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Editorial

What to know about insulin treatment?

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Diabetes Mellitus is a chronic and complex disease with glycemic control at the center of its treatment and requires continuous monitoring and treatment of complications. Clinical studies such as DCCT/EDIC and UKPDS have shown that proper glycemic control is effective in preventing early and late complications of diabetes.[1-4] Insulin therapy is a critical part of treatment for people with type 1 diabetes and also for many patients with type 2 diabetes.

Type 1 Diabetes

In type 1 diabetes, there is no insülin production at all due to the autoimmune destruction of beta cells.[5] Since 1923, insulin has been a lifesaving miracle drug in the treatment of type 1 diabetes. Patients with type 1 diabetes generally needs multiple daily insulin injection from the onset of the disease.

Two types of insulin, long/longer-acting (basal) and rapid-acting (bolus), are used in the intensive treatment that called basal-bolus regimen .[6,7] While, basal insulin provides glycemic control between meals, rapid-acting analog insulin that administered just before the meals control post-prandial hyperglycemia. Studies have shown that long-acting insulins have better effects on glycemic control and have lower risk of hypoglycemia.[8-11]

Initially, the total daily insulin requirement is determined between 0.4-1.0 IU/kg/day according to the patient's metabolic status and weight. In patients with stable metabolic status 0.5 IU/kg/day is usually preferred as the initial dose.[6,12] Half of the calculated daily dose is administered as a basal insulin, while the other half is divided into three and administered before each meals as a bolus injection.[13,14] In patients with a healthy lifestyle, if hypoglycemia occurs during fasting in the morning, basal insulin dose should be reviewed, and bolus insulin dose should be reviewed if it occurs at 2 hours after meal.

Following the initial dose recommended in the guidelines, the individual insulin dose that required by the patient should be determined as soon as possible with intensive blood glucose monitoring. The diet and individualized insulin dose titration according to the efficacy characteristics of the selected insulin should be dynamically performed just after starting insulin treatment. Fasting blood glucose measurements are important to determine basal insulin dose and post-pandial blood glucose levels are necessary for the judgment of bolus insulin dose. Post-prandial blood glucose levels are directly related to the meal ingredients. Patients' training on nutrition-based insulin dose adjustment is crucial to sustain daily life.[15-17]

Learning carbohydrate counting is essential for the patients to assume required bolus insulin dose.[18]

Type 2 Diabetes

In patients with type 2 diabetes, initially, beta-cell usually have insulin synthesis and secretion disorders, as well as insulin resistance in peripheral tissues such as liver, skeletal muscle, adipose tissue, and brain.[19]

In these patients, oral antihyperglycemic

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treatment is applied primarily to provide glycemic control.[17, 20] In patients who can not maintain adequate glycemic control with oral antihyperglycemic combination therapies, combination with basal insulin or GLP-1 analogs are considered as the most appropriate treatment.[21,22]

Since insulin has the advantage of being effective when other agents are not effective in type 2 diabetes, it should be considered to include it in oral therapy in the presence of severe hyperglycemia symptoms such as weight loss and ketosis.[23] There are studies showing that glycemia can be controlled better, and the risk of hypoglycemia is lower by using longer-acting insulins as basal insulin.[24-29] It has been reported that glycemic control is very successful, and weight gain and hypoglycemia risk are low in type 2 diabetic patients with long-acting basal insulin and GLP-1 combined preparations, which have been used in recent years.[30-34]

Many patients with type 2 diabetes require insulin treatment over time. Patients with type 2 diabetes should be explained in simple language that insulin treatment may be needed over time due to the progressive nature of the disease, which is a normal process for this disease.

Insulin therapy should be considered as the initial treatment in patients with type 2 diabetes with a blood glucose of 300-350 mg/dl and/or HbA1c 10-12%. When combination therapy with insulin is required in the treatment of oral antidiabetic agents in type 2 diabetes, it is recommended to add basal insulin therapy in the first step. Basal insulin starting dose is 10 IU/day or 0.1-0.2 IU/kg/day depending on the degree of hyperglycemia.

After starting insulin treatment with the initial dose that recommended in the guidelines, actual personalized dose of the patient should be determined as soon as possible. Basal insulin dose adjustments are made every 3-4 days until fasting glycemia levels reach the target value. In patients with a healthy lifestyle, if morning fasting hypoglycemia occurs, the switch of basal insulin to oral agents should be evaluated. If dose adjustments were not applied, and the treatment with initial doses continued, most of the patients will remain in poorly controlled conditions with insufficient doses of insulin for many years.

It is not recommended to stop oral antihyperglycemic agents when basal insulin therapy is initiated, unless there is a contraindication. Due to the water-retaining effect of pioglitazones, patients' condition should be evaluated carefully before the addition of basal insulin to previous therapy which already had the water-retaining effect. Metformin is usually added into the combination with basal insulin therapy.

Post-prandial glucose elevations should be considered after fasting glycemia has reached target levels with basal insulin titration, but HbA1c levels persist above the target.[6] When basal insulin doses are >5 IU/kg/day, the addition of bolus insulin to the most intense meal or a combination with a GLP-1 analog should be considered.[6] Options include a GLP-1 receptor analog or the addition of bolus insulin prior to the most substantial meal of the day. Since the effects of rapid-acting analog insulins begin within a few minutes, they are used as a bolus to prevent hyperglycemia after meals.[35-37]

If one basal and one bolus insulin treatment is not sufficient, GLP-1 receptor agonist or bolus insulin may be added to the other meals.[38,39] In patients with type 2 diabetes, prandial insulin is usually started at 4 IU or 10% of the basal dose.[6]

While insulin doses are personalized, basal insulin dose should be monitored with fasting glycemia in the morning, and bolus doses should be regulated with the glucose monitoring 2 hours after meal.

Premixed insulins are preferred less because of the risk of hypoglycemia.[6] Although 2-3 doses of premixed (biphasic) insulin treatments are cheap, they can only be used in patients with low risk of post-prandial hypoglycemia.

Insulint types in market are listed in Table 1.

Continuous subcutaneous insulin pumps

Subcutaneous pumps have been used as an alternative to basal-bolus insulin treatment, although they are costly. These pumps use rapid-acting insulins, and the basal insulin requirement is met automatically by the pump at frequent intervals throughout the day, and the bolus insulin requirement is determined by the patient based on the condition of the meal to be taken. In meta-analysis studies comparing subcutaneous continuous insulin pumps with basal-bolus treatment, there was a slight difference in the reduction of HbA1c levels and in favor of pump therapy.[40]

For the last two years, hybrid closed-loop

Table 1. Insulin types in use

		Action start time	Peak time	Action duration time
Prandial (bollus) insulins				
Short-acting human Recombinant DNA	Human regular	30-60 min.	2-4 hours	5-8 hours
Rapid-acting analogs	Glulisine Aspart Lispro	15 min.	30-90 min.	3-5 hours
Basal insulins				
Intermediate-acting	Human NPH	1-3 hours	8 hours	12-16 hours
Long acting	Glargine U-100 Glargine U-100 biosimilar Detemir	60-90 min.	No peak	20-26 hours
Longer acting	Glargine U-300 Degludec U-200	6 hours 2 hours	No peak No peak	30 hours 40 hours
Premixed insulins				
NPH/Regular, %	70/30	30-60 min.	Changing	10-16 hours
NPL/Lispro, %	75/25 or 50/50	10-15 min.	Changing	10-16 hours
NPA/Aspart, %	70/30 or 50/50			
Degludec/Aspart, %	70/30	10-15 min.	Changing	40 hours
Glargine /Lixisenatide	Glargine U-100 20 or 30 IU/ Lixisenatide 10 μg.	60-90 min.	No peak	30 hours

pumps have been used in the USA to regulate both basal and bolus insulin doses throughout the day [41-43]

Inhaled Insulins

Inhaled insulins have been introduced to control postprandial glycemia. After starting treatment with these insulins, continuous monitoring of lung function is required about mouth, throat, upper respiratory tract, and lung problems.[44]

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Review

Obesity and Hypertension

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Abstract

Obesity is an important public health problem with increasing frequency, leading to different comorbidities including hypertension and can cause mortality. Possible mechanisms that increase blood pressure in overweight and obese people are renal damage, activation of the renin-angiotensin-aldosterone system, insulin resistance, hyperinsulinemia, sleep apnea syndrome, leptin-melanocortin pathway and genetic predisposition. Most of these mechanisms stimulate the sympathetic nervous system. Medical nutrition therapy, lifestyle interventions, medical and/or surgical antiobesity treatment modalities contribute to the control of blood pressure via weight loss. Besides antihypertensive medications should be chosen carefully in overweight and obese patients and drug groups preventing weight loss should not be preferred if possible.

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Keywords: Hypertension, kidney, obesity, overweight, treatment.

Introduction

Obesity is a very important public health problem worldwide as well as an important cause of morbidity and mortality. Obesity substantially increases the risk of diseases such as type 2 diabetes mellitus, fatty liver disease, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnea and breast or colon cancers, thereby contribute to a decline in both quality of life and life expectancy.[1,2] Obesity may occur after genetic and environmental factors and often occurs with the influence of environmental factors. Changing lifestyle and dietary habits increase the prevalence of obesity in both childhood and adulthood. Not only weight gain but also body fat distribution is important in hemodynamic and metabolic changes seen in obesity. The risks associated with obesity are higher in patients with abdominal or central obesity. Increased body fat amount presents with increased body mass index (BMI), body weight and waist circumference that relates with insulin resistance and hypertension.[3] In NHANES (National Health and Nutrition Examination Survey) 1999–2010,

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35.7% of obese individuals had hypertension.[4] Besides, being obese in childhood is known to increase the risk of developing adulthood hypertension by 2.7 times.[3,5] Nurses' Health Study, which included 18-year follow-up data for 77,690 women aged 30-55 years, and Health Professionals Follow-up study, which included 10-year follow-up data for 46,060 men aged 40-75 years, indicated that the incidence of hypertension is increased as the body weight and BMI increased.[6,7] In these studies it has also been reported that the frequency of hypertension is increased even when the BMI was within the normal range but elevated from the lower limit to the upper limit of normal.[5-7]

It's known that each 10 kg increase in body weight increases systolic blood pressure (SBP) by 3 mmHg, diastolic blood pressure (DBP) by 2.3 mmHg and these elevations in blood pressure increase the risk of coronary artery disease by 12% and stroke risk by 24%.[8] Increased blood pressure in obesity is associated with high cardiac output and increased systemic vascular resistance. When the haemodynamic difference between hypertensive and normotensive obese individuals is examined, it is seen that systemic vascular resistance is relatively higher in hypertensive than in normotensive subjects.[9]

Pathogenesis

Various possible mechanisms that increase blood pressure in overweight and obese people are considered which are genetic predisposition, renal damage, insulin resistance and hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, sleep apnea syndrome and leptin-melanocortin pathway. Most of these mechanisms stimulate the sympathetic nervous system, leading to increased blood pressure. The most basic difference is due to genetic predisposition.[10,11] Obesity and in particular excessive visceral fat distribution is accompanied by several alterations at hormonal, inflammatory and endothelial level. These alterations induce a stimulation of several other mechanisms that contribute to the hypertensive state. The main role in the mechanisms of obesity and obesity-related hypertension other than genetic and environmental factors is caused by the sympathetic nervous system, renal and renal functions, endothelium, adipokines and insulin resistance.[12]

Arterial baroreceptors have a central role in cardiovascular homeostasis control and represent the main restraining mechanism on sympathetic tone. Both sympatho-inhibitory and sympatho-excitatory components in the control of arterial baroceptor of sympathetic nerve activity show impairment in obesity and obesity-related hypertension.[12] There are additional factors affecting the relationship between body weight and blood pressure. Insulin has vasodilatory action normally. The presence of insulin resistance contributes to increased sympathetic system activation, water and salt reabsorption from the kidneys, endothelial dysfunction and the development of hypertension by inducing muscular hypertrophy in the vessels.[8,10,11] The relationship between adiposity and blood pressure varies among individuals. Adiponectin and leptin are the most important products of adipose tissue involved in blood pressure control by regulating arterial tone. Adiponectin levels decrease in obesity and may be protective against an increase in arterial blood pressure through an endothelium-dependent mechanism.[12] Leptin is the protein that transfers the amount of stored adiposity to the brain. The ratio of leptin's concentration in serum and stored fat is 0.9. High leptin levels due to increased adiposity increase renal sympathetic tone by long-term renal sympathetic stimulation and lead to hypertension. In this situation, leptin's effects on reduction in food intake and thermogenesis are eliminated.[10] Melanocortin receptors are found in leptin and insulin responsive neurons and play a role in the regulation of energy balance and blood pressure. Increased sympathetic activity caused by hyperinsulinemia has been shown to decrease when melanocortin receptors are antagonized.[13,14] Adipose tissue produces pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6. They can induced insülin resistance and promote endothelial dysfunction.[15]

Obstructive sleep apnea is a common disorder and is linked to an epidemic of obesity. While it's prevalence in the general population is 2-5% in women and 3-7% in men, the prevalence of the disease in overweight or obese people ranges from 40% to 90%.[16,17] Possible mechanisms to increase blood pressure associated with sleep apnea can be explained by increased sympathetic system activation, increased aldosterone levels and increased endothelin levels with recurrent

hypoxic episodes.[10,17] Depending on the severity of obesity and the concomitant presence of breathing alterations, chronic intermittent hypoxia and obstructive apnea, the reflex impairment involving other reflexogenic areas such as the cardiopulmonary receptors and the chemoreceptors may participate in the occurrence of the hyperadrenergic state.[12]

Renal abnormalities

Increased renal tubular sodium reabsorption plays an important role in the onset of obesity-related hypertension by disrupting pressure-associated natriuresis. They may be related to an increment in mineralcorticoid activity. Potential mechanisms of abnormal renal function in obesity are compression of the kidneys with surrounding adipose tissue, activation of the renin-angiotensin-aldosterone system and increased activity of the sympathetic nervous system.[10,11] Visceral obesity can lead the development of kidney disease with the accumulation of extracellular matrix in the renal medulla that causes both vascular and tubular compression.[12] BMI is an independent risk factor for chronic kidney disease. Obesity related glomerulopathy is observed in patients with BMI >30 kg/m^2. The most common histological changes in renal biopsy in obesity-related glomerulopathy are glomerulomegaly and focal segmental glomerulosclerosis. The electron microscope shows changes in the podocytes in the glomeruli. Major changes in podocytes are reported as swelling and vacuolization in cells, focal fusion site expansion and decreased cell density. Although the mechanisms of these changes are not clearly defined, they are tried to be explained by hemodynamic forces such as glomerular hyperfiltration and increase in renal plasma flow and the effect of growth factors such as insulin, renin-angiotensin-aldosterone and transforming growth factor β. In patients with renal damage, hypertension, edema, nephrotic syndrome and in long-term renal failure can be seen clinically in obese people.[18]

Nowadays, chronic renal complications of obesity are called obesity-related glomerulopathy (ORG). The diagnosis of ORG is based on BMI values of ≥30 kg/m^2 and exclusion of other renal diseases both clinically and histopathologically. There is no absolute relationship between the occurrence of ORG and the severity of obesity. The initial symptom in most cases is isolated proteinuria of unknown onset with or without renal failure.15 Typical features of renal histopathology for ORG patients include glomerulomegaly and focal segmental glomerulosclerosis (FSGS).[19,20] Glomerulomegaly is probably the result of abnormalities in renal hemodynamics associated with obesity. FSGS lesions may not be present in all cases of ORG, which may be related to the degree of obesity or renal impairment.[15] Obesity related FSGS exhibits a predominance of the perihilar variant, which reflects an excessive pressure load on the vascular poles of glomeruli due to the renal hemodynamic abnormalities of obesity.[19]

Glomerular hypertrophy and glomerulomegaly in ORG may cause glomerular podocytes to enlarge their foot processes to cover the expanded glomerular surface area. Consistently, there is a relative reduction in the coating area of glomerular podocytes on the glomerular surface in patients with ORG. In the result of changes in podocyte function, loss of protein selectivity, podocyte detachment and replacement by matrix deposition may result in FSGS.[15] Obesity related FSGS can be confused with idiopathic FSGS. It is important to make a differential diagnosis. The incidence of foot process fusion between glomerular podocytes in ORG was lower than in idiopathic FSGS (40% vs. 75%).[20] In ORG, the patients are older at the time of diagnosis compared to idiopathic FSGS (mean age 43-46 vs. 32 years). Although edema and nephrotic syndrome can be seen in both situations, it is milder in ORG. Lower proteinuria, higher serum albumin and lower serum cholesterol levels are detected in ORG. ORG progresses to renal failure slower.[19,21,22] Although ORG has a better prognosis than idiopathic FSGS, it is a serious disease with long-term poor prognosis.[21,23] It is important to prevent the damage and depletion of podocytes by treatment. To achieve this, weight loss, systemic and intraglomerular hypertension control is necessary. In obese hypertensive patients, angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEi) are able to significantly reduce sympathetic nerve activity and adequately control blood pressure.[19,24,25] However, it has been shown in studies conducted with patients with O-FSGS that ACEi can halt the progression of renal failure

if renal function is still normal.[21]

Typical ORG lesions were seen in 41% of biopsies of obese patients with proteinuria and renal dysfunction, but the rest were additional diseases. While proteinuria was the highest in patients with idiopathic FSGS and immune complex diseases, it was subnephrotic in obesity-related FSGS and tubulointerstitial diseases. Creatinine levels were highest in tubulointerstitial diseases and progressive diabetic nephropathy.[22] Various renal pathologies such as diabetic nephropathy, hypertensive nephrosclerosis, mesangial cell proliferation and matrix expansion can be seen in patients with hypertension and obesity. Obesity may worsen proteinuria in non-glomerulonephritis, IgA nephropathy and benign nephrosclerosis. Obesity is associated with structural changes such as glomerulomegaly and glomerular basement membrane thickening similar to changes in ORG.[26] Glomerulomegaly and increased glomerular basement membrane thickness resembling early diabetic nephropathy in the absence of diabetes are observed in kidney biopsies of patients with morbid obesity even before the appearance of microalbuminuria.[27] Some obese hypertensive patients with moderate to severe vascular lesions which are accompanied by collapsed glomeruli are diagnosed with hypertensive nephrosclerosis instead of ORG.[15] Occasionally, focal lipid vacuoles appear in the cytoplasm of glomerular mesangial cells and tubular epithelial cells.[28]

Relationship between weight loss and blood pressure

Weight loss is recommended to reduce blood pressure in overweight and obese patients with hypertension because various studies have shown that weight loss diets reduce body weight and blood pressure.[3,29] In a metaanalysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively.[30] A recent systematic review of eight studies in hypertensive patients revealed that behavioral weight loss reduced SDP and DBP by 4.5 and 3.2 mmHg, respectively.[31] Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure.[32] Medical nutrition therapy, lifestyle changes, medical and/or surgical methods contribute to the control of weight loss and blood pressure values in obese hypertensive patients.[8]

The drugs used in the medical treatment of obesity in our country are orlistat and liraglutide. Orlistat is a gastrointestinal lipase enzyme inhibitor that prevents fat absorption and provides weight loss. Many weight loss medications, particularly sympathomimetic amines, raise blood pressure despite a decrease in weight. However, some weight loss medications such as orlistat can lower blood pressure.[33] The recommended daily dose for orlistat is 3x120 mg orally. Liraglutide is a GLP-1 analogue and shows its main effect by suppressing appetite and creating a sense of satiety. The recommended daily dose of liraglutide for antiobesity treatment is 1x3 mg/day subcutaneously, which is obtained by gradually increasing the dose in weeks. In studies evaluating the effect of orlistat related weight loss on blood pressure in obese or overweight hypertensive patients and comparing it with placebo, it was shown that both weight loss and SBP and DBP reductions were significantly higher in orlistat group.[34] Orlistat reduced SBP as compared to placebo by -2.5 mmHg and DBP by -1.9 mmHg.[35] In studies evaluating the effect of weight loss with liraglutide on blood pressure in obese patients, it has been shown that weight and blood pressure controls were better in patients receiving liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet compared to patients receiving intensive behavioral therapy alone or with liraglutide after 52 weeks of interventions (-15.3, -14.1, -13.3 mmHg at SBPs and -3.5, -3.0 and -2.9 at DBPs, respectively).[36]

Gastric bypass, sleeve gastrectomy, gastroplasty and gastric bandage are several different methods that can be used in obesity surgery.[8,34,36,37] In a study in which surgical and medical treatments were compared in terms of long-term obesity-related comorbidities in obese patients, the rates of patients having remissions in comorbidities such as hypertension, diabetes and dyslipidemia were significantly higher and the rates of patients with newly diagnosed hypertension, diabetes and dyslipidemia were significantly lower in the surgical group compared to the medical group at the end of 6.5-year follow-up period. However, the rates of new onset depression and anxiety were significantly higher in the surgical group compared to the medical group.[37] In

some studies that compared the effects of anti-obesity treatments on blood pressure in obese patients, the weight loss ratios were significantly higher in the surgical group, while there was no significant difference between the medical and surgical groups in terms of blood pressure reduction rates.[8] The long-term effects of weight loss surgery on blood pressure over an 8-year period were examined in the SOS (Swedish Obese Subjects) study.[38] Bariatric surgery controlled hypertension by reducing blood pressure in two years compared to obese patients who had not undergo surgery. However, the weight reduction (20.1±15.7 kg, 16.3%) after bariatric surgery had a dramatic effect on the 8-year incidence of diabetes, whereas it had no effect on the 8-year incidence of hypertension.[38] Therefore, the relationship between the duration of obesity and hypertension and the effect of cardiometabolic bariatric surgery on blood pressure remains unclear. Perhaps, bariatric surgery in obese individuals may prevent the development of resistant hypertension and target organ damage.[39]

Antihypertensive drug selection in overweight and obese patients

Antihypertensive medications should be chosen carefully in overweight and obese patients and drug groups which make losing weight difficult should not be preferred if possible. Weight loss can also improve efficacy of antihypertensive medications and cardiovascular risk profile.[40] Because this axis plays a particularly prominent role in the pathophysiology of hypertension in obesity, treatment of inhibition of the renin-angiotensin-aldosterone system by ACEi or ARB should be used as the first drug for blood pressure control in these patients. These drugs are equally or more effective than other antihypertensive drugs in blood pressure control, left ventricular hypertrophy and insulin resistance reduction, kidney protection, sympathetic attenuation and baroreflex control improvement without adverse effects on weight and metabolism.[41,42] Most obese hypertensive patients require two or more antihypertensive drugs. If necessary, the combination of antihypertensive treatment with calcium channel blockers may be considered.[41]

The preferred antihypertensive drugs in overweight or obese patients should not only lower blood pressure but also maintain body weight and have no adverse effect on metabolism (eg, glycemia, insulin sensitivity and lipids). In CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan) study, the new occurrence of diabetes mellitus in candesartan (an ARB) group was significantly lower than amlodipine (a long-acting calcium channel blocker) group. This preventive effect was more marked in obese patients with a BMI of 25 kg/m^2 or greater based on the results of subanalysis.[43] Although not recommended, thiazide diuretics and beta blockers may be used in some patients. If beta blockers are mandatory, labetolol, carvedilol and nebivolol might be preferred.[8] Also beta blockers and alpha blockers can promote weight gain.[42] Although the exact mechanisms how beta blockers prevent weight loss and cause weight gain has not been demonstrated yet, decreased basal metabolic rate due to decreased sympathetic tonus and/or inhibitory effects of catecholamines on appetite are thought to be the main mechanisms. Studies have shown that beta blockers reduce total energy expenditure by 5-10%, which means 100-200 kcal less energy expenditure per day. It has also been shown that beta blockers increase insulin resistance and reduce lipolysis.[44] Diet-induced thermogenesis, fat oxidation rate and weekly activity were lower in patients receiving beta blockers than in control patients.[45] Thiazide diuretics are known to increase insulin resistance, making weight lost difficult. Some studies have shown that hypopotasemia due to diuretics increases insulin resistance by suppressing insulin secretion.[46] In a study, administration of hydrochlorothiazide in combination with a calcium channel blocker (amlodipine) or an ARB (valsartan) significantly and similarly reduced blood pressure in patient groups with obesity. However, the combination of amlodipine and hydrochlorothiazide was associated with more postprandial glucose peaks than the valsartan combination.[47]

In the ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial compared the effects of benazepril (an ACEi) combined with amlodipine (a long-acting calcium channel blocker) or hydrochlorothiazide in hypertensive patients.

The subgroup analysis of 2,842 diabetic patients at very high risk (previous cardiovascular or stroke events) showed that combination of benazepril with amlodipine was superior in reducing cardiovascular events when compared with hydrochlorothiazide.[48] A subanalysis of the ACCOMPLISH Study with respect to the BMI level, the cohort was divided into obese (BMI ≥30 kg/m^2, n=5709), overweight (≥25 kg/m^2 to <30, n=4157), or normal weight (<25 kg/m^2, n=1616) categories. Combination therapy with an ACEi and a calcium channel blocker prevented cardiovascular events regardless of the BMI level, whereas cardiovascular protection with an ACEi and a diuretic combination did not differ between the three BMI groups. Diuretic-based regimens can be a reasonable choice in obese patients in whom excess volume.[49]

The primary objective of antihypertensive drug therapy is to achieve the target of blood pressure control. Hypertension and obesity guidelines have not clearly defined target blood pressures in hypertensive obese patients. However, in these patients, the target blood pressure can be determined individually considering the presence of diabetes, renal or cardiovascular diseases. The ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) Study investigated the significance of strict blood pressure control in hypertensive patients with diabetes mellitus. The preventive effects of strict treatment targeting a SBP of 120 mmHg on cardiovascular disease were more marked in obese patients.[50] In patients with resistant hypertension or poorly controlled hypertension, obesity can be one of responsible factors. If a sufficient decrease in blood pressure is not achieved with ARB or ACEi, combination therapy with long-acting calcium channel blockers or thiazide diuretics (at a half of the standard dose) should be considered.[51] Hypertensive patients with obesity and chronic kidney disease have particularly increased sympathetic nervous system activity and are at high risk of refractory hypertension. Renal denervation does not appear to have a role in the management of obesity or chronic kidney disease associated hypertension.[52]

Conclusion

The 2018 ESC/ESH Guidelines state that body weight control is important to prevent obesity (BMI> 30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women). A healthy BMI (approximately 20-25 kg/m^2) and waist circumference values (<94 cm in men, <80 cm in women) reduce blood pressure and cardiovascular risk.[53] Although the optimal BMI is unclear, maintenance of a healthy body weight (BMI of approximately 20-25 kg/m^2 in people <60 years of age; higher in older patients) and waist circumference (<94 cm for men and <80 cm for women) is recommended for non-hypertensive individuals to prevent hypertension, and for hypertensive patients to reduce blood pressure.[54] The Prospective Studies Collaboration concluded that mortality was lowest at a BMI of approximately 22.5-25 kg/m^2, whereas a more recent meta-analysis concluded that mortality was lowest in overweight subjects.[55-57] Although weight loss medications can be an effective adjunct to lifestyle modifications in individuals with obesity, there is limited evidence regarding their benefit with regard to blood pressure.[58] Increased weight leads to increased blood pressure via different mechanisms, and long-term hypertension and obesity may lead to renal damage. Current drugs are not successful due to adverse effects and inadequate weight loss in a significant proportion of obese patients. New compounds and new molecular targets need to be developed for the effective treatment of all obese patients in the near future.[59] As a public health problem, controlling and preventing weight gain and obesity may prevent development of related comorbidities including hypertension and renal damage in long-term.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Evaluation of the effects of diabetes mellitus and metformin usage on serum vitamin B12 levels in cobalamin deficient subjects

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Abstract

Introduction. Although there are studies evaluating vitamin B12 levels in different patient groups, there is none encountered in Turkish adult patients with or without DM reported in the English literature. The aim of the study was to evaluate the possible additional effects of diabetes and metformin usage on serum levels of vitamin B12 in cobalamin deficient Turkish adult patients.

Methods. Medical records of subjects ≥18 years of age, having a vitamin B12 level <180 pg/mL were screened, consecutive 98 subjects were included in the study.

Results. Among a total of 75 female and 23 male subjects with a mean age of 51.3±15.9 years and vitamin B12 level of 139.3±29.2 pg/mL, 34 had the diagnosis of type 2 diabetes mellitus and 64 had no diabetes diagnosis. Mean ages were 59.0±10.8 years for diabetics and 47.2±16.8 years for nondiabetics. Vitamin B12 levels were found to be insignificantly low in people with the diagnosis of diabetes compared to without diabetes (131.2±30.6 and 143.5±27.7 pg/mL, respectively, p=0.05). Vitamin B12 levels had no correlation with diabetes duration, presence of complications, metformin usage duration.

Conclusions. In conclusion, our results demonstrated that people with diabetes had lower levels of vitamin B12 compared to nondiabetics, but this fact could not solely be explained by the duration of disease, accompanying complications, metformin treatment duration. All patients with or without the diagnosis of diabetes should be encouraged for sufficient vitamin B12 intake and all possible factors that lead to deficiency should be eliminated.

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Introduction

Vitamin B12 or cobalamin is mainly found in animal origin food products. It has important roles in many different biochemical reactions.[1] The minimum daily requirement of vitamin B12 is 6 mcg and a Western type diet contains 5 to 7 mcg of cobalamin.[2] Total body store of vitamin B12 is 2 to 5 milligrams. Main storage is in the liver being approximately one-half. A serum vitamin B12 level of <200 pg/mL is consistent with cobalamin deficiency with a specificity of 95-100%.[3] Insufficient cobalamin intake due to strict vegan diets, insufficient cobalamin absorption due to malabsorption syndromes, hereditary transcobalamin II deficiencies and some drugs like metformin, proton pump inhibitors (PPI) and histamine 2 receptor antagonists may lead to vitamin B12 deficiency. The frequency of vitamin B12 deficiency varies between 3 to 40 % in different populations. Inadequate intake is the main problem in most populations with low socioeconomic level.[4,5] Metformin is the first-choice therapy for people with type 2 diabetes mellitus (DM). It improves insulin resistance and decreases cardiovascular risk with its efficacy and favorable safety profile. Besides it has some side effects, one of them being vitamin B12 malabsorption.[6-10] The mechanisms leading to vitamin B12 deficiency due to metformin in patients with type 2 DM are not clear. Alterations in small bowel motility, bacterial flora and intrinsic factor levels and competitive inhibition of the calcium dependent absorption of vitamin B12- intrinsic factor complex are supposed to be the main problems in metformin usage.[10-12] Although there are many studies in the literature evaluating vitamin B12 levels in different patient populations including those with DM and the effect of metformin usage on vitamin B12 levels in the groups with DM.[1,5,7,9-12], we could not encounter a study conducted and reported in the English literature in Turkish adult patients with or without DM. Our present study was carried out in Turkish adult patients with detected vitamin B12 deficiency, with or without the diagnosis of DM, to evaluate the possible additional effects of DM and metformin usage on serum levels of vitamin B12.

Methods

This was a retrospective cross-sectional study carried out in Endocrinology and Metabolism outpatient clinic of a university hospital during 1-year period. The study was performed with the approval of the local ethics committee and in accordance with the Declaration of Helsinki.

Medical records of subjects 18 years of age or older, having lower than normal vitamin B12 level, with or without the diagnosis of DM and for DM patients with or without metformin usage were screened. Ninety-eight consecutive subjects were included in the study. Vitamin B12 level less than 180 pg/mL which was the lowest limit of the normal range according to our laboratory was taken as the limit value for cobalamin deficiency. Data of the patients were obtained through a retrospective screening of the patient files. Age, gender, height, weight, body mass index (BMI), autoimmune disease status, other accompanying diseases and medications were recorded in all subjects. In the DM group presence, duration, type and complications of DM and dosage and duration of metformin usage were evaluated since all of these factors were shown to affect vitamin B12 levels in different studies in the literature.[9-12] As the laboratory data, fasting blood glucose, hemoglobin A1c (HbA1c), vitamin B12 levels were recorded from the files. Fasting blood glucose level was measured with photometric method using Abbott 16000 device, HbA1c was measured with high performance chromatography using Adams A1c HA 8160 device and vitamin B12 level was measured with chemiluminescence method using Abbott Architect device. Normal ranges for fasting blood glucose were between 70-100 mg/dL, HbA1c were 4.0-6.1% and vitamin B12 were 180-1162 pg/mL.

Statistical analysis

All statistical analysis was done with statistical package program SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test of normality was used to verify distribution of the variables. The categorical variables were expressed as actual numbers with percentages and the continuous variables as mean ± standard deviation. Unpaired Student's two sampled t test or Mann-Whitney U-test were used to compare two groups. Nonparametric data were analyzed using Kruskal–Wallis test among three groups. In

case of significance, the difference was confirmed by Mann–Whitney test. The significance level was determined as $p<0.05$.

Results

A total of 75 (76.5%) female subjects and 23 (23.4%) male subjects were included in the study. Mean age of all subjects was 51.3±15.9 years. Mean age for women was 50.4±15.5 years and men 54.3±17.2 years. Mean BMI was determined to be 27.8±6.2 kg/m2 for whole population, 29.1±6.5 kg/m^2 for women and 24.6±3.8 kg/m^2 for men. Mean value for vitamin B12 level was determined to be 139.3±29.2 pg/mL for whole population, 140.9±28.9 pg/mL for women and 133.8±30.1 pg/mL for men.

DM diagnosis was available in 34 of the patients included in the study all being type 2. Sixty-four subjects were without diabetes. Mean age of subjects without DM was 47.2±16.8 years and with DM was 59.0±10.8 years. Mean vitamin B12 levels of subjects without DM (n=64) and with DM (n=34) were compared. Mean vitamin B12 level in subjects without DM was 143.5±27.7 pg/mL (median=148.5 pg/mL, min=83 pg/mL, max=179 pg/mL) and with DM 131.2±30.6 pg/mL (median=134.0 pg/mL, min=81 pg/mL, max=177 pg/mL). Vitamin B12 levels were found to be low in subjects with DM compared to others but this difference was statistically insignificant (p=0.05) (Table 1, Figure 1).

Table 1. Age, body mass index and vitamin B12 values of all group and subjects with and without diabetes

Variables	All group (n=98)	Without diabetes mellitus (n=64)	With diabetes mellitus (n=34)
Age (year)	51.3±15.9	47.2±16.8	59.0±10.8
Body mass index (kg/m^2)	27.8±6.2	26.9±6.4	28.9±5.9
Vitamin B12 (pg/mL)	139.3±29.2	143.5±27.7	131.2±30.6*

*: p=0.05, when compared with the group without diabetes mellitus

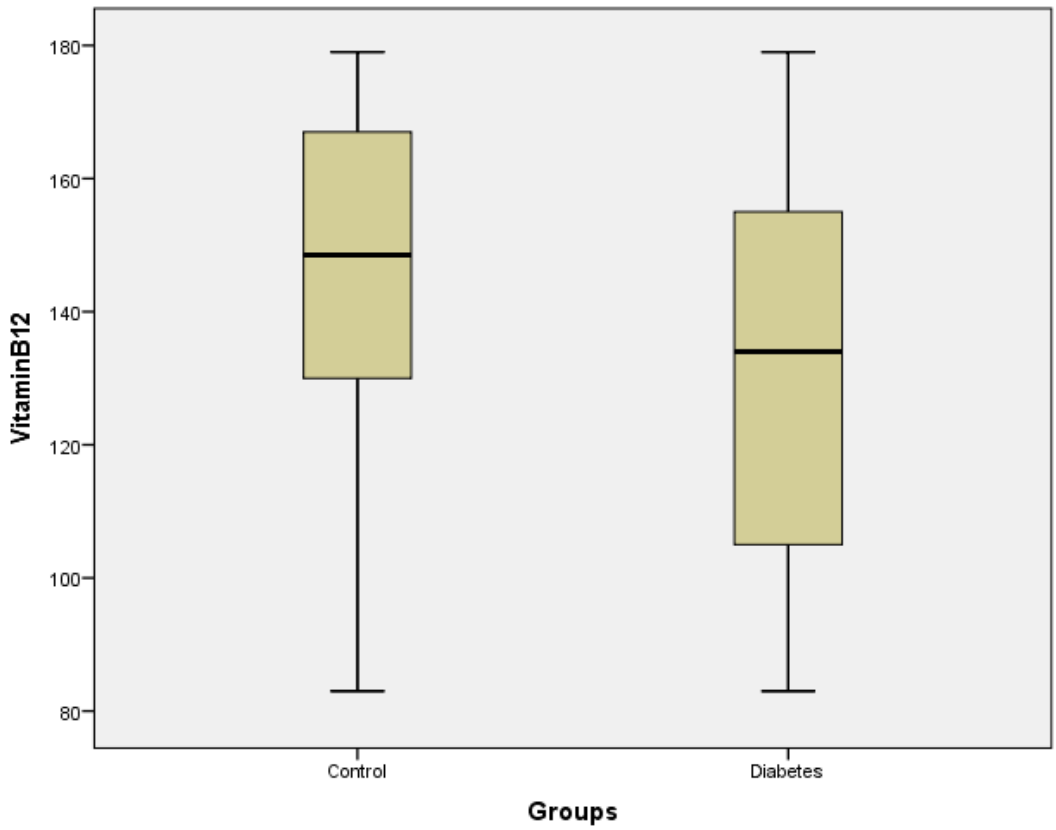

Figure 1. Vitamin B12 levels for subjects with and without diabetes mellitus (p=0.05)

Table 2. Age, body mass index and vitamin B12 values of all subjects with diabetes with and without diabetic complications*

Variables	All subjects with diabetes mellitus (n=34)	Without diabetic complications (n=18)	With diabetic complications (n=16)
Age (year)	59.0±10.8	55.7±8.9	62.8±11.7
Body mass index (kg/m^2)	28.9±5.9	28.2±6.9	29.5±5.2
Vitamin B12 (pg/mL)	131.2±30.6	126.1±33.1	137.0±27.5

*:p>0.05

There were accompanying illnesses other than DM in whole group. Thyroid abnormalities without autoimmunity including multinodular goiter were present in 22 patients (22.4%), dyslipidemia in 16 (16.3 %), Hashimoto thyroiditis in 16 (16.3%), hypertension in 10 (10.2%), hirsutism in 5 (5.1%), hyperprolactinemia in 5 (5.1%), gastric problems in 4 (4.0%), chronic kidney disease in 3 (3.0 %), panhypopituitarism in 3 (3.0%), osteoporosis in 2 (2.0%), heart failure in 2 (2.0%), parathyroid adenoma in 2 (2.0%), stomach cancer in 1 (1.0%) and lung cancer in 1 (1.0%) patient. Among comorbidities, as being autoimmune, Hashimoto thyroiditis can be together with insufficient absorption of vitamin B12. When subjects with and without Hashimoto thyroiditis were compared, no statistically significant difference was detected between 2 groups concerning vitamin B12 levels (142.6±32.5 vs 138.6±28.7 pg/mL, respectively, p=0.489). In the group with DM only 3 had accompanying Hashimoto thyroiditis.

The patients with DM diagnosis were categorized into 3 groups according to diabetes duration as being less than 5 years, 5 to 10 years and more than 10 years. The number of patients with diabetes duration less than 5 years was 12 (35.2%), between 5 to 10 years was 16 (47.0%), and 10 years or longer was 6 (17.6%). When vitamin B12 level was evaluated according to diabetes duration, it was 125.5±31.6 pg/mL in patients with less than 5 years duration, 131.5±32.3 pg/mL in patients between 5-10 years duration and 142.0±25.2 pg/mL in patients with 10 years or longer duration. Vitamin B12 levels were comparable among three groups. There was also no significant correlation between known disease duration and vitamin B12 levels in 34 patients with diabetes mellitus (r=0.160, p=0.367).

When diabetes related complications were evaluated 18 (52.9%) subjects out of 34 had no microvascular complications. One (2.9%) patient had diabetic nephropathy, 2 (5.8%) had diabetic retinopathy, 3 (8.8%) had diabetic neuropathy, 4 (11.7%) had diabetic gastropathy, 6 (17.6%) had multiple diabetic microvascular complications. There was no significant difference between vitamin B12 levels in patients with or without diabetic complications (p=0.578). Age, body mass index and vitamin B12 values of all subjects with diabetes, with and without diabetic complications are given in Table 2.

Mean fasting blood glucose levels of diabetics involved in the study was computed to be 128.1±8.3 mg/dL and mean HbA1c was 6.3±0.2%. They were well regulated subjects concerning glycemic parameters. Thirty DM patients were using metformin treatment, and all were receiving metformin in a dosage of 2 grams per day. Eleven (32.3%) patients were using metformin for less than 5 years, 15 (44.1%) patients between 5 to 10 years and 4 (11.7%) patients for 10 years or longer. The other antidiabetic medications used in combination with metformin were sulfonylureas, glinides, glitazones, alpha-glycosidase inhibitors, dipeptidyl peptidase 4 inhibitors and insulins. When vitamin B12 level was evaluated according to metformin duration, it was 133.3±30.1 pg/mL in patients with metformin usage less than 5 years, 137.2±32.3 pg/mL in patients with metformin usage between 5-10 years and 130.2±19.7 pg/mL in patients with metformin usage 10 years or longer. When duration of metformin usage was considered, vitamin B12 levels did not differ (p=0.280).

There were drugs used by the subjects other than antidiabetics. Among all subjects 26 (26.5%) were using levothyroxine, 9 (9.1%) lipid lowering agents, 5 (5.1%) PPIs, 3 (3.0%) antihypertensives and 37 (37.7%) multiple drugs. Among the drugs only PPIs were shown to affect absorption of vitamin B12. Vitamin B12 levels of two groups

using PPI or not were comparable (137.8±17.0 vs 139.3±29.8 pg/mL, respectively, p= 0.657).

Discussion

In this study, we evaluated the possible additional effects of DM and metformin usage on serum levels of vitamin B12 in cobalamin deficient patients with DM and compared them with those of without DM. The prevalence of vitamin B12 deficiency differs among different studies.[1,10,13,14] The prevalence is reported to be less in people living actively within the society (12%) and higher in those who are older and reside at the care homes (30-40%).[13] Similarly, the prevalence of cobalamin deficiency in the Framingham elderly population was reported to be 20%.[14] The prevalence of vitamin B12 deficiency in patients with long term metformin usage was reported to be 5.8-30% in different studies.[1,10] The mean age of our patients was 51 years who were living actively in the population.

The causes of vitamin B12 deficiency can be divided into three groups as nutritional deficiencies, gastrointestinal malabsorption syndromes and other causes.[15] DM is a metabolic disorder affecting many people worldwide, and its complications are important including autonomic neuropathies.[16] Many factors; including suboptimal intake, contribute vitamin B12 deficiency in people with or without DM. Low intake may be the result of low socioeconomical levels and preferring vegetarian diets. People with DM may have additional defects in vitamin B12 absorption as a result of motility problems due to gastroparesis and absorption problems due to autoimmune comorbidities other than metformin usage. Fortunately, even in situations of serious malabsorption, people store as much vitamin B12 as to be adequate for the following two and five years.[15] Although Hashimoto thyroiditis is an autoimmune disorder, we could not demonstrate its effect on vitamin B12 levels. Our subjects with and without Hashimoto thyroiditis had similar levels of vitamin B12. This result might be due to the small number of subjects in our study.

Being diabetic and having diabetic complications like autonomic neuropathy and diabetic gastroparesis may be risk factors for developing vitamin B12 deficiency. In our study, overall group was having low vitamin B12 levels with a mean value of 139.3±29.2 pg/mL. Besides diabetic people had lower vitamin B12 levels compared to nondiabetics (131.2±30.6 vs 143.5±27.7 pg/mL) which was statistically insignificant. On the other hand, we could not demonstrate any correlation between vitamin B12 levels and diabetes duration and presence of diabetic complications.

According to American Diabetes Association (ADA) and The Society of Endocrinology and Metabolism of Turkey (SEMT), first line oral antidiabetic agent to be initiated in newly diagnosed type 2 diabetic patients is metformin.[8,10,16] It has the opportunity of lowering insulin resistance which is the core problem in many type 2 diabetics. Most of our diabetic patients were using metformin in accordance with the ADA and SEMT guidelines. All of them were using maximum effective dose of metformin 2 grams/day alone or in combination and had good glycemic control with the mean fasting blood glucose of 128 mg/dL and mean HbA1c level of 6.3%. Metformin has advantages of experience in long term usage, lower cost and excellent reliability reports. Nevertheless, it has been reported that long term use of metformin may lead to side effects particularly on the vitamin B12 metabolism.[9,10,16]

It is known that decrease in vitamin B12 levels can start as early as 4th month of metformin usage. Clinical features of deficiency usually appear by 5 years due to body stores which can be affected by age and metformin dosage used.[11] In a study conducted, during a 4.3 year follow up of type 2 diabetic patients who received metformin and insulin treatment, vitamin B12 level had decreased approximately 19%.[17] A study conducted in type 2 diabetics indicated that metformin usage >4 years and average daily dose >1000 mgs are at increased risk for vitamin B12 deficiency.[10] Unlike these results, we could not demonstrate any correlation between vitamin B12 levels and duration of metformin usage in the diabetic group in our study. We also could not demonstrate any correlation between vitamin B12 levels and PPI usage.

There are some limitations of our study. It was a small sample sized retrospective study indicating that people with type 2 DM had

lower level of vitamin B12 compared to ones without DM but diabetes duration and presence of complications, duration of metformin usage were not contributors. The inconsistency with the results of the studies from the literature might be due to small sample size which may lead to type II statistical error and comparisons might not reach statistical significance. Our results should be confirmed in studies with larger patient numbers. On the other hand, the inconsistency with the results of the studies from the literature might also highlight the importance of factors other than metformin usage like low vitamin B12 intake in people with DM as well as without DM. Since type 2 DM usually coexists with dyslipidemia dietary restrictions in cholesterol might limit the intake of animal products rich in vitamin B12.

Conclusions

Our results demonstrated that although statistically insignificant, people with type 2 DM had lower levels of vitamin B12 compared to nondiabetics but this fact could not solely be explained by the duration of disease, accompanying complications, metformin treatment duration. As should be done in whole population, people with DM should also be courage for sufficient vitamin B12 intake and other possible factors that can aggravate the deficiency should be eliminated. Keeping the possible unfavorable effect of metformin on vitamin B12 in mind, we should be aware that all people with or without DM can be a candidate for vitamin B12 insufficiency and care must be given to whole population to prevent the problem.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Effect of conversion from azathioprine to mycophenolate mofetil on renal function in stable kidney transplant recipients

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Abstract

Introduction. This study investigated the effect of mycophenolate mofetil (MPA) treatment instead of azathioprine (AZA) on renal function after kidney transplantation.
Methods. Thirteen of all recipients were taking a cyclosporine-based regimen and serum creatinine levels were above 1.5 mg/dL. In 13 patients, MPA treatment was started instead of AZA. Renal functions were evaluated for 12 months after MPA treatment.
Results. Serum creatinine levels increased from 2.11±0.48 mg/dL to 2.16±0.72 mg/dL at 12th months. This increase was not statistically significant. Serum creatinine levels decreased in 5 of 13 patients.
Conclusions. In selected patients, conversion from AZA to MPA may slow down the rate of deterioration in graft functions.

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Keywords: Azathioprine, mycophenolate mofetil, kidney transplant recipients.

Introduction

Recipients receive immunosuppressive therapy in order to prevent acute rejection after kidney transplantation. Current maintenance immunosuppression may include glucocorticoids, calcineurin inhibitors (CNIs; tacrolimus: TAC or cyclosporine: CsA), antimetabolic agents (mycophenolate mofetil: MMF, enteric-coated mycophenolate sodium,: EC-MPS or azathioprine: AZA), mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) or costimulatory blockade agents (belatacept).[1] Antimetabolic agents interfere with the synthesis of nucleic acids and inhibit the proliferation of both T and B lymphocytes.[2] The 2009 KDIGO clinical practice guidelines suggest mycophenolate as the first-line antimetabolic agent rather than AZA.[3] Because mycophenolate is superior in preventing acute rejection and has a better side-effect profile.[4] MMF is an ester pro-drug which is metabolized to the active compound mycophenolic acid (MPA) in the body. MPA is a noncompetitive inhibitor of a rate-limiting purine biosynthetic enzyme, inosine-5'-monophosphate dehydrogenase (IMPDH). IMPDH is involved in de novo synthesis of

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purines, and lymphocytes rely exclusively on this de novo pathway for nucleotide synthesis. Therefore, MMF selectively targets lymphocyte proliferation.[5,6] The Symphony study showed that a combination of low-dose TAC and MMF was the best of various combined immunosuppressive therapies investigated.[7] In A retrospective analysis of 51,303 patients undergoing deceased-donor kidney transplantation, MPA treatment was associated with a lower risk of acute rejection and a higher risk of hospitalization because of infection when compared to AZA.[8] Renal allograft failure is one of the most common causes of end-stage renal disease and accounts for 25 to 30% of patients awaiting kidney transplantation. MMF may positively affect the long-term graft survival in the long term as well as reduce the occurrence of acute rejection. This study aimed to evaluate changes of graft function in kidney transplant recipients who received MMF treatment instead of AZA.

Methods

For this retrospective study, patients who underwent transplant surgery in our center were evaluated. Thirteen (11 male, 2 female, live donor) recipients with CsA-based regimen and serum creatinine levels above 1.5 mg/dL were included in the study. These patients with chronic allograft dysfunction without biopsy were treated with 2 g/day MMF instead of AZA. Serum creatinine levels were measured at 1th, 3rd, 6th and 12th after MMF treatment.

The data was analyzed using SPSS Software package of version 20. Numerical variables were given as mean±standard deviation (SD). The Wilcoxon signed-rank test was used for intragroup comparisons. P values less than 0.05 were considered to be significant.

Results

The mean age of the patients was 35±5.4 (range: 26-41) years. Serum creatinine levels before MMF were 2.11±0.48 mg/dL. The mean serum creatinine levels after MMF were 2.28±0.75, 2.19±0.73, 2.16±0.67 and 2.16±0.72 mg/dL at the 1st, 3rd, 6th and 12th months, respectively. The difference between mean creatinine levels before and after MMF treatment was not statistically significant ($p>0.05$). Serum creatinine levels decreased in 5 patients, increased in 4 patients and remained unchanged in 4 patients during the MMF follow-up period. In two patients, symptoms of diarrhea alleviated by reducing the MMF dose (1.5 g/day). No other MMF-related side effects observed. None of the patients had cytomegalovirus (CMV) infection.

Discussion

In our study, we observed that at least some transplant patients with chronic allograft dysfunction preserved renal function by conversion from AZA to MMF over a one-year period. Despite improving immunosuppressive protocols in kidney transplantation, chronic allograft nephropathy (CAN) is one of major causes of graft failure after the first year. This clinical condition is expressed in various terms: chronic rejection, CAN, chronic allograft dysfunction, transplant nephropathy, transplant glomerulopathy or chronic allograft injury. This clinicopathological entity is incompletely understood. A retrospective single-center study on 214 recipients with chronic allograft dysfunction among 1,534 kidney transplant recipients revealed that type of immunosuppression (MMF vs AZA), age of donor, proteinuria, pre-transplant hypertension, pre-transplant diabetes, delayed graft function and stage of allograft dysfunction at the start of chronic allograft dysfunction are the major risk factors for late renal allograft dysfunction.[9] Additionally, using MMF versus AZA reduced death-censored graft loss.[9]

The optimal immunosuppressive regimen for a patient with CAN is unknown. CNI withdrawal is safe and conversion to MMF or mTOR inhibitors may be beneficial.[10] In a systematic review of 23 trials involving 3,301 kidney transplant recipients, MMF reduced the risk of death-censored graft loss, acute rejection and CAN when compared with AZA.[4] Numerous large trial and meta-analysis results support lower acute rejection rates and better graft survival with MMF compared with AZA.[4,11-19] Renal function

can be better preserved in patients using MMF instead of AZA.[11,20] After conversion from AZA to MMF with concomitant CsA withdrawal in 31 patients with chronic allograft dysfunction, proteinuria decreased with improved graft survival and renal function.[21] In 49,666 transplant recipients, continuous use of MMF versus AZA was associated with a protective effect against declining renal function beyond 1 year after transplantation.[22]

MMF may also be useful in patients with CAN or chronic progressive allograft dysfunction.[23-28] In the Creeping Creatinine study, addition of MMF followed by withdrawal of CsA in 122 patients with progressively deteriorating renal function secondary to CAN resulted in a significant improvement in graft function without the risk of acute rejection.[27] In an another study, renal function after introduction of MMF in patients with biopsy-proven chronic allograft nephropathy remained stable with a significant change in the slope of the glomerular filtration rate.[28] Three years after conversion to MMF in patients with progressive CAN, patient and graft survival were reported to be 95% and 79%, respectively.[29] In a large cohort, MMF reduced the relative risk for CAN development by 27%.[30] In a study evaluating the effect of immunosuppression conversion on CAN progression, MMF or low dose CsA was superior to TAC-for-CsA and standard dose CsA in patients with CAN, at least in the short term.[31]

In our study, no serious side effects were observed in patients after the transition from AZA to MMF. Leukopenia is the most serious side effect of AZA. Mycophenolate treatment combined with prednisolone and CsA in fifty-nine transplant patients shifted to an AZA-based regimen for 720 days. Absolute leukocyte counts statistically significant decreased 12 months after starting AZA.[32] While thrombocytopenia and elevated liver enzymes were more frequent with AZA, gastrointestinal symptoms such as diarrhea and risk of tissue-invasive CMV disease were higher with MMF.[4,9-17]

The important limitations of our study were the relatively low number of patients, the lack of graft biopsy and the short follow-up period. In conclusion, conversion from AZA to MMF in patients with chronic allograft dysfunction can be a safe strategy for improvement of graft survival. However, the transplant physician should evaluate the potential benefits (graft survival) and harms (infections, malignancies and possible side effects) of the two drugs in the individual patient.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CASE REPORT

Fatal Central Venous Catheterization Complication: Right Ventricular Rupture and Hemopericardium

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Abstract

Central venous catheterization (CVC) is frequently used in urgent intervention needed cases, and in patients that require long-term vascular access. The catheter tip perforating the ventricular wall leading to a cardiac tamponade is a complication with high mortality. A 26-year-old female patient with IgA nephropathy was admitted to the emergency department with complaints of fainting at home. The echocardiographic evaluation revealed fibrin-rich, intense pericardial fluid located in front of the right ventricle and causing a collapse in the right structures. The patient was evaluated as pericardial tamponade and pericardiocentesis was performed through the sub-xiphoid region. A pigtail catheter inserted, and 650 mL of hemorrhagic pericardial fluid was evacuated. Clinically stabilized patient discharged from the hospital, and nephrology follow-up was suggested. This rare, mostly mortal complication had a dramatic response to the appropriate treatment if it is recognized earlier. Adequate training and following procedures for catheter placement will be the most effective prevention to reduce the risk of such complications.

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Keywords: Cardiac tamponade, central venous catheter, complication.

Introduction

Central venous catheterization (CVC) is frequently used in cases of urgent intervention (acute hemodialysis, plasmapheresis, cardiopulmonary resuscitation). Long-term vascular access is needed particularly in intensive care units. The femoral vein is preferred in acute short-term hemodialysis and the internal jugular vein is preferred in case that needs long-term hemodialysis. Interventional procedures carry the complication risk even in the most experienced practitioners. The catheter tip perforating the ventricular wall leading to a cardiac tamponade is a complication with high mortality.[1]

We present a 26-year-old woman with a diagnosis of IgA nephropathy who was admitted to the emergency department with the complaint of fainting at home due to right ventricular damage and hemopericardium, 2-months after starting 3/7 hemodialysis program with a jugular venous catheter.

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Case Report

A 26-year-old female patient who was under nephrology follow-up with IgA nephropathy diagnosis was included into a hemodialysis program due to the progressive decrease in renal function by using a temporary jugular venous catheter 2 months ago. Her general condition and physical capacity have worsened day-by-day. She was admitted to the emergency department with the complaint of fainting at home. She had a general impairment, hypotension, tachycardia, dyspnea, cough and phlegm complaints, and transferred to internal medicine inpatient clinic for further examination. Chest-x-ray shows cardiomegaly (Figure 1) and echocardiographic evaluation revealed a fibrin-rich, dense pericardial fluid located in front of the right ventricle and causing a collapse in the right structures (Figure 2). Pericardial tamponade diagnosis was made with the addition of clinical parameter such as hypotension (70/40 mmHg) and tachycardia (140 beats/min) (Figure 3). Temporary dialysis catheter was removed and pericardiocentesis was performed through the sub-xiphoid region. About 650 mL of hemorrhagic pericardial fluid was evacuated with a pigtail catheter inserted under ultrasound guidance.

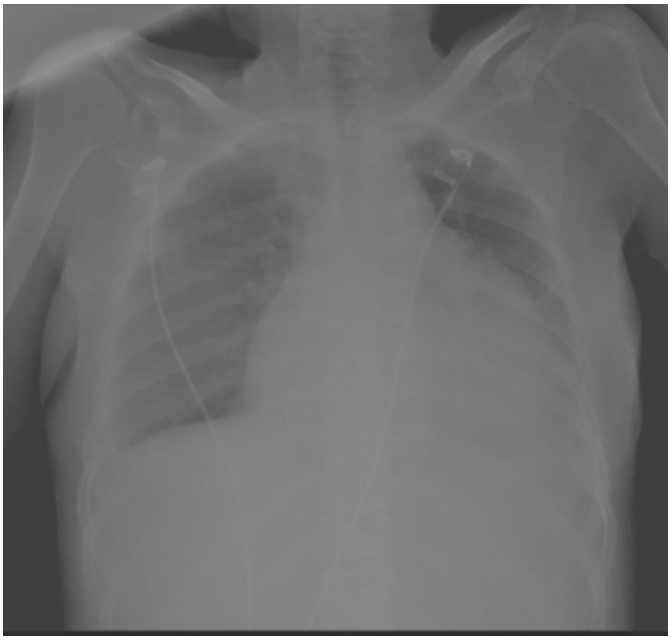

Figure 1. Chest-x-ray represents cardiomegaly

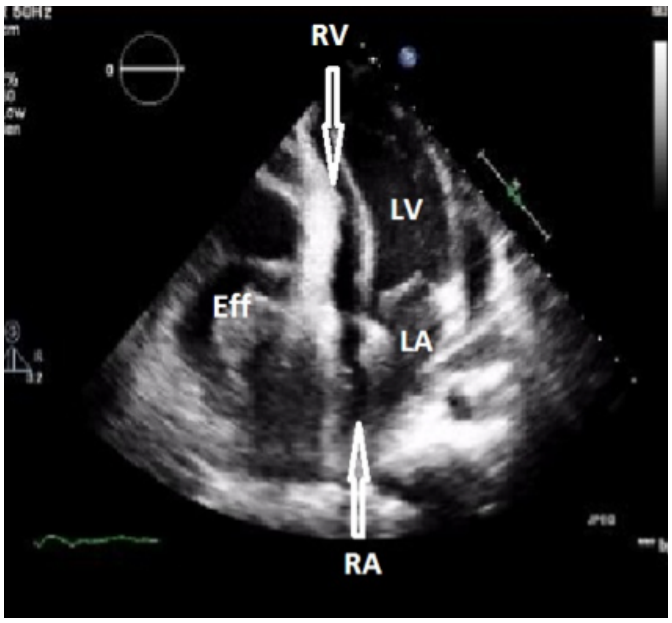

Figure 2. Pericardial effusion caused compression in both the right atrium and ventricle. 4-cavity transesophageal echocardiographic image. LV= Left Ventricle, LA= Left Atrium, RA= Right Atrium, RV= Right Ventricle, Eff= pericardial effusion

Pericardial fluid analysis showed hemoglobin: 11.7 g/dL, total protein: 6.2 g/dL, albumin: 3.1 g/dL, LDH: 953 U/L in synchronous blood biochemistry total protein: 6.5 g/dL, Albumin: 3.3 g/dL, LDH: 348 U/L. Cytologic evaluation of the effusion revealed no malignancy and no reproduction in the bacterial cultures.

In the follow-up of the patient, a dramatic improvement was observed in her clinical condition and a pigtail catheter was removed when the volume of the incoming fluid fell below 25 cc/day. Patients whose hemogram levels were stabilized, blood pressure and heart rate returned to normal was discharged from the hospital. The kidney function was re-evaluated, and she was removed from the hemodialysis program due to sufficient renal parameters, and nephrology outpatient clinic follow-up was suggested.

Discussion

CVC is a commonly applied intervention in case of an acute need for hemodialysis. It is often the preferred vascular access point in routine hemodialysis patients during the fistula opening period or fistula-related complications. Since there is a high risk of stenosis in the subclavian vein after

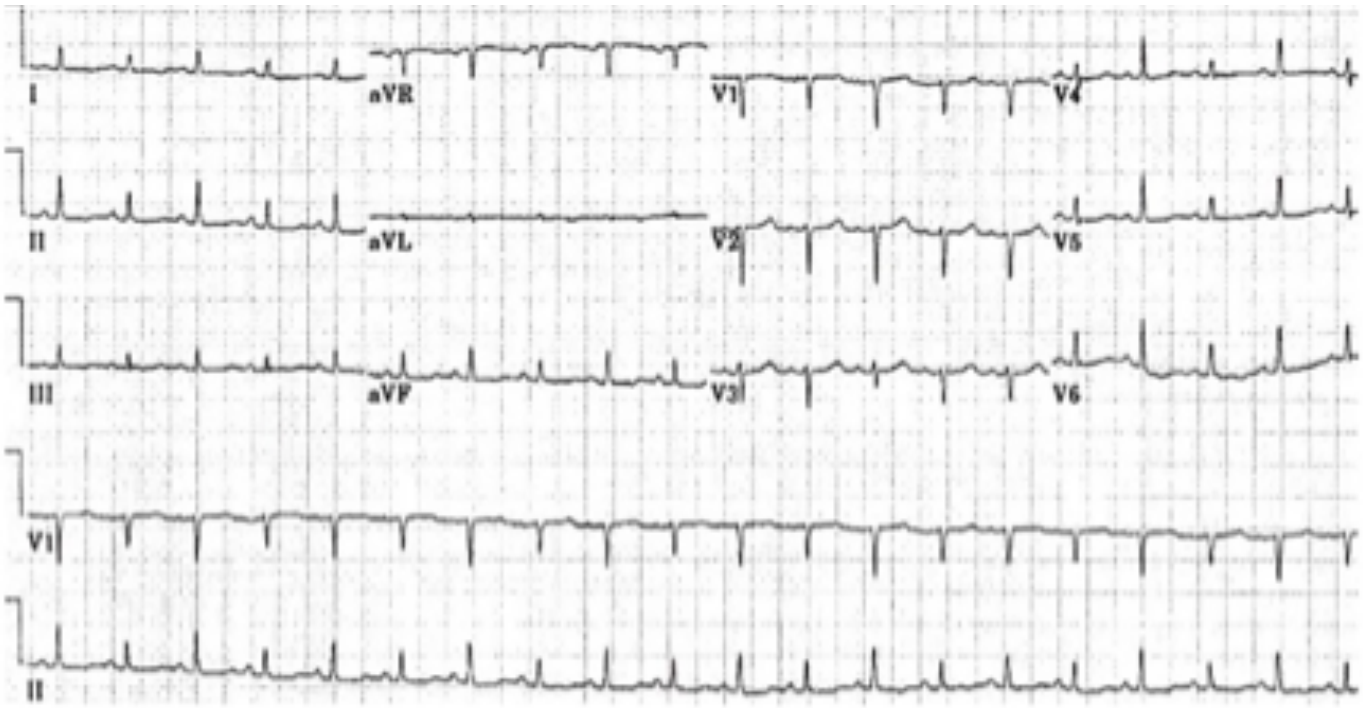

Figure 3. Sinus tachycardia and QRS alternans is present in the ECG

hemodialysis, internal jugular vein is preferred in acute hemodialysis. The femoral vein may also be preferred in acute short-term hemodialysis and non-mobilized patients. Interventional procedures carry-out the risk of complications even in the most experienced practitioners. Catheter-related complications that may be encountered at each stage of catheter placement and after the catheter insertion cause catheters to be considered as prone to complication tools.[2] The frequency of complications related to central venous catheter placement varies between 5-19%, depending on the used anatomic site, the use of ultrasonography and the experience and ability of the practitioner.[3,4] The frequency of cardiac tamponade is not clearly known, but it is a complication that can be avoided by the practitioner taking into account the guidelines.[1]

In a retrospective review of 23 patients by Collier et al.[1], it is reported that patients had shortness of breath (12 patients), palpitation sensation (8 patients) and air hunger (15 patients) up to 6 hours before the change was observed in vital signs. In the same study, tachycardia, and bradycardia developed in 56% and 46% of the patients, respectively. There was unexplained hypotension in all of the patients.[1] In our case, it was determined that the patient had shortness of breath before she had fainted, and tachycardia and hypotension were observed in the hospital.

The most suitable site for the catheter tip is 3-5 cm proximal of the junction of the vena cava superior with the atrium. The perforation may depend on the displacement of the catheter tip at the beating heart as well as the neck movements of the patient. In the left-sided interventions, the distance between the puncture site and the Caval-atrial junction is 19-21 cm while it is 16-18 cm at the right-side interventions. This distance is not depending on the gender or body structure of the patient. Catheter site should be verified with a direct radiographic examination after catheter insertion and it must be demonstrated that the catheter is not in the heart cavity by echocardiography in selected patients. On direct radiography, it should be demonstrated that the catheter is in the 2 cm of the proximal of the pericardial shadow into the vena cava.[5]

Conclusion

This rare, mostly mortal complication had a dramatic response to the appropriate treatment if it is recognized earlier. Adequate training and following procedures for catheter placement will be the most effective prevention to reduce the risk of such complications.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CASE REPORT

Chronic kidney disease presenting with bilateral spontaneous femoral neck fracture: A case report

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Abstract

Bone and mineral metabolism disorders are common in patients with chronic kidney disease (CKD). These patients are susceptible to fractures. Bilateral femoral neck fracture secondary to renal osteodystrophy is a rare complication. We report a case of CKD with bilateral spontaneous femoral neck fracture associated with secondary hyperparathyroidism and osteoporosis.

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Keywords: Bone and mineral disorders, chronic kidney disease, fracture, osteoporosis, secondary hyperparathyroidism.

Introduction

Progression of chronic kidney disease (CKD) leads to various bone diseases and mineral metabolism disorders due to changes in calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and vitamin D metabolism in these patients. Chronic kidney disease-mineral and bone disorder (CKD-MBD) may present with different clinical manifestations depending on existing metabolic abnormality and characteristic bone disease. Patients with end-stage renal disease (ESRD) are at increased risk for bone loss and are susceptible to fractures, especially hip fractures.[1,2] Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, and CKD-MBD is one of the possible causes of osteoporosis.[2] Here we report a patient who was diagnosed with new CKD and bilateral femoral neck fracture.

Case Report

A 22-year-old male patient was admitted to another hospital with complaints of weakness and difficulty in walking and was referred to our hospital because of high serum urea and creatinine levels. His previous medical history was unremarkable, and his blood pressure was 110/60 mmHg and pulse 72 beats/min. He had bilateral diffuse hip sensitivity and limitation of motion. His laboratory tests revealed that serum glucose 94 mg/dL, urea 87 mg/dL, creatinine 6.3 mg/dL,

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uric acid 10.7 mg/dL, albumin 4.8 g/dL, sodium 131 mEq/dL, potassium 3.9 mEq/dL, Ca 6.7 mg/dL, P 3.5 mg/dL, AST 54 IU\L, ALT 17 IU\L, serum alkaline phosphatase (ALP) 573 IU\L, hemoglobin 9.29 g/dL, CRP 30.4 mg/dL, 25OH vitamin D 4 ng/mL, intact PTH 559 pg/mL and ferritin 238 ng/mL. Hepatitis B and C tests were negative. Renal ultrasonography showed reduced renal size and grade III echogenicity and was consistent with CKD. eGFR was 4 mL/min/1.73 m^2. The patient' findings were consistent with ESRD. Direct anterioposterior pelvic radiograph revealed a bilateral femoral head fracture (Figure 1). In his dual-energy x-ray absorptiometry (DEXA) scan, the T score was -2.8 and the Z score was -1.6. In MR imaging of the left and right hip joints, there was complete fracture in the both femoral necks. It was displaced about 3-4 cm from the level of fracture on both sides towards the superior of the trochanteric section of the femur. It was thought that fractures might be related to CKD-MBD in the patient who had no history of trauma or seizure. He underwent total hip replacement operation for fractures in both femoral neck (Figure 1). Dialysis treatment, calcium and vitamin D supplements were started.

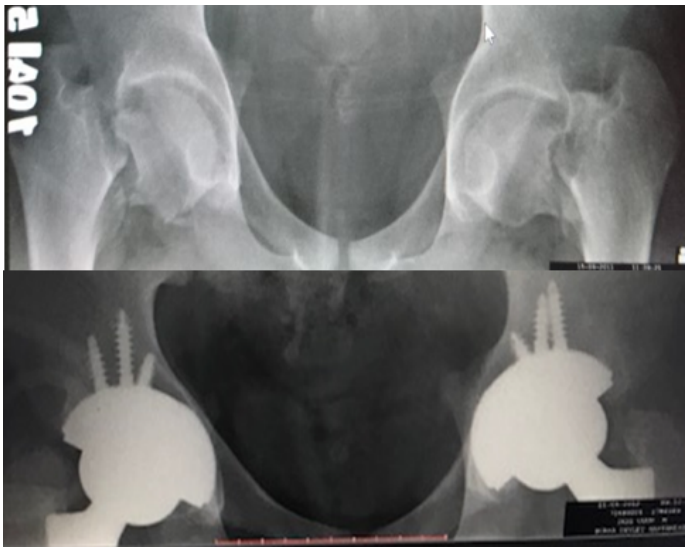

Figure 1. Pre- and post-operative radiographs of the patient showing bilateral femoral neck fractures

Discussion

The risk of fracture in hemodialysis, peritoneal dialysis and kidney transplant patients is higher when compared with the general population.[3] The recent observational study showed that the fracture risk of dialysis patients was 16% higher than that of pre-dialysis CKD patients.[4] In another study including 68,764 individuals with confirmed CKD with a median follow-up of 2.7 years, 9,219 fractures occurred, of which 3,105 were hip fractures. A more severe CKD stage was associated with a higher risk of fractures, particularly hip fractures: compared with CKD Stage 3a, the adjusted HR was 1.10, 1.32 and 2.47 for CKD Stage 3b, 4 and 5, respectively.[5]

Risk factors for fracture in CKD patients are similar to those in the general population, such as low body weight, menopause, a history of personal and familial osteoporosis, chronic inflammatory diseases and corticosteroid usage.[6] Some bone histology types such as osteomalacia, high turnover bone disease or adynamic bone disease in CKD-MBD is associated with the elevated rates of bone fracture.[7] Spontaneous bilateral femoral neck fracture in a renal disease patient is a rare complication. A retrospective analysis of etiological factors in 26 pathological fractures of the femoral neck of 19 chronic hemodialysis patients with 11 (range 2 to 21) years of mean duration of dialysis was found the presence of beta-2-microglobulin amyloidosis, aluminic osteomalacy, osteoporosis, and cortisonic necrosis and porosis.[8] Certain risk factors including high PTH levels and the use of narcotics and psychoactive medications may increase the likelihood of fracture.[9] Secondary hyperparathyroidism may cause lead bilateral spontaneous simultaneous rupture of the Achilles tendon and pathological fracture of right femur neck in patients after the long-term hemodialysis without predisposing factors such as previous use of corticosteroids or fluoroquinolones.[10] Femoral neck fractures in elderly dialysis patients are associated with advanced renal osteodystrophy and multiple medical problems such as confusion caused by narcotics and analgesics, pneumonia, hepatic coma, decubitus ulcers, severe depression and severe hypoalbuminemia.[11] There was no history of injury, trauma, fall, seizure, steroid medication, fluoride treatment, smoking and alcohol abuse in our case. Several cases of bilateral femoral neck fractures have been reported in patients with CKD in the literature.[11-23] Hypocalcaemic convulsions or muscle cramps can also cause fractures in patients with CKD.[11,14-16]

Bone mineral density (BMD) was low in our case with secondary hyperparathyroidism.

BMD was also significantly lower in patients with secondary hyperparathyroidism than in those with adynamic bone disease. A prospective study including 62 hemodialysis patients that 11% of all had a positive fracture history showed that osteopenia was frequent in patients on hemodialysis, especially those with biochemical and histological findings of secondary hyperparathyroidism.[24] A meta-analysis investigating the relationship between BMD values and fractures in patients with stage 5 CKD shows that BMD is lower in patients with fractures.[25] A total of 374 patients with CKD G3a-G5 was followed by DEXA for a total of 5 years, and measured BMD. 14.3% of patients with G3a and G3b, 15.7% of of patients with G4, and 19.7% of of patients with G5 experienced a clinical fracture during the study period. The multivariate analysis showed that each decline of 1.0 SD in total hip BMD T-Score was associated with a significant increase in the risk of fracture (OR = 1.46).[26] Furthermore, both genders with impaired kidney function are at increased risk of bone loss, even with minimal reduction in kidney function.[27] PTH can stimulate bone resorption which renders the bone susceptible to fractures. Ayurvedic medications also may accelerate osteoporosis of the proximal femur, and lead to bilateral femur neck fractures. A 41-year-old male who was diagnosed with CKD for 6 months and started taking Ayurvedic medications after the diagnosis had a trivial trauma 2 months before. As our case, the patient was admitted for inability to walk, and was diagnosed bilateral femur neck fracture.[28]

Hip and long-bone fractures are associated with an increased risk of all-cause mortality, major cardiovascular and infectious events in the dialysis population.[29,30] In our patient who was diagnosed as end-stage renal disease, high PTH, low vitamin D, low calcium and high ALP levels were consistent with high-turnover bone disease. Serum ALP is a marker of high-turnover bone disease and is associated with coronary artery calcification and death risk in hemodialysis patients. A relationship between high serum ALP and worse BMD has been reported in dialysis patients.[31] A large cohort study revealed that higher serum ALP levels were independently associated not only with mortality but also with the incidence of hip fracture in Japanese hemodialysis patients.[32]

As a result, bilateral femoral neck fractures without risk factors such as trauma, convulsion and steroid medication are rare in a young patient with CKD. Since the presence of secondary hyperparathyroidism and osteoporosis increases the risk of fracture in patients with CKD even in the early stages, physicians should consider the possibility of developing this complication in the follow-up of such patients.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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