breathing problem and coma.

Differential Diagnosis of Hypophosphatemia
The most common manifestation is generalized weakness. As such, any other electrolyte aberrations should also be suspected, including hypokalemia and hypomagnesemia. Additionally, the following diagnoses can be considered:

- Benzodiazepine toxicity
- Delirium
- Delirium tremens
- Dilated cardiomyopathy
- Guillain-Barre syndrome
- Hypothyroidism
- Hyperparathyroidism
- Insulin overdose
- Myopathies
- Multiple myeloma
- Primary muscle disorders
- Rhabdomyolysis
- Uremic encephalopathy

Inorganic Phosphate and Type-2 DM
Diabetes mellitus is a chronic metabolic disease with high rate of morbidity and mortality characterized by impaired glucose metabolism and other energy yielding fuels as well as development of vascular and neuropathic complications in advance disease. It is suggested to be associated with several metabolic disturbances including changes in serum calcium, zinc, magnesium, or phosphate. In severe uncontrolled diabetes mellitus, raised sugar results in low phosphate levels due to intracellular phosphorylation of glucose. Former studies had found decreased in phosphate concentration in uncontrolled diabetic subjects and the level stabilize when blood sugar is controlled.

Yousfani AH, et al. studied in 100 diabetic patients and found that serum phosphate levels were significantly decreased in 67% patients in context to age and gender while raised HbA1c, shown inversely proportional relationship with HbA1c respectively. It was observed in a study in 2005 that patients with metabolic syndrome showed significantly lower phosphate and magnesium levels compared with controls. Haap M, et al. in 2006 showed that there was a significant association of low serum phosphate concentration with high 2-hr blood glucose levels independent of anthropometric parameters like body fat, age, and gender.

A previous study which included 162 patients with type-2 DM vs 82 hospitalized non-diabetic patients showed that serum phosphate levels were lower in type-2 DM, due to the disturbance in metabolism. Gartner JM, et al. studied mineral metabolism in juvenile onset of diabetic patients and observed that as plasma glucose decreased from an average of 221 mg/dL to 95.9 mg/dL, serum Pi rose from 4.09 to 5.01 mg/dL due to a 25% rise in renal tubular threshold for phosphate. Nagasaka S, et al. also showed their study that when there was significant reduction of HbA1c percentage in NIDDM patients, the serum phosphate level rose significantly.

In a study, the prevalence of hypophosphatemia among diabetic patients was found to be 10.5%, which was much higher than the prevalence observed among non-diabetics in the population-based national study (3.2%). That study showed the significant association between uncontrolled diabetes and hypophosphatemia. Diabetic patients with HbA1c between 7 and 9% and ≥9% were 1.8 and 1.7 times, respectively, more likely to have hypophosphatemia as compared to those with HbA1c less than 7%.

In contrast to the above findings, Dalili S, et al. found no significant association between hypophosphatemia and HbA1c level. Another studies by Haglin L, et al. in 2001, Park W, et al. in 2009 showed the negative correlation between serum phosphate levels and fasting blood sugar levels.

Causes of Hypomagnesemia in Type-2 Diabetes
Hypophosphatemia is seen most frequently in hospitalized patients. Generally, three primary
mechanisms leading to hypophosphatemia are: (1) transcellular shift of phosphorus (from extracellular volume to either soft tissues or bones); (2) poor dietary intake, especially when associated with impaired GI absorption or diarrhea; and (3) increased phosphate excretion resulting from renal and nonrenal causes. The nonrenal loss occurs through the gut, primarily malabsorptive states or diarrheal conditions.

The pathophysiology of hypophosphatemia in diabetic patients is not fully understood. It is suggested that, early in the progression of diabetes, a paradoxical metabolic imbalance in inorganic phosphate (Pi) occurs that may lead to reduced high energy phosphate and tissue hypoxia. These changes take place in the cells and tissues in which the entry of glucose is not controlled by insulin, particularly in poorly regulated diabetes. Various conditions are involved in this disturbance in Pi. First, the homeostatic function of the kidneys is suboptimal in diabetes because elevated blood glucose concentrations depolarize the brush border membrane for Pi reabsorption and lead to lack of intracellular phosphate and hyperphosphaturia. Second, during hyperglycemic-hyperinsulinemic intervals, high amounts of glucose enter the muscle and fat tissues, which are insulin sensitive. Intracellular glucose is metabolized by phosphorylation, which leads to a reduction in plasma Pi, and subsequent deleterious effects on glucose metabolism in insulin insensitive tissues. While low and high uncontrolled blood glucose can be easily recognized by clinical symptoms, low and high plasma inorganic phosphate remains unrecognized. Instead, it may be presented by vague and non-specific symptoms such as tissue hypoxia, muscular weakness, neurological problems, erythocyte and leukocyte dysfunction and impaired myocardial performance.

Management of Hypophosphatemia
Management of hypophosphatemia involves the treatment of underlying cause and phosphate replacement. So, in diabetes mellitus it is necessary to control the blood sugar level. Normalization of blood sugar levels possesses maintaining the capacity of the renal tubules to reabsorb inorganic phosphorus and gradually increase in inorganic phosphorus serum levels is an appropriate step in the management. The blood glucose control will also positively influence and help in preventing long term complications of diabetes mellitus as proved by former studies.

Conclusion
Hypophosphatemia in type-2 diabetic patients may have a contributing role in the progression of the disease and development of complications of diabetes. A well-balanced diet will maintain the impairment of essential macro and micronutrients in this patient and the potential utility of supplementation is relevant to the prevention and/or management of type-2 diabetes mellitus.

Conflict of interest
The authors declared that they have no conflict of interest.

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