Chapter 5
Pathology of Diabetes and Hypertension

5.1 Impact of diabetes mellitus on functions of different organs

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus.

1. Type I diabetes- also called insulin-dependent diabetes mellitus (IDDM) is caused by lack of insulin secretion.
2. Type II diabetes- also called non-insulin-dependent diabetes mellitus (NIDDM) is caused by decreased sensitivity of target tissues to the metabolic effect of insulin.

Reduced sensitivity to insulin is called insulin resistance. In both types of diabetes mellitus, metabolism is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by the cells in the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and proteins increases.

When the plasma glucose level changes from 300 to 1200 mg/100 ml., blood glucose causes more glucose to filter into the renal tubules than can be reabsorbed, and the excess glucose spills into the urine. This normally occurs when the glucose concentration in the blood rises above 180 mg/100 ml, a level that is the threshold for the appearance of glucose in the urine. When the blood glucose level rises to 300 to 500 mg/100 ml common values in people with severe untreated diabetes 100 or more grams of glucose can be lost into the urine each day. [12]

1) Increased blood glucose causes dehydration

The very high levels of blood glucose (sometimes as high as 8 to 10 times normal in severe untreated diabetes) can cause severe cell dehydration throughout the body. [12] This occurs partly because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the extracellular fluids causes osmotic transfer of water out of the cells. In addition to the direct cellular dehydrating effect of excessive glucose, the loss of glucose in the urine causes osmotic diuresis. That is, the osmotic effect of glucose in the renal tubules greatly decreases tubular re-absorption of fluid. The overall effect is massive loss
of fluid in the urine, causing dehydration of the extracellular fluid, which in turn causes compensatory dehydration of the intracellular fluid. Thus, polyuria (excessive urine excretion), intracellular and extracellular dehydration and increased thirst are symptoms of diabetes.

2) **Chronic high glucose concentration causes tissue injury**

When glucose level in blood is inadequately controlled over long periods in diabetes mellitus, blood vessels in multiple tissues throughout the body begin to function abnormally and undergo structural changes that result in inadequate blood supply to the tissues. This in turn leads to increased risk for heart attack, stroke, serious kidney disease, retinopathy, blindness, ischemia and gangrene of the limbs. Chronic high glucose concentration also causes damage to many other tissues. For example, peripheral neuropathy, which is abnormal function of peripheral nerves, and autonomic nervous system dysfunction are frequent complications of chronic, uncontrolled diabetes mellitus. These abnormalities can result in impaired cardiovascular reflexes, impaired bladder control, decreased sensation in the extremities, and other symptoms of peripheral nerve damage. The precise mechanism that causes tissue injury in diabetes is not well understood but probably involves multiple effects of high glucose concentrations and other metabolic abnormalities. Hypertension and atherosclerosis often develop in patients with diabetes and amplify the tissue damage caused by the elevated glucose.

3) **Diabetes Mellitus causes increased utilization of fats and metabolic acidosis**

The shift from carbohydrate to fat metabolism in diabetes increases the release of keto acids, such as aceto-acetic acid and β-hydroxybutyric acid, into the plasma more rapidly than they can be taken up and oxidized by the tissue cells. As a result, the patient develops severe metabolic acidosis from the excess keto acids, which, in association with dehydration due to the excessive urine formation, can cause severe acidosis. This leads rapidly to diabetic coma and death unless the condition is treated immediately with large amounts of insulin. All the usual physiologic compensations that occur in metabolic acidosis take place in diabetic acidosis. They include rapid and deep breathing, which causes increased expiration of carbon dioxide; this buffers the acidosis but also depletes extracellular fluid bicarbonate stores. The kidneys compensate by decreasing bicarbonate excretion and generating new bicarbonate and is added back to the extracellular fluid. The overall changes in the electrolytes of the blood as a result of severe diabetic acidosis. Excess fat utilization in the liver occurring over a long time causes large
amounts of cholesterol in the circulating blood and increased deposition of cholesterol in the arterial walls. This leads to severe arteriosclerosis. [12]

4) Diabetes causes protein depletion

Use of protein and fat to generate energy causes decreased storage of proteins as and fat. Therefore, a person with severe untreated diabetes mellitus suffers rapid weight and energy loss despite eating large amounts of food. Without treatment, these metabolic abnormalities can cause severe wasting of the body tissues and death within a few weeks.

5.1.1 Type II Diabetes - Resistance to the metabolic effects of insulin

Type II diabetes is far more common than type I accounting for about 90 per cent of all cases of diabetes mellitus. In most cases, the onset of type II diabetes occurs after age 30, often between the ages of 50 and 60 years, and the disease develops gradually. Therefore, the syndrome is often referred to as adult-onset diabetes. Recently, there has been a steady increase in the number of younger individuals, some less than 20 years old, with type II diabetes. This trend appears to be related mainly to the increasing prevalence of obesity, the most important risk factor for type II diabetes in children as well as in adults.

Type II diabetes is associated with increased plasma insulin concentration (hyper-insulinemia). Diminished sensitivity of target tissues to the metabolic effects of insulin is a condition referred to as insulin resistance. The decrease in insulin sensitivity impairs carbohydrate utilization and storage, raising blood glucose and stimulating a compensatory increase in insulin secretion. Development of insulin resistance and impaired glucose metabolism is usually a gradual process, beginning with excess weight gain and obesity.

Most of the insulin resistance appears to be caused by abnormalities of the signaling pathways that link receptor activation with multiple cellular effects. Insulin resistance is closely related to toxic effects of lipid accumulation in tissues.

Also it is more likely associated with accumulation of adipose tissue in the abdominal cavity around the visceral organs.

The major adverse consequence of the metabolic syndrome is cardiovascular disease, including atherosclerosis and injury to various organs throughout the
body. Several of the metabolic abnormalities associated with the syndrome are risk factors for cardiovascular disease.

5.1.3 Development of Type II Diabetes during Prolonged Insulin Resistance

With prolonged and severe insulin resistance, even the increased levels of insulin are not sufficient to maintain normal glucose regulation. As a result, moderate hyperglycemia occurs after ingestion of carbohydrates in the early stages of the disease.

**Fasting blood glucose and insulin levels**

The fasting blood glucose level in the early morning is normally 80 to 90 mg/100 ml, and 110 mg/100 ml is considered to be the upper limit of normal. A fasting blood glucose level above this value often indicates diabetes mellitus or at least marked insulin resistance. In type II diabetes, plasma insulin concentration may be several times higher than normal and usually increases to a greater extent after ingestion of a standard glucose load during a glucose tolerance test.

**Glucose tolerance test**

Glucose tolerance curve shows, when a normal, fasting person ingests 1 gram of glucose per kilogram of body weight, the blood glucose level rises from about 90 mg/100 ml to 120 to 140 mg/100 ml and falls back to below normal in about 2 hours. In a person with diabetes, the fasting blood glucose concentration is almost always above 110 mg/100 ml and often above 140 mg/100 ml. On ingestion of glucose, blood glucose level changes as demonstrated by the upper curve in figure 5.1. The glucose level falls back to the control value only after 4 to 6 hours; furthermore, it fails to fall below the control level. The slow fall of this curve and its failure to fall below the control level demonstrate that either the normal increase in insulin secretion after glucose ingestion does not occur or there is decreased sensitivity to insulin. The figure-5.1 shows the glucose level in the blood for normal and diabetic subject. [37]
Hypoglycemic episodes or large variability in glucose blood levels develop sympatho-vagal imbalance of cardiac autonomic function. Hypoglycemia can influence long-term prognosis of onset and progression of microvascular and macrovascular complications. Thus an intensive glycemic control has been suggested to improve prognosis in patients with diabetes. However, recent trials failed to demonstrate a significant reduction in cardiovascular events with an intensive glycemic control. These data might be related to an increased incidence of hypoglycemic episodes or large variability in glucose blood levels. Previous studies reported that episodes of hypoglycemia may indeed impair cardiac autonomic function causing sympathetic activation and vagal withdrawal which, in patients with coronary artery disease (CAD), may trigger or help in enhancing ischemic or arrhythmic events. [10]

5.1.4 Hormonal effects on SA node activation due to diabetes mellitus

The concentrations of neurotransmitters can change the depolarization rate of an SA nodal cell to regulate heart rate, the concentrations of Norepinephrine and Acetylcholine as the modulating signals for the SA node activation rate. The heart rate accelerates when the concentration of Norepinephrine increases, and that it decelerates when the concentration of Acetylcholine increases. Under normal physiological circumstances linear combination of both hormones govern the SA node activation. Under diabetic conditions, the concentration of Acetylcholine is more than the norepinephrine thus vagal tone is more dominating. As a result, any
demand from the body for increased blood not fulfilled as SA node firing rate cannot be increased. As a compensatory mechanism for this limitation, the basal heart rate is more and heart rate variability is restricted. [10]

It has also been observed that due to the diabetic autonomous neuropathy, there is reduced conduction of the chemoreceptors at the nerve endings. The conduction of the synapse is delayed due to microvascular conduction of neural cells is reduced due to prevailing diabetic conditions. [53] and [54]

To conclude about complications and disorders due to diabetes, the continuous monitoring by noninvasive diagnostic technique can modify the prognosis. Strict glycemic control and regular exercise also may control the mortality and morbidity rate. HRV analysis as routine checkup is the solution for all the above mentioned complications.

Whenever there is any stimulus, the heart rate increases to meet the sudden demand of blood in accordance to the stimulus. The RR interval is reduced and heart rate is increased according to the demand of the blood from the body. In accordance with the homeostasis (phenomenon tries to maintain the body organs to normal conditions) the R-R interval retains to normal average by hormonal balance at pre-ganglionic stage. The hormones are of two types-Sympathetic and parasympathetic hormones. Sympathetic hormones stimulate the heart to act fast so as to meet sudden blood requirement. Parasympathetic hormone acts the opposite way. The chemical norepinephrine stimulate sympathetic hormone whereas acetylcholine stimulates parasympathetic hormone.

In diabetic subjects, it has been observed that parasympathetic activity is predominant. Under prolonged diabetic condition, with poor glycemic control, the secretion of acetylcholine is more.

The action of acetylcholine brings about the following changes-

1) The diastolic depolarization rate is reduced. The reduced depolarization rate is associated with reduced relaxation time. This reduces the blood volume filled from pulmonary vein and affects the cardiac throughput. [66]
2) Acetylcholine secretion is also associated with release of Ca\(^{2+}\)- Na\(^{2+}\) that enhances the contractility thereby reducing the relaxation period required for ventricular filling.[67]

3) Acetylcholine facilitates vasodilatation that affects the ventricular filling from pulmonary vein. All the above stated facts combine to reduce the cardiac output and the left ventricular ejection fraction.[40]

4) Diabetic metabolism reduces bioavailability of NO in vascular beds. This causes vasoconstriction. As a result, the flow and supply of nutrients is restricted to various organs. [40]

5) The vasoconstriction also causes micro neuropathy as the capillary beds are constricted.[40]

6) Due to delayed oxygen supply due to atherosclerosis and vasoconstriction, diabetic subjects have low exercise tolerance.[40] and

5.2 Complication due to hypertension

Introduction

Prevalence of primary hypertension or essential hypertension is 90-95%. It is the hypertension is of unknown origin. (Secondary hypertension is caused, due to renal or arterial stenosis.) In some patients with primary hypertension, there is a strong hereditary tendency, the same as occurs in animal strains of genetic hypertension discussed above. In most patients, excess weight gain and sedentary lifestyle cause hypertension. [40]

For the heart to function normally, blood pressure control is required. The normal adult blood pressure is systolic below 120mm Hg and diastolic below 80 mm Hg. When the blood pressure is low, blood cannot reach all the peripheral organs effectively. [40]

Effects of hypertension
1. Cardiac output is increased due, in part, to the additional blood flow required for the extra adipose tissue. However, blood flow in the heart, kidneys, gastrointestinal
tract, and skeletal muscle also increases with weight gain due to increased metabolic rate and growth of the organs and tissues in response to their increased metabolic demands. As the hypertension is sustained for many months and years, total peripheral vascular resistance may be increased.

2. Sympathetic nerve activity, especially in the kidneys, is increased in overweight patients. The causes of increased sympathetic activity in obesity are not fully understood, but recent studies suggest that hormones, such as leptin, released from fat cells may directly stimulate multiple regions of the hypothalamus, which, in turn, have an excitatory influence on the vasomotor centers of the brain medulla.

3. Angiotensin II and aldosterone levels are increased two- to threefold in many obese patients. This may be caused partly by increased sympathetic nerve stimulation, which increases renin release by the kidneys and therefore formation of angiotensin II, which, in turn, stimulates the adrenal gland to secrete aldosterone.

4. The renal-pressure natriuresis mechanism is impaired, and the kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high or unless kidney function is somehow improved. If the mean arterial pressure in the essential hypertensive person is 150 mm Hg, acute reduction of the mean arterial pressure artificially to the normal value of 100 mm Hg (but without otherwise altering renal function except for the decreased pressure) will cause almost total anuria, and the person will retain salt and water until the pressure rises back to the elevated value of 150 mm Hg. Chronic reductions in arterial pressure with effective antihypertensive therapies, however, usually do not cause marked salt and water retention by the kidneys because these therapies also improve renal-pressure natriuresis. [40]

5.2.1 Role of hormones in Blood pressure control

The predominant hormones regulating the blood pressure are-

1) Angiotensin II causes vasoconstriction to increase the blood pressure.
2) There is a family of kinin hormones that decrease blood pressure by vasodilation. Bradykinin is one example of kinins.
3) Norepinephrine and Epinephrine are associated with sympathetic and parasympathetic activity controlling the blood pressure.

Norepinephrine and Epinephrine

Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less so and in some tissues even cause mild vasodilation. Sympathetic nervous system stimulates during stress or exercise, the sympathetic nerve endings in the individual tissues release norepinephrine, which excites the heart and contracts the
veins and arterioles. In addition, the sympathetic nerves to the adrenal medullae cause these glands to secrete both norepinephrine and epinephrine into the blood. These hormones then circulate to all areas of the body and cause almost the same effects on the circulation as direct sympathetic stimulation, thus providing a dual system of control:
(1) Direct nerve stimulation and
(2) Indirect effects of norepinephrine and/or epinephrine in the circulating blood.

5.2.3 Role of ions in blood pressure control

Many different ions and other chemical factors can either dilate or constrict local blood vessels. Most of them have little function in overall regulation of the circulation, but some specific effects are:
1. Increase in calcium ion concentration causes vasoconstriction. This results from the general effect of calcium to stimulate smooth muscle contraction.
2. An increase in potassium ion concentration causes vasodilation. This results from the ability of potassium ions to inhibit smooth muscle contraction.
3. An increase in magnesium ion concentration causes powerful vasodilation because magnesium ions inhibit smooth muscle contraction.
4. An increase in hydrogen ion concentration (decrease in pH) causes dilation of the arterioles. Conversely, slight decrease in hydrogen ion concentration causes arteriolar constriction.
5. Anions that have significant effects on blood vessels are acetate and citrate, both of which cause mild degrees of vasodilation.
6. An increase in carbon dioxide concentration causes moderate vasodilation in most tissues, but marked vasodilation in the brain. Also, carbon dioxide in the blood, acting on the brain vasomotor center, has an extremely powerful indirect effect, transmitted through the sympathetic nervous vasoconstrictor system, to cause widespread vasoconstriction throughout the body. [38]

5.2.4 Treatment of Essential Hypertension

Current guidelines for treating hypertension recommend, as a first step, lifestyle modifications that are aimed at increasing physical activity and weight loss in most patients. Unfortunately, many patients are unable to lose weight, and pharmacological treatment with antihypertensive drugs must be initiated. Two general classes of drugs are used to treat hypertension:
(1) vasodilator drugs that increase renal blood flow and
(2) natriuretic or diuretic drugs that decrease tubular reabsorption of salt and water.
Different ones act in one of the following ways:
(1) By inhibiting sympathetic nervous signals to the kidneys or by blocking the action of the sympathetic transmitter substance on the renal vasculature,
(2) By directly relaxing the smooth muscle of the renal vasculature, or
(3) By blocking the action of the renin-angiotensin system on the renal vasculature or renal tubules. [38]

The types of treatment is-
1) β blockers:
   The stress receptors that stimulate the sympathetic input is blocked.
2) ACE inhibitors:
   The Angiotensin converting enzyme is inhibited.
3) Diuretics:
   To get rid of extra sodium ions, body’s ability to reabsorb sodium is inhibited.

5.2.5 Effect of hypertension on HRV

Initial prevalence of hypertension increases the cardiac output, increases the sympathetic power and heart rate variability is reduced. The heart rate variability of hypertensive subjects under β blocker treatment is similar as normotensives of the same age. [25] Whereas the hypertensives undergoing other type of treatment record a reduced Heart Rate Variability. There is no constant decrease in HRV with prevalence of the hypertensive condition. At later stage, cardiac output is decreased, sympathetic power is reduced and heart rate is increased. The annual rate of decline of HRV is more in hypertensives than control group. Untreated hypertensives have highest decline rate. [25] It is also observed that normotensives with lower HRV are more likely to develop hypertension. [25]

The complications of hypertension are left ventricular diastolic dysfunction and left ventricular hypertrophy. To avoid complications, it is very essential to control the blood pressure.