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Aims and scope

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YUJM aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

YUJM publishes editorials, review articles, original articles, case reports, and communications. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all fields of medicine.

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Review article
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Can antioxidants be effective therapeutics for type 2 diabetes?

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The global obesity epidemic and the growing elderly population largely contribute to the increasing incidence of type 2 diabetes. Insulin resistance acts as a critical link between the present obesity pandemic and type 2 diabetes. Naturally occurring reactive oxygen species (ROS) regulate intracellular signaling and are kept in balance by the antioxidant system. However, the imbalance between ROS production and antioxidant capacity causes ROS accumulation and induces oxidative stress. Oxidative stress interrupts insulin-mediated intracellular signaling pathways, as supported by studies involving genetic modification of antioxidant enzymes in experimental rodents. In addition, a close association between oxidative stress and insulin resistance has been reported in numerous human studies. However, the controversial results with the use of antioxidants in type 2 diabetes raise the question of whether oxidative stress plays a critical role in insulin resistance. In this review article, we discuss the relevance of oxidative stress to insulin resistance based on genetically modified animal models and human trials.

Keywords: Antioxidants; Insulin resistance; Oxidative stress; Reactive oxygen species

Introduction

Although reactive oxygen species (ROS) are produced as a by-product of oxygen metabolism, they play a significant role in normal cellular functions [1,2]. A well-organized antioxidant system maintains the physiological levels of ROS [3]. However, an imbalance between ROS production and antioxidant capacity causes ROS accumulation, which induces chemical modifications of DNA, protein, and lipids, leading to cellular damage, known as oxidative stress [1-3].

Oxidative stress is closely linked to a variety of diseases, including type 2 diabetes [1]. Type 2 diabetes is increasing globally due to the obesity pandemic and the growth of the aging population, and insulin resistance is a critical link between these two. Insulin resistance is known to be a critical risk factor for type 2 diabetes and other chronic diseases, such as cardiovascular diseases and cancers [4]. It is known that hyperglycemia in diabetic patients leads to serious complications by enhancing oxidative stress in the heart, kidney, and eyes [2]. Recently, oxidative stress has also been suggested to be a cause of insulin resistance [3,5]. Oxidative stress is increased in the plasma and tissue of patients and experimental animals with type 2 diabetes. Genetic modulation of antioxidant enzymes in rodents also supports the causative role of oxidative stress in insulin resistance. However, the inconsistent effects of antioxidant treatment on type 2 diabetes raise the question of whether oxidative stress induces insulin resistance. Thus, we sought to identify the role of oxidative stress in the development of insulin resistance based on animal experiments and human trials.

Reactive oxygen species and antioxidant systems

ROS are defined as oxygen-containing reactive species and include superoxide anion, hydrogen peroxide, hydroxyl radical, peroxyni-

trite, hypochlorous acid, and singlet oxygen [6]. The mitochondria electron transport chain, cell membrane nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, cytochrome p450, and xanthine oxidase are the main intracellular sites of ROS generation, and among them, mitochondria is the primary source of ROS [7].

In the mitochondria, the generated superoxide anion is converted into hydrogen peroxide superoxide dismutase 2 (SOD2). Subsequently, hydrogen peroxide is detoxified to form water in the presence of antioxidant enzymes such as glutathione peroxidase (GPx) or peroxidase or is exported to the cytoplasm (Fig. 1). Superoxide anions are also generated in the cell membrane and cytoplasm by NADPH oxidase and xanthine oxidase, respectively. In the cytoplasm, superoxide dismutase 1 (SOD1) catalyzes the conversion of superoxide anion to hydrogen peroxide, which is then detoxified to form water by enzymatic or nonenzymatic antioxidants, including glutathione, GPx, catalase, peroxiredoxin, and thioredoxin. In addition, catalase is a primary antioxidant that catalyzes hydrogen peroxide formation in the peroxisome. Oxidized methionine is reduced by methionine sulfoxide reductase in the cytoplasm, mitochondria, and endoplasmic reticulum. Moreover, peroxynitrite, produced by the reaction between nitric oxide and superoxide anion, and responsible for a wide array of tissue damage, is decomposed by peroxiredoxin, glutathione, and GPx [8,9].

Even though the intracellular antioxidant system is well developed to prevent ROS accumulation, ROS production can overwhelm the antioxidant capacity and induce oxidative damage to DNA, protein, and lipids.

Insulin signaling pathways

An increase in blood glucose levels after a meal induces insulin secretion from pancreatic β-cells, which leads to glucose uptake in skeletal muscle and adipose tissue by activating intracellular insulin signaling pathways. In the liver, insulin suppresses glycogen breakdown and gluconeogenesis while increasing glucose oxidation and glycogen synthesis. Inhibition of insulin signaling pathways in these peripheral tissues results in the development of insulin resistance. In this review, we will focus on insulin resistance in skeletal muscle (Fig. 2).

Secreted insulin binds to insulin receptors on the plasma membrane and promotes autophosphorylation of tyrosine residues in the beta-subunit of the insulin receptor [10]. The activation of the insulin receptor immediately induces tyrosine phosphorylation of the insulin receptor substrate (IRS) proteins, which are initial downstream

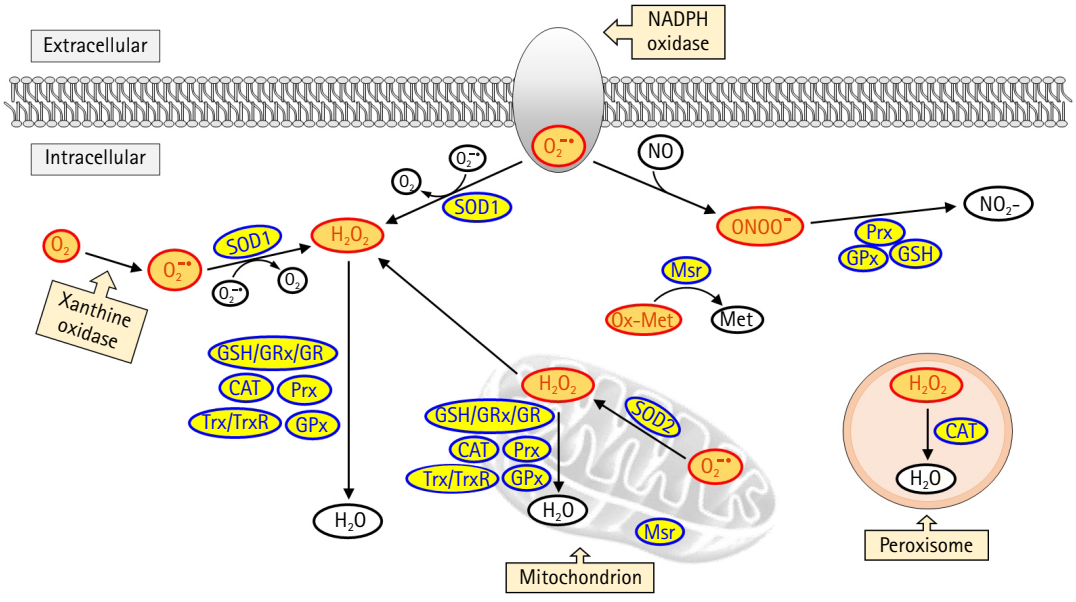

Fig. 1. Intracellular reactive oxygen species (ROS) generation and the antioxidant scavenging system. ROS is produced from mitochondria, peroxisome, nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, and xanthine oxidase. Among these sources, the mitochondrial electron transport chain is the primary source for ROS production. Superoxide dismutase 2 (SOD2) catalyzes the conversion of superoxide anion (O_2^-) into hydrogen peroxide (H_2O_2) in the mitochondria. The H_2O_2 is then detoxified in the mitochondria or moves to the cytoplasm. Cytoplasmic superoxide anion is generated from NADPH oxidase and xanthine oxidase, and subsequently converted into H_2O_2 by superoxide dismutase 1 (SOD1). H_2O_2 is detoxified by glutathione (GSH)/glutaredoxin (GRx)/glutathione reductase (GR), catalase (CAT), peroxiredoxin (Prx), thioredoxin (Trx)/thioredoxin reductase (TrxR), and glutathione peroxidase (GPx). Oxidized methionine (Ox-Met) is reduced by methionine sulfoxide reductase (Msr) to methionine (Met). Nitric oxide (NO) reacts with superoxide anion to form peroxynitrite ($ONOO^-$), which is detoxified by Prx, GSH, and GPx.

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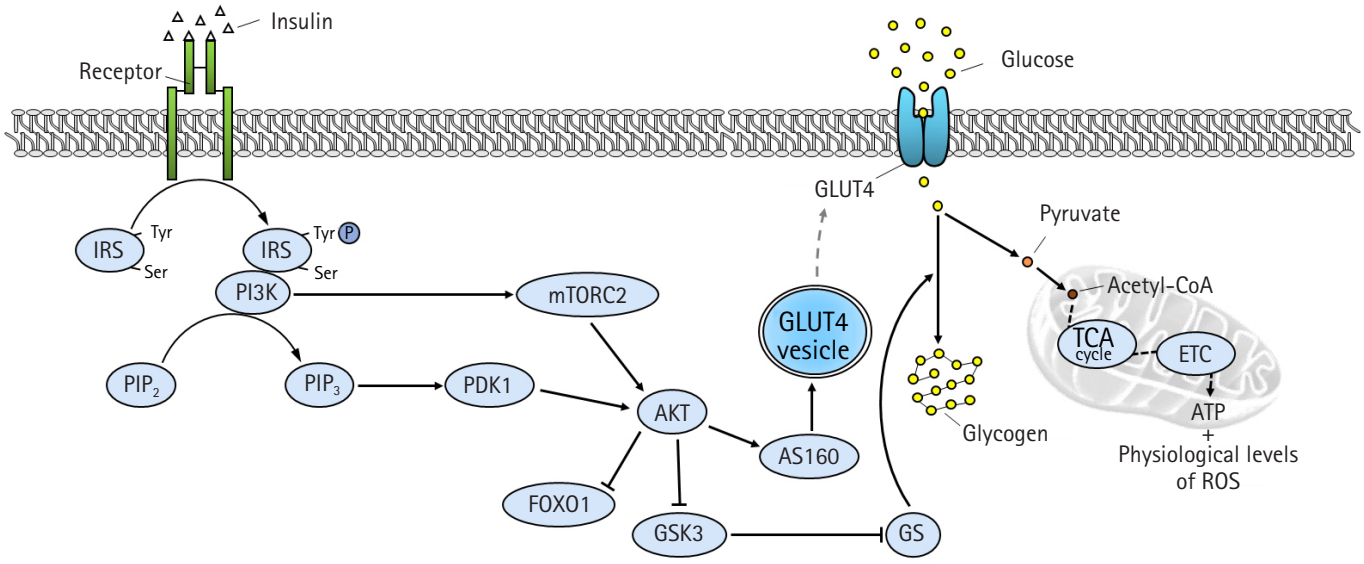

Fig. 2. Intracellular insulin signaling pathway in skeletal muscle. Binding of insulin to insulin receptors (IR) on the plasma membrane promotes tyrosine autophosphorylation at the IR, which in turn induces tyrosine phosphorylation of the IR substrate (IRS). IRS activates the downstream substrate phosphatidylinositol 3-kinases (PI3K)/protein kinase B (AKT) pathway, and the activated AKT leads to increased glucose uptake and glycogen synthesis by inducing phosphorylation of AKT substrate of 160 kDa (AS160) and glycogen synthase kinase 3 (GSK3) respectively. Activated AS160 increases glucose uptake by mediating the translocation of glucose transporter type 4 (GLUT4) from the cytoplasm to the plasma membrane. Intracellular glucose is used for adenosine triphosphate (ATP) generation and glycogen synthesis. Tyr, tyrosine; Ser, serine; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, phosphatidylinositide-dependent protein kinase 1; mTORC2, mammalian target of rapamycin complex 2; FOXO1, forkhead box protein O1; GS, glycogen synthase; acetyl-CoA, acetyl coenzyme A; TCA, tricarboxylic acid cycle; ETC, electron transport chain; ROS, reactive oxygen species.

substrates of insulin signaling [11]. Phosphorylated IRS contains binding sites for numerous signal transduction partners with Src homology 2 domains, such as phosphatidylinositol 3-kinases (PI3K) [12]. Activated PI3K generates phosphatidylinositol (3,4,5)-triphosphate (PIP_3) by catalyzing the phosphorylation of phosphatidylinositol 4,5-bisphosphate [13]. PIP_3 induces the activation of protein kinase B (AKT), which is a key divergence point in the insulin signaling pathway [14]. Activation of AKT is induced via phosphorylation of threonine and serine residues by phosphatidylinositide-dependent protein kinase 1 and mammalian target of rapamycin complex 2 [15]. Subsequently, activated AKT phosphorylates numerous downstream substrates, including forkhead box protein O1 (FOXO1), AKT substrate of 160 kDa (AS160), and glycogen synthase kinase 3 (GSK3) [16]. The phosphorylation of GSK3 releases the inhibitory effect of GSK3 on glycogen synthase, leading to increased glycogen synthesis [17]. Furthermore, the phosphorylation of FOXO1 suppresses FOXO1-regulated expression of pyruvate dehydrogenase kinase 4 [18]. Phosphorylated AS160 mediates the translocation of the glucose transporter type 4 (GLUT4) from the cytoplasm to the plasma membrane [19]. This reaction ultimately completes the action of insulin by increasing glucose utilization and storage, as well as promoting glucose uptake in the tissues.

Oxidative stress and insulin resistance

The insulin-mediated signaling pathway plays a crucial role in lowering blood glucose and regulating overall glucose metabolism *in vivo*. A reduction in the biological effect of insulin is called insulin resistance, in which blood glucose cannot be used effectively as an energy source due to decreased insulin responsiveness of insulin-sensitive tissues such as skeletal muscle, adipose tissue, and the liver. To escape this condition, β-cells produce more insulin, but this eventually leads to β-cell exhaustion [20]. A reduction in insulin secretion due to β-cell exhaustion increases blood glucose levels, resulting in the development of type 2 diabetes [20]. Although defects in insulin receptors contribute to insulin resistance, perturbations in intracellular insulin signaling pathways are mostly responsible for insulin resistance.

Free fatty acids (FFAs) in plasma are generally supplied through lipolysis and are used as a primary energy source through β-oxidation in the liver, heart, and skeletal muscle during fasting and exercise. However, chronically elevated levels of FFAs in the plasma are one of the key triggers leading to defects in the insulin signaling pathway [21,22]. Increased utilization of FFAs leads to the accumulation of fat metabolites, such as fatty acyl-coenzyme A, cera-

mides, and diacylglycerol in the liver and skeletal muscle [23-25]. High levels of fatty acid metabolites activate serine-threonine kinases, including protein kinase C (PKC), c-Jun N-terminal kinase (JNK), and inhibitory κB kinase (IKK) β, leading to the suppression of insulin-stimulated signaling pathways [23,26,27]. Serine phosphorylation of IRS by these serine-threonine kinases inhibits tyrosine phosphorylation of IRS by insulin, eventually reducing glucose uptake [27].

Recently, fatty acid-induced oxidative stress has drawn attention as one of the causes of insulin resistance. Increased plasma levels of FFAs enhance cellular ROS production [28]. Since mitochondria are a major source of ROS, mitochondrial overload caused by an excess of substrate has been regarded as the main cause of ROS production [29,30]. Recently, the fatty acid metabolite, ceramide, and inflammatory cytokines have also been shown to increase mitochondrial ROS generation [31].

Similar to fatty acid metabolites, ROS also activate PKC, IKK, and JNK, leading to inhibition of IRS tyrosine phosphorylation [28,32] (Fig. 3). Moreover, the activation of nuclear factor-κB by IKK exacerbates insulin resistance by increasing inflammatory cytokines [31]. ROS induce GLUT4 degradation by transporting GLUT4 to the lysosome instead of the plasma membrane via disruption of the retromer complex in a casein kinase 2-dependent manner [33]. In addition, peroxynitrite produced by the accumulation of nitric oxide inhibits the action of insulin by inducing the nitration of tyrosine residues and reducing the phosphorylation of IRS-1 [34]. The activation of AKT is also suppressed by peroxynitrite [35].

Increased ROS levels suppress the action of insulin by inducing mitochondrial dysfunction [36]. ROS induce mutations in the mitochondrial DNA, resulting in functional defects caused by altered expression of constituent proteins that are important for electron transport, such as complexes I, III, and IV [37]. These functional defects amplify oxidative stress and shut down mitochondrial energy production [38]. Therefore, the vicious cycle formed between ROS and mitochondria eventually leads to apoptosis.

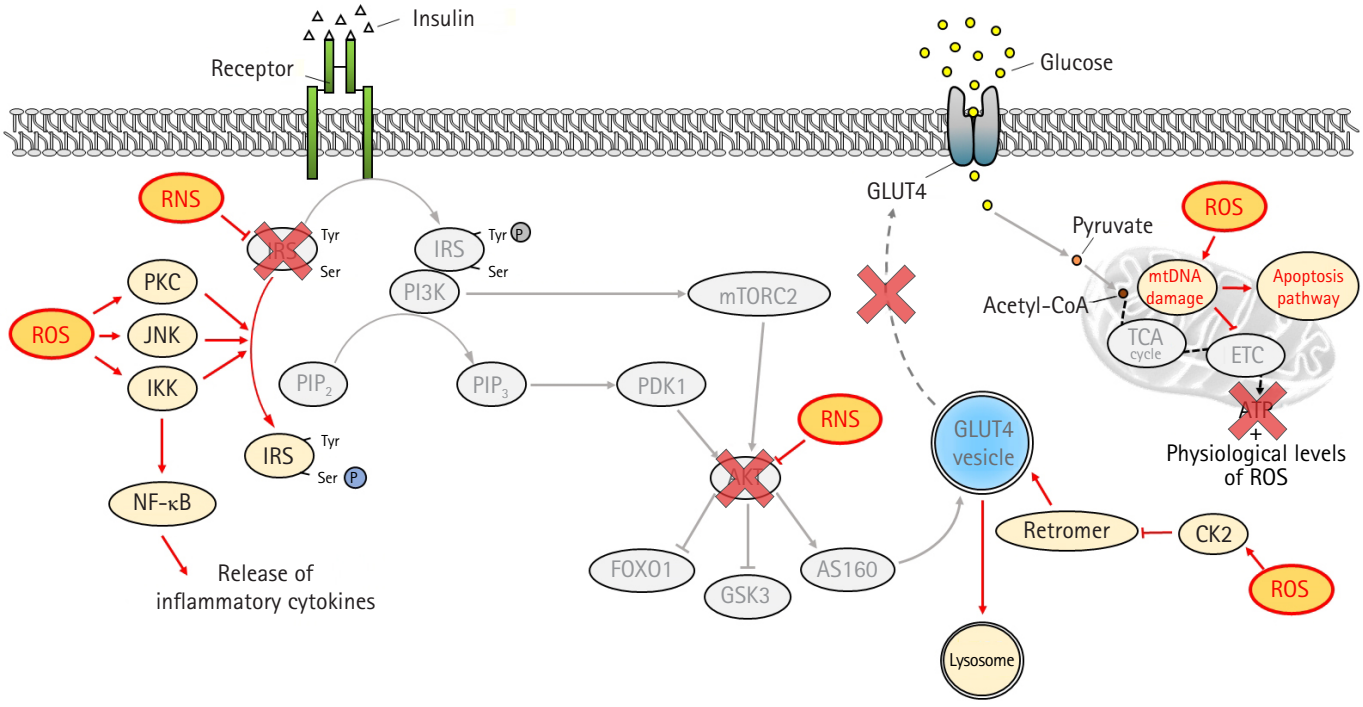

Fig. 3. Inhibition of the insulin signaling pathway by oxidative stress. Reactive oxygen species (ROS) interferes with insulin action by altering several substrates of the insulin signaling pathway. ROS activates serine/threonine kinases, including protein kinase C (PKC), c-Jun N-terminal kinase (JNK), and inhibitory κB kinase (IKK), which not only inhibit the activation of insulin receptor substrate (IRS) through serine phosphorylation but also induce inflammation by activating nuclear factor κB (NF-κB). In addition, ROS suppresses glucose absorption by degrading glucose transporter type 4 (GLUT4) in a casein kinase 2 (CK2)-dependent manner. Reactive nitrogen species (RNS) inhibits tyrosine phosphorylation of IRS and protein kinase B (AKT) activation by inducing nitration of tyrosine. Mitochondrial functional defects by ROS not only induce an explosive increase in oxidative stress but also suppress mitochondrial energy production, eventually leading to cell death. Tyr, tyrosine; Ser, serine; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PI3K, phosphatidylinositol 3-kinases; PDK1, phosphatidylinositide-dependent protein kinase 1; mTORC2, mammalian target of rapamycin complex 2; FOXO1, forkhead box protein O1; GSK3, glycogen synthase kinase 3; AS160, AKT substrate of 160 kDa; acetyl-CoA, acetyl coenzyme A; mtDNA, mitochondrial DNA; TCA, tricarboxylic acid cycle; ETC, electron transport chain.

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Genetic modification of antioxidant enzymes and insulin sensitivity

Obesity induced by a chronic high-fat diet (HFD) has been shown to increase oxidative stress accompanied by insulin resistance in insulin-sensitive tissues in rodents [39,40]. Generally, the genetic deletion of antioxidant enzymes increases oxidative stress and induces insulin resistance and/or glucose intolerance, while overexpression of antioxidants reduces oxidative stress and improves insulin resistance and/or glucose intolerance (Table 1) [39-64].

However, although ROS levels have been altered by genetic modulation of antioxidant enzymes, some of the studies reported unaltered insulin sensitivity, especially in the case of SOD modulation alone (Table 1). Moreover, unexpectedly, the global knockout of GPx1 improves insulin resistance [52], whereas overexpression of GPx1 impairs insulin sensitivity [51]. Although increased ROS

Table 1. The effect of deficiency or overexpression of antioxidant enzymes on glucose metabolism and insulin sensitivity in mice

Antioxidant	Gene modification	Metabolic phenotype
SOD1	Global KO	Reduction in β-cell volume and insulin secretion/unaltered insulin sensitivity and increased mitochondrial hydrogen peroxide production in muscle [41]
	Global OE	Improved glucose intolerance and reduced skeletal muscle hydrogen peroxide generation and oxidative stress in HFD-fed mice [42]
SOD2	Hz global KO	Impaired insulin secretion, increased ROS in islets, and unaltered insulin sensitivity [43]
	Global OE	Improved glucose intolerance and reduced skeletal muscle oxidative stress in HFD-fed mice [42]
		Unaltered insulin sensitivity and reduced hydrogen peroxide generation in HFD-fed mice [44]
	Skeletal muscle OE	Improved insulin resistance and reduced oxidative stress in the skeletal muscle of rats [45]
Catalase	Global KO	Exacerbated HFD-induced insulin resistance and increased oxidative stress in white adipose tissue [46]
		Accelerated HFD-induced obesity and increased oxidative stress in white adipose tissue [47]
	Global OE	Reduction in fat mass, oxidative stress, and glucose levels in *ob*/*ob* mice [48]
	Mitochondrial OE	Improved insulin resistance and reduced hydrogen peroxide generation and oxidative stress in skeletal muscle [44,49]
		Improved insulin resistance and reduced hydrogen peroxide generation and lipid accumulation in the skeletal muscle of HFD-fed mice [50]
SOD2 and catalase	Global SOD2 OE and mitochondrial catalase OE	Improved insulin resistance and reduced hydrogen peroxide generation and oxidative stress in skeletal muscle. No difference in insulin sensitivity or hydrogen peroxide generation compared with that of mitochondrial catalase OE only [44]
GPx1	Global OE	Increased fat mass and the development of insulin resistance [51]
	Global KO	Improved insulin resistance, enhanced production of ROS and oxidation of PTP [52]
	Liver KO	Improved insulin sensitivity, increased hydrogen peroxide generation in hepatocyte and oxidation of PTP [53]
GPx1 and catalase	Global KO	Prevention of obesity, improved glucose tolerance, and attenuated nonalcoholic fatty liver in HFD-fed mice [54]
GRx2	Global KO	Exacerbated obesity and insulin resistance in HFD-fed mice/exacerbated oxidative stress by HFD in brain [55]
Prx2	Global KO	Exacerbated aging-induced insulin resistance and oxidative stress in muscle [56]
		Prevented obesity and insulin resistance in HFD-fed mice [57]
		Reduced insulin sensitivity and increased oxidative stress in control diet/no effect on oxidative stress and insulin resistance in HFD-fed mice [58]
Prx3	Global KO	Induced obesity, increased oxidative stress, and impaired glucose tolerance and insulin sensitivity/increased superoxide levels in 3T3-L1 adipocytes [59]
	Global OE	Reduced mitochondrial hydrogen peroxide levels and oxidative stress and improved glucose intolerance [60]
Prx4	Global OE	Improved glucose intolerance in STZ mice and reduced oxidative stress and steatohepatitis in HFD-fed STZ mice [61]
Prx6	Global KO	Reduced insulin secretion and impaired glucose tolerance and insulin sensitivity [62]
MsrA	Global KO	Impaired glucose tolerance and exacerbated insulin resistance and oxidative stress in HFD-fed mice [63]
	Mitochondrial OE	Improved insulin resistance in HFD-fed mice/preserve insulin sensitivity without cytosolic MsrA [64]
	Cytoplasmic OE	Unaltered insulin resistance in HFD-fed mice [64]
MsrB1	Global KO	No effect on insulin sensitivity, hydrogen peroxide levels, or oxidative stress in HFD-fed mice [40]
SelW	Global KO	No change in oxidative stress or insulin sensitivity in the skeletal muscle of HFD-fed mice [39]

SOD1, superoxide dismutase 1; SOD2, superoxide dismutase 2; KO, knockout; OE, overexpression; HFD, high-fat diet; Hz, heterozygous; ROS, reactive oxygen species; GPx, glutathione peroxidase; PTP, protein-tyrosine phosphatase; GRx, glutaredoxin; Prx, peroxiredoxin; STZ mice, streptozotocin-injected mice; Msr, methionine sulfoxide reductase; SelW, selenoprotein W.

levels have been known to suppress insulin signaling pathways through activation of serine/ threonine kinases [65,66], paradoxical activation of insulin signaling pathways by ROS through oxidation of protein-tyrosine phosphatase 1B has been reported in GPx1-knockout mice [52]. Therefore, increased ROS may be associated with a combination of both favorable and unfavorable effects on insulin sensitivity.

In addition to the results of genetically modified mouse models, the treatment of experimental animals with antioxidants, such as hemin, glutathione, vitamin C, and polyphenols, has been reported to improve insulin resistance [67-70], suggesting that a reduction in oxidative stress could be a potential therapeutic approach for type 2 diabetes.

Oxidative stress in patients with type 2 diabetes

There is a large body of evidence indicating that oxidative stress is increased in the plasma or blood cells of diabetic patients. Compared with those in healthy glucose-tolerant individuals, the levels of biomarkers of oxidative damage to proteins [71,72], lipids [73-76], and DNA [74,77], such as carbonyl groups, malondialdehyde, thiobarbituric acid reactive substances, and 8-hydroxydeoxyguanosine, are increased in patients with type 2 diabetes. Moreover, these biomarker levels are positively correlated with hemoglobin A1c (HbA1c) or homeostatic model assessment for insulin resistance (HOMA-IR) in patients with type 2 diabetes [76-79], suggesting a close link between insulin resistance and oxidative stress.

Oxidative stress is higher in patients with diabetes than in healthy individuals, not only in the plasma but also in insulin-sensitive peripheral tissues, including skeletal muscles. Higher levels of biomarkers of DNA oxidation [80] and lipid oxidation [81] have been reported in skeletal muscle tissues of diabetic patients as compared to healthy controls. Lipid peroxidation levels are negatively correlated with glucose disposal [81]. Moreover, in a previous study assessing nitrosative stress in diabetes, nitrites and nitrates were increased in quadriceps muscle of diabetic patients as compared to the control group, and nitrotyrosine levels positively correlated with HbA1c levels [82]. However, even though the levels of oxidative stress markers are higher in patients with type 2 diabetes, some studies do not support the positive correlation between HbA1c and oxidative stress markers [83,84].

Considering the critical role of oxidative stress in the development of type 2 diabetes, the levels of oxidative stress markers are thought to increase in the prediabetic state. Consistent with this hypothesis, the plasma levels of thiobarbituric acid reactive substances have been shown to positively correlate with body mass index and waist circumference in obese, nondiabetic individuals [85]. Moreover, higher levels of mitochondrial ROS have been detected in the skeletal muscle tissue of obese human subjects as compared with lean controls [86,87]. Higher levels of circulating FFAs might be implicated in increased ROS levels in obese subjects, as suggested by previous studies. Two-consecutive fat-rich meals have been shown to increase plasma malondialdehyde levels in healthy young males [88]. Additionally, in nonobese sedentary humans, overfeeding with an HFD for 28 days induced insulin resistance and increased muscle protein carbonylation [89]. Furthermore, increased levels of carbonylated protein negatively correlated with insulin sensitivity in these overfed subjects [89].

As excess ROS are scavenged by the antioxidant system, increased oxidative stress in obese and type 2 diabetic subjects is followed by a reduction in antioxidant levels. Obese patients with body mass indexes above 35 kg/m^2 exhibit low levels of carotenoids and vitamin E [90]. Lower levels of vitamin E have been reported in plasma of patients with type 2 diabetes as compared to normal controls [91]. In the Rotterdam Study, the ferric reducing ability of plasma (FRAP) score, an index of dietary antioxidant capacity, was inversely related to the insulin resistance index [92]. Moreover, increased levels of total dietary antioxidant capacity were associated with a reduced risk of type 2 diabetes in a female cohort study [93]. However, not all studies support the close relationship between antioxidant levels and the risk of type 2 diabetes. No association has been found between the serum levels of α-tocopherol or β-carotene and the risk of diabetes in middle-aged males [94]. Moreover, in a cohort study, levels of dietary antioxidants, including vitamin C, vitamin E, carotenoids, flavonoids and flavones, were not associated with the risk of type 2 diabetes in middle-aged male smokers [55].

Additionally, the administration of antioxidants to humans has shown controversial results. Increased dietary intake of β-carotene for 10 years have been associated with reduced risk of diabetes [95]. Vitamin C intake is associated with a reduced risk of incident diabetes in Japanese women [96]. In contrast, the administration of α-tocopherol or β-carotene does not significantly affect the occurrence of diabetes in males [94]. Moreover, resveratrol-mediated attenuation of ROS production and oxidative damage does not affect HOMA-IR in patients with type 2 diabetes [97].

Based on experimental animal and human studies, oxidative stress is closely linked to type 2 diabetes. However, the antioxidant capacity of the serum or tissue is not consistently related to the risk of type 2 diabetes. Additionally, the administration of antioxidants to prediabetic and diabetic patients has produced inconsistent results. There might be several reasons for this inconsistency. A limit-

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ed number of antioxidants have been assessed for antioxidant capacity in serum. Additionally, it is difficult to assess the antioxidant capacity in insulin-sensitive tissues such as skeletal muscle and adipose tissue in humans. Serum levels of antioxidants are not always consistent with tissue levels. Furthermore, some of the currently used drugs for the treatment of type 2 diabetes have been shown to exert an antioxidant property which may conceal the therapeutic effect of vitamins and natural antioxidants in type 2 diabetes [98]. In most prospective studies, limited types of antioxidants have been used to assess the risk of type 2 diabetes. However, antioxidants still hold promise as potential therapeutic options for the prevention and treatment of type 2 diabetes and its complications. According to Clinicaltrials.gov, 23 clinical trials are recruiting or planning to recruit participants to take part in studies examining the effects of antioxidants on glucose levels or peripheral tissue complications in prediabetic and type 2 diabetic patients (Table 2). Dietary and natural antioxidants from various sources and vitamins are still popular agents for clinical trials, and melatonin is emerging as a potential therapy for type 2 diabetes. Pharmaceuticals targeting prooxidant and antioxidant enzymes, such as NADPH oxidase inhibitors, xanthine oxidase inhibitors, and SOD mimetics, are actively being developed for the treatment of oxidative stress-related diseases, including type 2 diabetes [99,100].

Conclusion

Oxidative stress is elevated in obese prediabetic and type 2 diabetic experimental animals and humans. However, although experimental animal studies show promising results, the effects of antioxidant administration on type 2 diabetes in humans are still inconsistent. Nevertheless, clinical trials examining the therapeutic effects of dietary antioxidants and vitamins on type 2 diabetes and its complications are still ongoing. Pharmaceuticals targeting redox regulating enzymes are actively under development, and the successful development of pharmaceuticals might help us understand the therapeutic effectiveness of antioxidants in the treatment of type 2 diabetes.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Table 2. Recruiting and not yet recruiting (August 2020) clinical trials of agents with antioxidant properties targeting type 2 diabetes

Trial start year	Drug	Target condition and disease
2010	Quercetin	Obesity/type 2 diabetes
2014	Blackcurrants/green currants	Type 2 diabetes
	Vitamin E and C	Type 2 diabetes/fatty liver/obesity/healthy volunteers
2015	Grape seed polyphenolic extract and resveratrol	Mild cognitive impairment and prediabetes or type 2 diabetes
	Blueberry tea	Type 2 diabetes
2016	Melatonin	Prediabetes/obesity
	Metadoxine	Nonalcoholic fatty liver disease/prediabetes
	Chlorogenic acid enriched coffee	Type 2 diabetes/chronic renal insufficiency
2017	Vitamin D	Vitamin D deficiency/glucose intolerance/oxidative stress/insulin resistance
2018	Hydrolyzed pine nut oil/hydrolyzed pine nut oil and olive oil	Type 2 diabetes/obesity
	Green tea extract	Diabetic nephropathy, type 2
	Sanprobi barrier (multispecies probiotic)	Type 2 diabetes/metformin adverse reaction
	Transresveratrol	Type 2 diabetes/coronary artery disease
	Pentoxifylline	Chronic kidney disease stage 3 and 4/type 2 diabetes
	Naturally-sweetened orange juice	Cardiovascular risk factor/type 2 diabetes/insulin sensitivity/metabolic syndrome
2019	Melatonin/metformin	Prediabetes
	Solarplast (a mixture of antioxidant enzymes and single antioxidant molecules)	Oxidative stress/healthy aging/skin health
	Melatonin	Diabetes mellitus
	Melatonin	Metabolic disease/insulin sensitivity/glucose metabolism disorders/type 2 diabetes/blood pressure/inflammation
	Olive oil	Type 2 diabetes/platelet dysfunction/postprandial hyperglycemia
2020	Docosahexaenoic acid and lutein enriched eggs	Diabetic retinopathy
	Vitamin C, D, and zinc	Type 2 diabetes
	Alpha-lipoic acid	Type 2 diabetes/diabetic polyneuropathy

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F-18 fluorodeoxyglucose positron emission tomography/computed tomography in the infection of heart

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Infections involving the heart are becoming increasingly common, and a timely diagnosis of utmost importance, despite its challenges. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a recently introduced diagnostic tool in cardiology. This review focuses on the current evidence for the use of FDG PET/CT in the diagnosis of infective endocarditis, cardiac implantable device infection, left ventricular assist device infection, and secondary complications. The author discusses considerations when using FDG PET/CT in routine clinical practice, patient preparation for reducing physiologic myocardial uptake, acquisition of images, and interpretation of PET/CT findings. This review also functions to highlight the need for a standardized acquisition protocol.

Keywords: Endocarditis; F-18 fluorodeoxyglucose; Heart valve prosthesis; Infections; Positron emission tomography computed tomography

Introduction

Infections of the heart primarily manifest as endocarditis, which affects 7.6 to 80/100,000 adult admissions [1]. Prosthetic materials, including valve replacements, grafts, implantable devices, and related materials, such as leads, can lead to the development of endocarditis [2]. Moreover, cardiac implantable electronic device (CIED) infections occur in approximately 1.8/1,000 pacemakers a year according to a nationwide cohort study [3]. The diagnosis of such infections can be difficult, and the clinical presentation, as well as microbiological and imaging approaches have been used to reach an accurate diagnosis.

The diagnosis of infective endocarditis (IE) is largely based on the modified Duke criteria (mDC), which has an overall sensitivity of 80%. The mDC comprises causative pathogen detection and echocardiographic features of endocardial involvement [4]. Echocardiography is useful in diagnosing and managing patients with IE, by showing the presence of a swinging intracardiac mass or vegetation, prosthetic valve partial dehiscence, annular abscesses, and new valve regurgitation, which are categorized as major criteria in the diagnosis of IE [4]. Furthermore, the diagnostic sensitivity for vegetation in native and prosthetic valves is better for transesophageal echocardiography (TEE) than transthoracic echocardiography (96% and 92% vs. 70% and 50%, respectively) [5]. Echocardiography has superior accuracy as a primary imaging tool for native valve imaging but has disadvantages such as acoustic shadowing and noise when imaging implanted material. Moreover, blood cultures often lead to indeterminate results for confirming suspected IE, and in up to 24% of patients with pathologically proven IE, it is misclassified as a "possible" IE based on the mDC alone [6]. Recently, the addition of F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) to the mDC has improved the diagnostic accuracy in patients suspected with prosthetic valve endocarditis (PVE) or intracardiac device infection. FDG PET/CT is also useful to evaluate the extent of valve and device infections, as well as the detection of extracardiac infections, such as septic embolism [6,7].

Unlike TEE, for which numerous well-designed prospective ran-

domized studies have been conducted, knowledge on FDG PET/CT is largely from observational case studies and retrospective data reviews. Despite this limitation, published data for cardiac-device related infections are generally consistent and support its judicious application in the workup of IE [8,9]. Furthermore, FDG PET/CT may have unique advantages over TEE in the following aspects: (1) to provide confirmatory information when TEE findings are inconclusive; (2) to diagnose IE earlier than TEE before morphological damage ensues; (3) to detect unexpected sources of infection and embolisms; and (4) to potentially guide clinical management [10]. The European Society of Cardiology (ESC) recommends adding abnormal FDG uptake as the major criterion for PVE in patients with suspected PVEs classified as "possible" or "denied" in initial mDC [5]. In the 2017 appropriate use criteria, FDG PET/CT was included as 'may be appropriate' for PVE and CIEDs [11]. However, the American Heart Association guideline states that more studies are needed to determine the role of FDG PET/CT in the diagnosis and management of patients with IE, although it is stated to be useful for detecting extracardiac complications [12].

Early adoption of a new technique in clinical care based on recommendations from a panel of experts may improve patient outcomes, even when scientific evidence is lacking. In this article, the general concepts and available evidence for FDG PET/CT use in heart infections are reviewed, and recommendations for image acquisition, interpretation, and pitfalls are given.

Prosthetic valve endocarditis

Several studies have examined the usefulness of FDG PET/CT for PVE. Saby et al. [7] reported that FDG PET/CT had a sensitivity of 73% and a specificity of 80% in a cohort of 72 patients. Furthermore, the sensitivity has significantly increased from 70% with the mDC to 93% with the addition of abnormal FDG uptake around the prosthetic valve as a new main criterion. A meta-analysis of 13 studies by Mahmood et al. [13] showed a pooled sensitivity of 80.5% and specificity of 73.1% and supported the utility of FDG PET/CT as an ancillary diagnostic tool in challenging IE cases. Recently, a large retrospective multicenter cohort study reported FDG PET/CT had a sensitivity of 74% and a specificity of 91%. In addition, if confusing factors, such as low inflammatory activity (defined as C-reactive protein [CRP] levels < 40 mg/dL), and the use of surgical adhesives during transplantation, are excluded, the sensitivity and specificity of FDG PET/CT in PVE diagnosis would increase to 91% and 95%, respectively. Moreover, FDG PET/CT is performed at the early stage of PVE diagnosis, positive results can be confirmed even if the existing diagnostic tests, such as blood culture and echocardiography, are negative. Another interesting finding is that by using FDG PET/CT with echocardiography for diagnosis of IE, the sensitivity increases from 65% to 96% compared to echocardiography alone; this facilitates early diagnosis before structural damage, and consequently reduces the incidence of serious complications, such as valve dehiscence or perivalvular abscesses [14].

Another single center prospective study of 151 patients with suspected PVE reported a sensitivity of 60% for echocardiography alone and 42% for mDC, which increased to 91% when focal uptake in PET/CT was included in the mDC. This study also confirmed that possible IE could be reduced from 33% to 8% if the diagnosis included FDG PET/CT findings [15]. Recent research has indicated that positive FDG PET/CT results are related to major cardiac events such as, death, recurrence of IE, acute heart failure, unsuspected cardiovascular hospitalization, and new embolic events [16].

Native valve endocarditis

In contrast to PVE, there is limited research for the use of FDG PET/CT in suspected native valve endocarditis (NVE). de Camargo et al. [15] reported on 115 patients with NVE, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 22%, 100%, 100%, and 66%, respectively. Furthermore, Kouijzer et al. [17] reported that although FDG PET/CT has a low sensitivity of 45% in NVE, its ability to diagnose NVE increases when FDG PET/CT is added to mDC, which is particularly useful in cases that are difficult to diagnosis using conventional techniques.

A recently published pathological study showed that a higher FDG uptake was related to higher inflammatory infiltration, higher fibrin, lower fibrosis, and a predominance of polymorphonuclear cells in tissues. The study also reported that polymorphonuclear cell infiltration was significantly increased and fibrosis was reduced in PVE, compared to NVE [15]. Therefore, the sensitivity of FDG PET/CT is expected to be lower in NVE than in PVE.

FDG PET/CT may influence the clinical management of patients with NVE by identifying the source of primary extracardiac infection or infective emboli. A prospective study showed that FDG PET/CT identified additional infection sites, such as the lungs, skeleton, brain, and other organs, in 74.5% of patients with diagnosed NVE. Based on these extracardiac findings on FDG PET/CT, the incidence of IE relapse decreased by two-fold as a result of appropriate treatment [18]. In line with this, moderate to intense FDG uptake in the perivalvular area is associated with worse prognosis, such as increased new embolic events (hazard ratio

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[HR], 8.8) and rehospitalization (HR, 3.57) [16].

Cardiac implantable electronic device infection

CIEDs, including pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices (with or without defibrillation capacity), consist of pulse generators to provide the electrical stimulus and transvenous or epicardial leads to deliver the stimulus to the heart. Approximately 1.2 million to 1.4 million CIEDs are implanted each year worldwide [19]. CIED infections have an incidence of 1.37/1,000 device-years for pocket infection alone and 1.14/1,000 device-years for device-related endocarditis. Among a cohort of 2,760 patients with definite IE, 177 cases (6.4%) involved CIED [20]. CIED infections are generally considered in two categories; pocket infection and systemic infection such as lead and/or valvular infection [21]. However, these categories are not exclusive, and the two forms can coexist (Fig. 1). Antibiotics alone can be useful for managing superficial soft tissue infections, but deep pocket infections or lead infections require complete removal of the device, which has important implications for patient care. Thus, fast and accurate diagnosis and, rapid treatment are of supreme importance; however, difficulties remain, especially if the symptoms are delayed or mild [19].

The role of FDG PET/CT in CIED infection has received increasing interest in recent years, and it is considered to be especially useful when a diagnosis of pocket or lead infection is unclear with other imaging techniques, such as TEE. Sarrazin et al. [22] reported that PET/CT could distinguish skin infections from pocket, lead, or intravascular infections in cases of unclear diagnosis or extension. They also proposed that PET/CT can help differentiate an active cardiac device infection from residual normal postoperative inflammation. In addition, Juneau et al. [23] presented a 93% sensitivity and 98% specificity for pocket infection, but 88% and 65% for lead/IE, respectively. Furthermore, a large meta-analysis involving 14 studies with a total of 492 patients showed that FDG PET/CT had a high sensitivity and specificity (96% and 97%, respectively) for pocket infection, but a relatively low sensitivity and specificity (76% and 83%, respectively) for lead infections or CIED-IE [24]. The reason for the poor diagnostic ability for lead infection or IE was only speculated. Of the included studies, only four involved physiological myocardial suppression, while lead in-

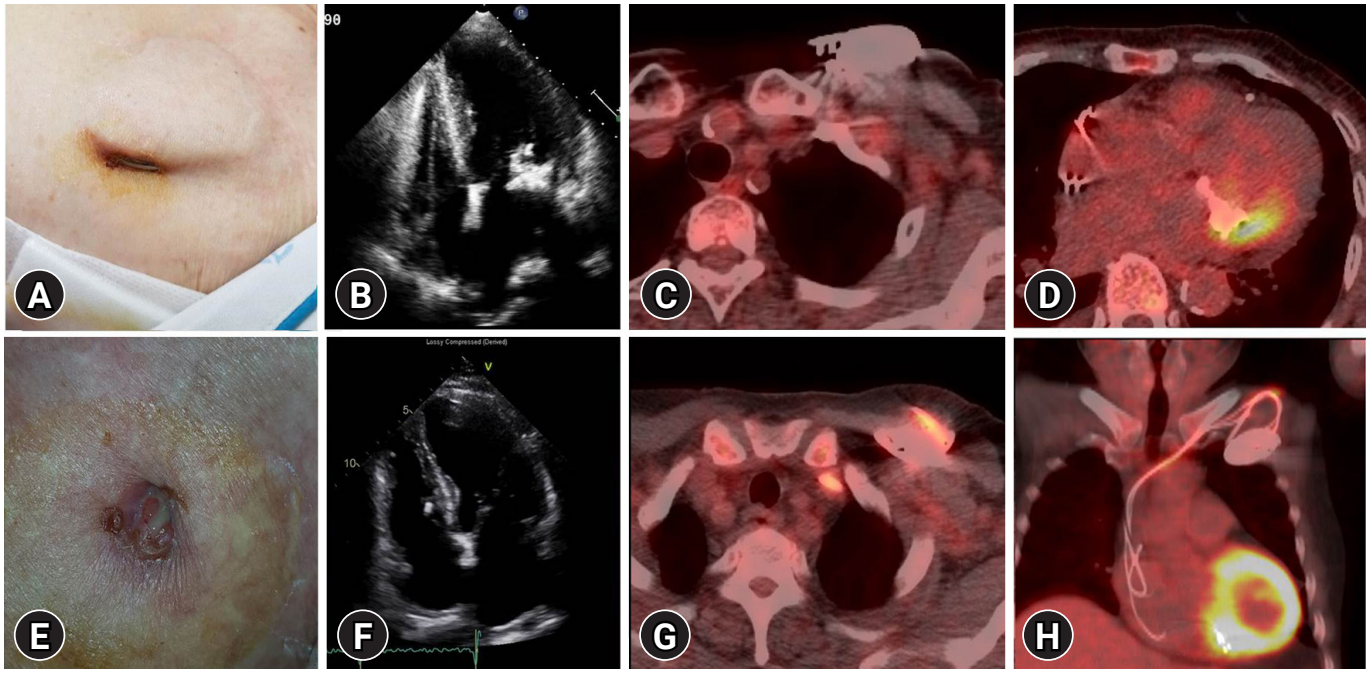

Fig. 1. Two patients (A–D and E–H) with suspected cardiac implantable electronic device (CIED) infection. (A) Gross photo showing CIED exposure with redness in a 79-year-old woman. (B) Echocardiography reveals vegetation in the mitral valve. (C, D) Axial FDG PET/CT shows no FDG uptake in the CIED pocket, but shows high uptake in the mitral valve. The patient did not undergo extraction of the CIED, and instead, was treated with vancomycin for CIED-infective endocarditis with positive blood culture for *Staphylococcus epidermidis*. (E) Gross photo showing pus drainage from the pacemaker insertion site in a 73-year-old man with positive wound culture for *Serratia marcescens*. (F) Echocardiography confirming absence of abnormal findings in the heart. (G, H) Axial and coronal FDG PET/CT shows increased FDG uptake in the pocket and along the lead. The patient underwent pacemaker removal. FDG, F-18 fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

fection was difficult to interpret in the other studies [25]. The vegetation in the lead or valve was too minimal and leukocyte induction was not sufficient for visualization of the FDG accumulation. Moreover, many patients were investigated after initiation of antibiotic therapy.

A recent study involving 105 patients with confirmed CIED infection demonstrated the ability of FDG PET/CT to predict the outcomes of post transvenous lead extraction. Patients with positive findings of CIED pockets on FDG PET/CT, with or without systemic involvement, had better survival rates (HR, 0.493). However, patients with CIED infection with no pocket infection in skin lesions or on PET/CT images showed poor long-term survival. The results can be explained by the hypothesis that CIED infection can arise from two mechanisms, which are associated with different long-term outcomes: (1) CIED infection can originate in a CIED pocket and later spread to the bloodstream; and (2) primary bloodstream infection (transient or recurrent bacteremia) can cause metastatic infection of the lead. The latter may explain why patients with no pocket infection in skin lesions or on PET/CT images have a poor outcome. In addition, approximately 25% of patients diagnosed with CIED infection can be restratified with the presence/absence of CIED-IE by incorporating the FDG PET/CT results [26]. The ESC guideline and appropriate use criteria refer to the usefulness of FDG PET/CT in CIED infection as "may be considered" [5,11].

Left ventricular assist device infection

A left ventricular assist device (LVAD) is mechanical circulatory support device that is surgically implanted in patients with acute or chronic refractory heart failure and serves as a bridge for transplant or destination therapy [27]. LVADs typically consist of a pump with an inflow conduit from the left ventricular apex and an outflow conduit to the ascending aorta. The pump is placed into a pocket, and a driveline, tunneled from the pump, is connected to an external power source through an exit site on the lower abdominal wall. The driveline is particular at risk of infection, with an infection incidence of between 17% to 30% and a mortality rate of 9.8% at 6 months and 31% at 12 months [28]. Early treatment can improve the prognosis, but proper diagnosis is difficult at the time of infection. Although the use of FDG PET/CT has shown good diagnostic results for driveline infection, the number of patients included in each study was small.

Bernhardt et al. [29] reported the sensitivity of FDG PET/CT in LVAD infections as 87.5%, the specificity as 100%, the PPV as 100%, and the NPV as 86.7%. They also confirmed the utility of FDG PET/CT in the location and quantification of the extent of infection. Moreover, a recent case series and meta-analysis of four studies showed a pooled sensitivity of 92% and specificity of 83% for the diagnosis of LVAD infection, but the specificity varied considerably between studies (25% to 100%) [30]. Akin et al. [31] showed that FDG PET/CT imaging provided accurate information on the location and extent of LVAD-related infections 3 weeks after implantation. Although data are limited, preliminary studies have shown that FDG PET/CT can differentiate and localize the site and extension of infection within the central portion of the device, or along the peripheral driveline. This finding has clinical significance, in that patients with infection involving the central portion of a LVAD (including the pump and cannula) have a poorer survival rate than those with an infection involving the peripheral driveline and exit site [32].

de Vaugelade et al. [33] compared the diagnostic performance of FDG PET/CT and leucocyte labeled scintigraphy and demonstrated that FDG PET/CT showed greater sensitivity (95.2% vs. 71.4%, respectively). A recent analysis of 57 patients who underwent 85 PET/CT scans showed that a threshold of peak standardized uptake value (SUVpeak) of 2.5 could accurately diagnose driveline infections. On dividing the LVAD infection into four components on FDG PET/CT, patients with three or more components showed lower survival. Moreover, the presence of thoracic lymph nodes with FDG avidity was also associated with lower survival. Patients who underwent early surgical revision after PET/CT had a shorter hospital stay [34].

Although visual analysis by FDG PET/CT is highly associated with LVAD infection, quantitative parameters provide greater sensitivity and specificity than visual grading alone. A retrospective study that evaluated both visual and semiquantitative approaches reported that FDG uptake along the driveline is rarely an artifact; however, this depends on the reader's experience and is not suitable for inter-examination or patient-to-patient comparison. In a semiquantitative analysis of FDG PET/CT, the diagnostic ability could be further improved with a sensitivity and specificity of 100%, and the maximum SUV (SUVmax) increased by 3.88 or more compared to the basal scan [35]. Dell'Aquila et al. [36] reported that quantitative FDG PET/CT analysis using SUVmax was accurate in diagnosing superficial and deep driveline infections, but had limited use in pump housing infections, in which visual analysis was better. Furthermore, Avramovic et al. [37] proposed that metabolic volume had more diagnostic capability than visual score or SUVmax for LVAD driveline infection. The results demonstrated that the sensitivity, specificity, PPV, and NPV were 87.5%, 79%, 81%, and 86% for visual score; 87.5%, 87.5%, 87.5%, and 87.5% for SUVmax; and 96%, 87.5%, 88.5%, and 95.5% for metabolic volume, respectively.

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The use of surgical adhesives to strengthen inflow and outflow cannulas can lead to false-positive findings. Careful review of each patient's surgical report with regard to the implantation procedure could improve the discriminant power for LVAD infection. Moreover, the large, dense structures of the pump housing are susceptible to beam hardening and scatter in the low-dose CT images used for attenuation correction (AC), which can lead to false uptake. In addition, FDG uptake by a foreign body reaction around the LVAD, physiologic FDG uptake by the adjacent left ventricular myocardium, presence of chronic fistula, and the possibility of internal surface infection of pump housing are all possible reasons for false uptake in FDG PET/CT [36].

Extracardiac complications of infective endocarditis

Extracardiac complications following IE and CIED infection occur in 22% to 43% of patients within the first 2 weeks of treatment [38]. Metastatic infection, spondylodiscitis, osteomyelitis, septic arthritis, and metastatic soft tissue abscess can occur. Previous studies have shown that FDG PET/CT is useful to detect and localize these complications before clinical suspicion in patients with NVE [17,38-40] (Fig. 2). As such, the ESC guidelines recommend the use of FDG PET/CT in combination with other imaging studies, such as whole-body CT and brain magnetic resonance imaging, for the examination of embolic events [5]. Orvin et al. [40] reported on the use of FDG PET/CT in patients with confirmed IE and demonstrated that pertinent extracardiac findings on FDG PET/CT were present in 75% of patients. Consequently, treatment plans were changed in up to 35% of patients and included antibiotic treatment prolongation, referral to surgical procedures, and avoidance of unnecessary device extraction.

Monitoring response to antimicrobial therapy

For treatment of IE, the duration of antimicrobial therapy depends on the causative organism and the site of infection (NVE, PVE, or CIED infection). The recommended duration of treatment in the 2015 ESC guidelines [5] and the Northern American guidelines [41] is based on early randomized studies conducted in the 1990s or expert opinion, and there are very few recent comparative stud-

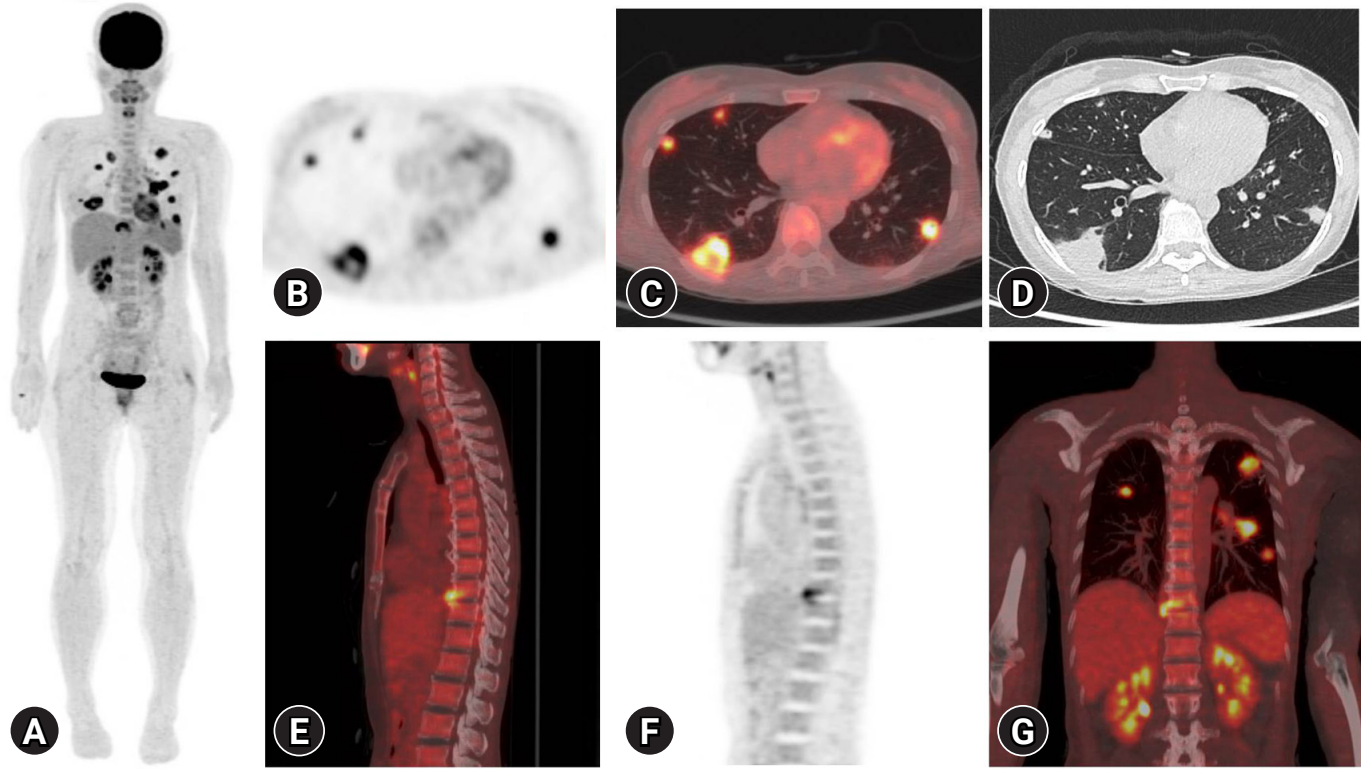

Fig. 2. (A) Extracardiac metastatic infection in a 51-year-old woman demonstrating bilateral lung infection and spondylodiscitis resulting from *Staphylococcus aureus*. (B) Axial FDG PET, (C) axial FDG PET/CT, and (D) axial lung CT showing extensive lung septic emboli. (E) Sagittal FDG PET/CT, (F) sagittal FDG PET, and (G) coronal FDG PET/CT showing infective spondylodiscitis in T10 to T11. FDG, F-18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

ies on the treatment duration [42]. An encouraging role of FDG PET/CT in evaluating the effectiveness of antimicrobial therapy in IE was recently proposed in a small observational study [43]. Moreover, García et al. [44] reported the usefulness of determining a need for continued therapy in cases with remnants of infection at the end of standard treatment; thus, continuation of therapy is needed until increased metabolism is no longer observed on FDG PET/CT. Further large-scale studies are necessary to utilize and prove the usefulness of this application.

Practical consideration in clinics

The main limitation of FDG PET/CT in the diagnosis of cardiac infections is the absence of current standardized protocols, which have varied across previous studies. FDG PET/CT guidelines for diagnosis and monitoring in IE should include information on patient preparation, such as the diet protocol, FDG dosage, duration of uptake, acquisition time, and imaging processing including motion correction of cardiac and respiratory gating and image interpretation.

1. Patient preparation

In an oncological setting, myocardial FDG uptake varies from patient-to-patient and even for serial examinations of the same patient. This variation is considered to be due to nonspecific FDG uptake patterns in which diffuse myocardial activity is higher than liver activity or uptake in the lateral wall and/or ring shaped/circumferential basal uptake. Since this physiological uptake can mask pathological activities, patient preparation methods to inhibit physiological uptake have been proposed [45,46]. The degree of myocardial glucose metabolism varies greatly depending on the patient's overall metabolic status, while the fasting myocardium uses free fatty acids (FFAs) as the main energy source (90%) [47]. Following dietary carbohydrate intake, myocardial metabolism shifts to glucose, following the Randle cycle [47,48]. The myocardium metabolizes glucose when blood sugar and insulin are elevated and FFAs are decreased. Conversely, as glucose and insulin levels decrease and FFAs increase in the fasting state, FFAs are used as the primary source of myocardial energy. The glucose metabolism in inflammatory cells is regulated by glucose transporter 1 (GLUT1) and GLUT3, unlike in the myocardium, where it is regulated via GLUT 4 and is independent of insulin effects [49,50]. Therefore, a patient preparation method that enables myocardial FFA metabolism, while simultaneously suppressing physiologic glucose uptake, is essential for successful FDG PET cardiac infection/inflammation imaging.

Most previous studies have implemented a high-fat, low-carbohydrate (HFLC) diet prior to a prolonged fast, or prolonged fast alone, while some studies have also used additional intravenous heparin administration. Although many preparation methods have been proposed to suppress physiologic myocardial glucose uptake, most studies included a small number of patients, and the preparation strategies were heterogeneous. Therefore, no clear consensus has been reached on the optimal method [51]. The guidelines of Society of Nuclear Medicine and Molecular Imaging, American Society of Nuclear Cardiology, and Society of Cardiovascular CT (SNMMI/ASNC/SCCT guideline) recommend a preparation regimen that incorporates a fat-rich and low-carbohydrate diet for 12 to 24 hours before scanning, and fasting 12 to 18 hours before and/or the infusion of intravenous heparin approximately 15 minutes before FDG injection [52]. More recently, the Japanese Society of Nuclear Cardiology (JSNC) performed an analysis of previous research and suggested a more detailed method, which involved fasting for 12 to 18 hours, and a low-carbohydrate diet, with a total carbohydrate content of less than 5 g for dinner the day before the scan. In addition, they suggested that patients with diabetes underwent same preparation as those without diabetes, albeit with particular attention to sugar control [53].

Regarding the effect of heparin preadministration on inhibition of physiologic uptake, Osborne et al. [51] reviewed 31 dietary preparation studies and found that the myocardium appropriately suppressed FDG uptake in 87% to 93% of patients who fasted for 4 hours after two HFLC meals. In addition, the same effect was reported when unfractionated heparin was injected 15 minutes before FDG injection after at least one HFLC meal and overnight fasting. Moreover, the authors did not recommend the fasting-only methods, food or drink intake, unrestricted diets, and high-fat supplements within 4 hours prior to scanning [51]. Furthermore, heparin showed an anticoagulant effect at doses above 10 U/kg, and the majority of published studies used unfractionated heparin 50 U/kg [54]. In order to lower the risk of heparin-induced thrombocytopenia (HIT), an uncommon but potentially life-threatening risk, low molecular weight heparin has been suggested; however, low molecular weight heparin undergoes approximately 60% lesser lipolysis than unfractionated heparin [55]. The aforementioned SNMMI/ASNC/SCCT guidelines suggest the use of 15 to 50 U/kg heparin, while the JSNC guideline does not recommend the use of heparin. By way of explanation, the JSNC explained that when fasting for more than 18 hours after a low carbohydrate diet, the inhibition of physiological myocardial uptake by heparin was limited, and the risk of HIT following unfractionated heparin is not negligible. However, only a small number of patients were included in the studies cited in these guidelines or review, and studies may provide varying suggestions owing to different fasting times,

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dietary methods, and frequency; therefore, one is not absolutely correct. The JSNC performed an analysis of fasting over 18 hours by dividing 82 patients into two groups [53], while Scholtens et al. [56] performed an analysis by dividing 150 people into three groups, and found that heparin additionally induced a significant decrease in myocardial intake during 12 hours of fasting.

Intracellular calcium is known to stimulate glucose uptake, and Gaeta et al. [57] reported a significant decrease in myocardial FDG uptake in mice treated with verapamil prior to FDG injection. However, these findings have not been replicated in humans [58].

Studies to date have failed to establish a single preparation technique that is far superior to all others, and metabolic profiles vary among patients; therefore, each center must optimize its own protocols that adhere to the principles described above.

2. Imaging acquisition

Hyperglycemia has been shown to impair the inflammatory cell uptake of FDG, as a result of competition with endogenous blood glucose; thus, it is recommended to perform scanning when the patient's blood glucose is below 200 mg/dL. While most studies perform imaging acquisition 1 hour after FDG injection, Caldarella et al. [59] reported that an improved target-to-back-ground ratio is possible if imaging is delayed by 2 to 3 hours. This finding may have additional value for CIED infections, especially in lead infections with low diagnostic sensitivity. However, a patient series study comparing 1- and 2.5-hour post-injection images in PVE patients reported a false-positive interpretation trend for late images, requiring attention to interpretation [60].

Whole-body (head to feet) FDG PET/CT scanning has an advantage with regard to assessing localization of extracardiac infection, including clinically unpredicted distant foci [40,61]. In addition, treatment can be modified depending on the presence or location of the lesions [40]. Although physiological uptake leads to difficulty in visualizing small intracranial lesions, additional infectious lesions have been found on whole-body PET/CT in 17% of patients [13].

Gated cardiac PET imaging can improve spatial resolution and enhance the detection of small moving lesions with the heartbeat, and comparison with CT angiography (CTA) images is easier [62]. However, gated cardiac PET requires a surplus scan time, and there are currently no publications that have examined the additional value of gated cardiac PET for the diagnostic performance of endocarditis.

Pizzi et al. [63] suggested that a combination of FDG PET with CTA could improve the sensitivity in PVE and CIED infection. In their study, they demonstrated that the sensitivity, specificity, PPV, and NPV were 54.5%, 93.8%, 92%, and 60.9% for mDC; 86.4%, 87.5%, 90.2%, and 82.9% for PET/nonenhanced CT; and 91%, 90.6%, 92.8%, and 88.3% for PET/CTA. They also demonstrated that the use of PET/CTA significantly reduced the proportion of suspicious cases to 8%, from 20% in PET/nonenhanced CT. Furthermore, the high sensitivity of FDG PET for diagnosing infections, combined with the high spatial resolution of cardiac CTA, which delineate structural damage, was able to the nine possible cases in PET/nonenhanced CT to be reclassified into eight rejects and one definite case [6]. Moreover, in a study of adult patients with congenital heart disease and suspected IE and/or CIED infection, FDG PET/CTA enhanced the diagnostic sensitivity from 39.1% to 89% and confirmed the diagnosis in 92% of cases [63].

It has been advised that FDG PET/CT is untrustworthy in the 2 months after surgery [64]. Moreover, the ESC guidelines recommended that it should be used with caution in interpreting FDG PET/CT results in patients < 3 months after cardiac surgery, as postoperative inflammatory responses may cause nonspecific FDG uptake; thus, in these cases, radio-labeled leucocyte single photon-emission CT (SPECT)/CT can be considered as an alternative [5]. However, recent studies refuted that scanning for an early after the surgery can be correctly displayed true-negative and the waiting may not resolve potential misidentification problem [14,65,66].

3. Image interpretation

Most studies used visual image analysis, to distinguish diseased states from physiologic uptake. The visual evaluations have been reported to have 74%, 91%, 89%, and 78% sensitivity, specificity, PPV, and NPV for PVE, respectively; and were significantly improved by excluding confounders, as described above (91%, 95%, 95%, and 91%) [14]. The most typical finding in infection is an increased localized uptake in the valve annuli, near the valve leaflets, or in prosthetic materials, where FDG uptake is not observed physiologically. In contrast, a mild homogeneous uptake near mechanical prosthetic valves should be considered as a physiologic uptake. However, a high uptake near prosthetic valves, particularly in cases with clinically high suspicion of infection without other infectious foci, should be considered as possible infection, even if homogeneous.

FDG PET/CT can overlook small vegetations, and endocarditis can be ruled out if there is no FDG uptake in the heart. However, if FDG avid metastatic infection lesions, such as septic pulmonary emboli, fungal aneurysms, or brain abscesses, are found, they may be considered as evidence of endocarditis, even in the absence of cardiac abnormalities [67]. This guidance is especially important when FDG PET/CT is less sensitive at the primary focus, such as

in NVE or lead endocarditis, as mentioned earlier.

AC artifacts occur when high-density structures produce beam hardening or scattering artifacts in low-dose CT used for AC, and can result in false uptake. Non-AC PET images are difficult to evaluate quantitatively, but if the lesion uptake is less than two-fold that of the liver uptake, the artifacts should be excluded by comparing the non-AC images with the corresponding AC images to reduce the possibility of false positives (Fig. 3) [25]. In addition, metal artifact reduction algorithms can improve the confidence of AC image analysis in patients with metallic cardiac devices or valves [68,69].

Semiquantitative measurements of the metabolic activity of lesions using SUVs are less subjective and provide a more objective threshold for determining infection. For this purpose, Scholten et al. [70] analyzed studies on the SUV value of PVE. However, inter-center exchanges were not possible due to the lack of standardized protocols between studies; and because the threshold for rejected PVEs (0.5 to 4.9) and definite PVEs (4.2 to 7.4) showed wide ranges. A semiquantitative measure of FDG uptake, the European Association of Nuclear Medicine Research Ltd.-standardized SUV value ratio (affected valve/blood pool) of ≥ 2.0, was a 100% sensitive and 91% specific interpreter of PVE [14]. It has been proposed that grading of valvular FDG uptake as intense, moderate, mild, or absent is more useful than a simple grading of positive or negative. Similar to the mDC for echocardiography, it is also possible to set up a registry to predict the probability of PVE for each uptake intensity [71].

False-positive findings may occur in areas where surgical adhesives have been applied, which may last for 2 or 3 months [14,45]. False-negative findings may be due to low inflammatory activity at the time of imaging or as a result of prolonged antibiotic treatment [14]. Swart et al. [14] reported that a CRP value less than four-fold the upper normal limit (< 40 mg/L) was a remarkable false-negative factor. Although PET is highly sensitive to detecting disease activity, it has lower spatial resolution than CT. To visualize sites with an abnormal uptake by PET, the target structure should have a volume larger than 1 cm^3, with significant accumulation of the administered radio-tracer [72]. In addition, PET requires data collection for a relatively longer time compared to CT, and motion from the heart beat and breathing during data acquisition can degrade the spatial resolution of PET. However, the detrimental effect caused by motion cannot be noticeably overcome by physiological gating during data collection. Therefore, the use of PET is not optimal for detecting and characterizing small lesions [73]. Overall, clinicians face considerable challenges in diagnosing and characterizing infectious heart diseases with structural or functional imaging, and further improvement in imaging technology will be needed.

Conclusion

FDG PET/CT imaging is a valuable diagnostic modality for patients with suspected IE with prosthetic valves or intracardiac devices. Proper use of PET/CT imaging increases the diagnostic capacity of the mDC. Although the role of FDG PET/CT in NVE is limited, adding the results of FDG PET/CT to the mDC is helpful in diagnosis, particularly if the decision is difficult with convention-

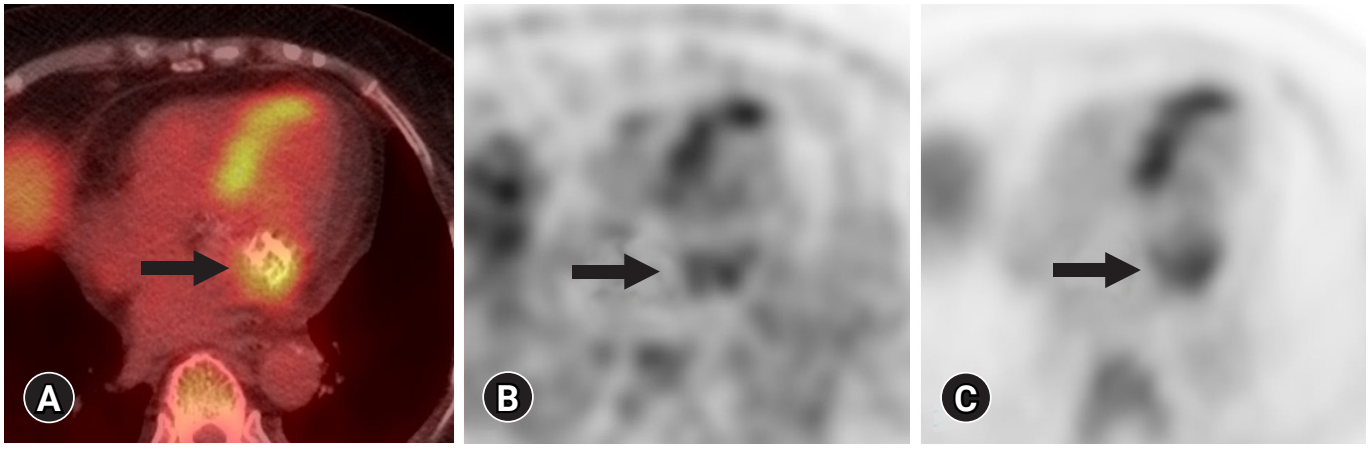

Fig. 3. (A) Axial FDG ETP/CT, (B) non-attenuation, and (C) AC PET images of a case of definite infective endocarditis (IE) resulting from *Escherichia coli* in an 89-year-old patient with a mitral native valve. She suffered from fever of unknown origin, and FDG PET/CT was performed to evaluate the source of the fever. FDG PET/CT shows focal areas of enhanced glycolytic metabolism (arrow) around the calcified mitral valve, in which the standard uptake value was 5.8. Dense calcification can result in false uptake through AC, and therefore, readers should check for non-AC PET. FDG, F-18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

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al approaches. FDG PET/CT can help determine treatment regimens related to CIED infection and the monitoring of antimicrobial therapy in IE. In LVAD, FDG PET/CT is considered to be accurate in diagnosing driveline infections, although it has limited value in evaluating pump housing infections. For all cases of IE, whole-body FDG PET/CT is advantageous in the early detection of metastatic infection and embolic events. The patient should be carefully prepared using a HFLC diet, heparin infusion prior to imaging, and increasing the specificity through AC and non-AC images to reduce impact on metal artifacts. The benefits of using FDG PET/CT for cardiac infection will become more apparent through the development of standardized protocols and large-scale prospective studies.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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The role of microRNAs in cell death pathways

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MicroRNAs (miRNAs) are a class of noncoding RNAs that negatively regulate target messenger RNAs. In multicellular eukaryotes, numerous miRNAs perform basic cellular functions, including cell proliferation, differentiation, and death. Abnormal expression of miRNAs weakens or modifies various apoptosis pathways, leading to the development of human cancer. Cell death occurs in an active manner that maintains tissue homeostasis and eliminates potentially harmful cells through regulated cell death processes, including apoptosis, autophagic cell death, and necroptosis. In this review, we discuss the involvement of miRNAs in regulating cell death pathways in cancers and the potential therapeutic functions of miRNAs in cancer treatment.

Keywords: Apoptosis; Autophagy; Endoplasmic reticulum stress; MicroRNAs; Necroptosis

Introduction

MicroRNAs (miRNAs or miRs) are small (20–23 nucleotides) noncoding RNAs that negatively regulate messenger RNAs (mRNA) expression by blocking translation or by directly promoting degradation of the target mRNA [1]. It is estimated that miRNAs regulate approximately 30% of the protein-coding genes in humans. Individual miRNAs can regulate the expression of multiple genes, and conversely, a single target gene can be regulated by many miRNAs [1].

More than half of the miRNA genes are commonly located in introns. miRNAs are produced by endogenously transcribed long primary miRNA (pri-miRNA) by RNA polymerase (Pol) II or Pol III and show a typical mRNA form with a 5'-cap structure and a 3'-poly (A) tail [2,3]. The pri-miRNAs are further processed into a hairpin-shaped structure, 60 to 100 nucleotides in length, known as precursor miRNA (pre-miRNA) by the nuclear RNase III Drosha. This nuclear processing event is site- specific and critical for determining the mature miRNA sequence. After being exported to the cytoplasm by double-stranded RNA-binding proteins (exportin-5), pre-miRNAs undergo a final processing event by RNase III family enzymes (Dicer) to form a 20-nucleotides miRNA duplex. These mature miRNA duplexes are unwound and the mature strand is incorporated into the RNA-induced silencing complex (RISC) together with an Argonaute (AGO) protein, subsequently forming an active RISC complex [4]. This complex binds to specific mRNA with a complementary sequence, usually in the 3'-untranslated regions (UTRs) of mRNAs to trigger mRNA silencing by translational repression or degradation [5,6]. In general, miRNAs partially base pair with the sequence of the 3'-UTRs of the target mRNAs. This partial complementarity often facilitates translational repression [7]. In contrast, perfect or near-perfect complementary miRNA-mRNA interaction induces the cleavage of mRNA through AGO endonuclease activity, exerting a strong repressive effect on target mRNA expression [8].

The modulation of miRNAs including suppressing the oncogenic miRNAs (oncomiRs) and replacing the deficient tumor-suppressive miRNAs (oncosuppressor miRs) in cancer cells may be a reliable tool to improve cancer therapy [9]. miRNAs are involved in many biological processes, such as cell proliferation, cell death, and tumorigenesis. In addition, regulation of gene expression by miRNAs is important for cellular responses to environmental stresses such as starvation, hypoxia, oxidative stress, and DNA damage. miRNAs can strongly affect the expression of various cell

death-related genes such as pro- and antiapoptotic genes, autophagy regulation genes, endoplasmic reticulum (ER) stress genes, and/or necroptosis-related genes [10]. Abnormal expression of miRNAs associated with cell death pathways can affect physiological conditions and promote disease, including carcinogenesis [11].

Numerous miRNAs can function as oncogenes or tumor suppressors, and it is widely accepted that dysregulation of miRNA expression is closely related to the initiation, progression, and metastasis of cancer. An aberrant miRNA expression is a common event in malignant tissues compared to that in their normal counterparts because many miRNAs are frequently located at vulnerable sites in the human genome, causing gene amplification and deletion, chromosomal rearrangement, and epigenetic changes [11].

miRNAs are classified as oncomiRs or oncosuppressor miRs, which specifically target oncogenes and tumor-suppressor genes, respectively. Generally, oncomiRs are overexpressed, while oncosuppressor miRs are underexpressed in cancers [12]. OncomiRs are associated with specific cancer forming (oncogenic) events, including carcinogenesis, malignant transformation, and metastasis. Abnormal expression of these miRNAs favors uncontrolled proliferation and survival, promotes invasive behavior, and contributes to tumor initiation and progression by regulating cell death. Oncosuppressor miRs generally prevent tumor development by suppressing oncogenes and/or genes that control cell differentiation or cell death. Oncosuppressor miRs can be downregulated as a result of deletions, epigenetic silencing, or loss of transcription factor expression.

Despite global dysregulation, most miRNA expression is globally suppressed in cancer tissues compared to that in normal tissue counterparts [13]. Genetic deletion of the miRNA-processing machinery causes global depletion of miRNAs, which favors cell transformation and tumorigenesis *in vivo* [14]. This indicates that miRNA alterations play a causative role in the development of cancer, not just the effect of tumorigenesis [15]. In this review, we discuss the recent progress in the understanding of miRNA function in the regulation of apoptosis, autophagy, ER-stress-mediated cell death, and necroptosis in cancer cells.

The role of microRNAs in apoptotic pathways

Apoptosis is a programmed cell death that is precisely coordinated by genes and plays an important role in maintaining cellular homeostasis. Apoptosis occurs physiologically in cells that are no longer needed, as observed during many developmental processes. Apoptosis also occurs when cells commit a regulated suicide for the overall benefit of the organism in pathological situations such as infections, neoplasm formation, and irreversible cell damage. The two main types of apoptotic pathways are "intrinsic pathways" and "exogenous pathways" [16,17]. The intrinsic apoptotic pathway receives signals to destroy cells from one of its genes or proteins due to the detection of DNA damage. In the extrinsic apoptotic pathway, cells receive signals from other cells in the organism or from outside the cell, instructing it to commit programmed cell death. The extrinsic and intrinsic pathways can be linked by different signaling pathways to common pathways, for example, by Bid, a BH3 domain-containing protein of B-cell lymphoma 2 (Bcl-2). The truncated Bid trigger switches from the external to the internal signaling pathway [18].

The extrinsic pathway transmits extracellular death signals by the cell-surface death receptor (DR), leading to the formation of the death-inducing signaling complex (DISC) [19]. DRs belong to the tumor necrosis factor (TNF)/nerve growth factor superfamily. DRs possess the death domain (DD), death effector domain, the transmembrane domain, and cysteine-rich motifs [20]. There are six mammalian DRs (TNF receptor 1 [TNFR1], Fas, DR3, DR4 [TNF-related apoptosis-inducing ligand receptor 1, TRAILR1], DR5 [TRAILR2], and DR6) [21,22].

The intrinsic pathways are regulated by the release of cytochrome *c* from mitochondria or loss of the mitochondrial membrane potential. The release of cytochrome *c* into cytosol triggers the activation of caspase-3 through the formation of the apoptosome [23]. Anti-cancer drug-induced caspase activation may be initiated through an extrinsic pathway or the intrinsic mitochondrial pathway [24]. Caspases play an essential role in apoptotic signaling pathways. Caspases are of two types; initiator caspases and executioner caspases. The initiator caspases (caspase-2, -8, -9, and -10) are responsible for the conversion of the inactive form of the executor caspase into the active form. Executioner caspases (caspase-3, -6, and -7) directly trigger the apoptotic process in cells [25]. For example, caspase-8 induces cell death through caspase-3 activation, an important primary caspase in the intrinsic and extrinsic pathways of apoptosis [26]. Mitochondrial damage resulting from drug-induced apoptosis is often accompanied by the release of cytosolic cytochrome *c* from the mitochondria. X-linked inhibitor of apoptosis protein (XIAP), a member of the inhibitor of apoptosis family of proteins, is a protein that inhibits apoptotic cell death by inhibiting caspase-3, -7, and -9 activations [27]. Additionally, Mcl-$1_{(L)}$, a Bcl-2 family protein that inhibits apoptosis, and cellular FLICE (Fas associated with death domain [FADD]-like interleukin-1β-converting enzyme)-inhibitory protein (c-FLIP), an antiapoptotic protein that inhibits apoptosis receptor-mediated apoptosis signaling pathway, are important miRNA targets [28,29].

Many miRNAs are involved in extrinsic signaling pathways.

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miR-7 is a specific sensitizer for TRAIL-mediated apoptosis in glioblastoma multiforme and hepatocellular carcinoma cells [30]. miR-590 is regulated via the signal transducer and activator of transcription 5 (STAT5) pathway and targets Fas ligand (FasL) to promote cell survival in human acute myelogenous leukemia cells [31]. miR-21 is a direct target of FasL in pancreatic cancer, and its ectopic expression protects cancer cells from gemcitabine-mediated apoptosis [32]. miR-20a inhibits the expression of Fas in osteosarcoma cells, thereby facilitating the survival of tumor cells and enhancing their metastatic capacity [33]. Besides, miR-146a and miR-196b inhibit Fas expression, and ectopic expression of miR-196b causes rapid leukemia [34,35]. In addition, the expression of miR-196b-5p has been shown to possess a significant negative correlation with the expression of Fas in non-small cell lung cancer (NSCLC) [35]. miR-25, which has been observed to directly target DR4 and protect against TRAIL-mediated apoptosis, is upregulated in intrahepatic bile duct cancer [36]. FADD is regulated by miR-128a or miR-155. The expression level of miR-128a is increased in acute lymphoblastic leukemia. The ectopic expression of miR-128a enhances Fas resistance in Jurkat cells by targeting FADD, but antagonizing miR-128a sensitizes Fas-mediated apoptosis [37]. Curcumin induces A549 cell apoptosis through downregulation of miRNA-186* expression that targets caspase-10, which is homologous to caspase-8 [10,38]. c-FLIP is a major antiapoptotic protein and an important chemotherapy resistance factor [39]. miR-708 negatively regulates the expression of c-FLIP and enhances the sensitivity of renal cancer cells to various apoptotic stimuli [40]. miR-378, miR-155, and miR-let-7a can regulate cancer cell apoptosis via target caspase-3 [41]. miR-106b is associated with the recurrence of prostate cancer and directly targets caspase-7 [42]. miR-133 and miR-24a directly suppress caspase-9 to regulate apoptosis in pancreatic cancer cells [43].

In the intrinsic apoptotic pathway, apoptotic regulator genes are also regulated by many different miRNAs. miR-365 has been shown to directly target Bcl-2-like protein 4 (Bax) and the adaptor protein Src homology 2 domain-containing 1 (SHC1) in lung adenocarcinoma and lung cancer cell lines [44]. miR-125b is significantly downregulated in gastric cancer cells. However, overexpression of miR-125b inhibits proliferation, migration, and invasion in gastric cancer cell lines (HGC-27 and MGC-803) [45]. miR-148a and miR-204 induce apoptosis by negatively targeting Bcl-2 at the posttranscriptional level [46,47]. In prostate cancer cell lines, ectopic expression of miR-204 has been shown to decrease cell viability and promote apoptosis through the downregulation of Bcl-2 expression [47]. miR-608 directly targets Bcl-extra large (Bcl-xL) and significantly inhibits chordoma cell proliferation by inducing apoptosis [48]. miR-23a/b and miR-27a/b can target apoptotic protease activating factor 1 (Apaf1) and thereby control the sensitivity of neurons to apoptosis [49]. The miRNAs that regulate apoptosis are summarized in Fig. 1.

The role of microRNAs in endoplasmic reticulum stress pathways

Since the ER is involved in the localization and folding of intracellularly secreted transmembrane proteins, the accumulation of unfolded proteins in cells causes cellular stress and leads to a specific ER response called the unfolded protein response (UPR) [50]. UPR is regulated by three sensor proteins; protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor (ATF) 6 [51]. When ER stress is increased, the sensor initiates an adaptive response, including induction of ER chaperone proteins and inhibition of protein synthesis. UPR shows a cascade pattern that activates protein synthesis inhibition and induction of ER stress-related gene expression. If the adaptive response fails to alleviate ER stress and goes beyond what the cell can tolerate, both the intrinsic and extrinsic apoptotic pathways can become activated to remove the stressed cells [52]. Players involved in apoptosis include IRE1α, PERK, and ATF6 [53]. PERK hyperactivation can upregulate the CCAAT-enhancer-binding protein homologous protein (CHOP, also known as growth arrest and DNA damage 153) transcription factor. CHOP inhibits the expression of antiapoptotic Bcl-2 and upregulates proapoptotic BIM and DR5 [53]. Hyperactivated IRE1α activates apoptosis signal-regulating kinase 1 (ASK1) and its downstream target c-Jun NH2-terminal kinase (JNK). Phosphorylated JNK activates proapoptotic BIM and inhibits antiapoptotic Bcl-2. ATF6 likely has proapoptotic targets such as apoptotic factors caspase-12, -9, and -3 [54].

miR-199a-5p directly binds to the binding sites of GRP78, ATF6, and IRE1α [55]. PERK has been reported to be a direct target of miR-204, which increases ER stress-induced cell death in β-cells; however, ATF6 and IRE1α are not affected by miR-204 [56]. Interestingly, PERK induces miR-483 expression, which is associated with the activation of ATF4, but not CHOP [57]. A recent study showed that miR-7112-3p directly targets PERK and regulates the ER stress signaling pathway (activation of the PERK/ATF4/CHOP/caspase cascade) and apoptosis in colorectal cancer CX-1 cells [58]. Besides, colorectal cancer tissues show high expression of miR-7112-3p [58]. The enforced expression of active ATF6 decreases the expression of miR-455 [59]. miR-702 directly regulates ATF6, which inhibits apoptosis in cultured cardiomyocytes treated with isoproterenol [60]. IRE1α cleaves miR-17, miR-34a, miR-96, and miR-125b during ER stress to suppress the

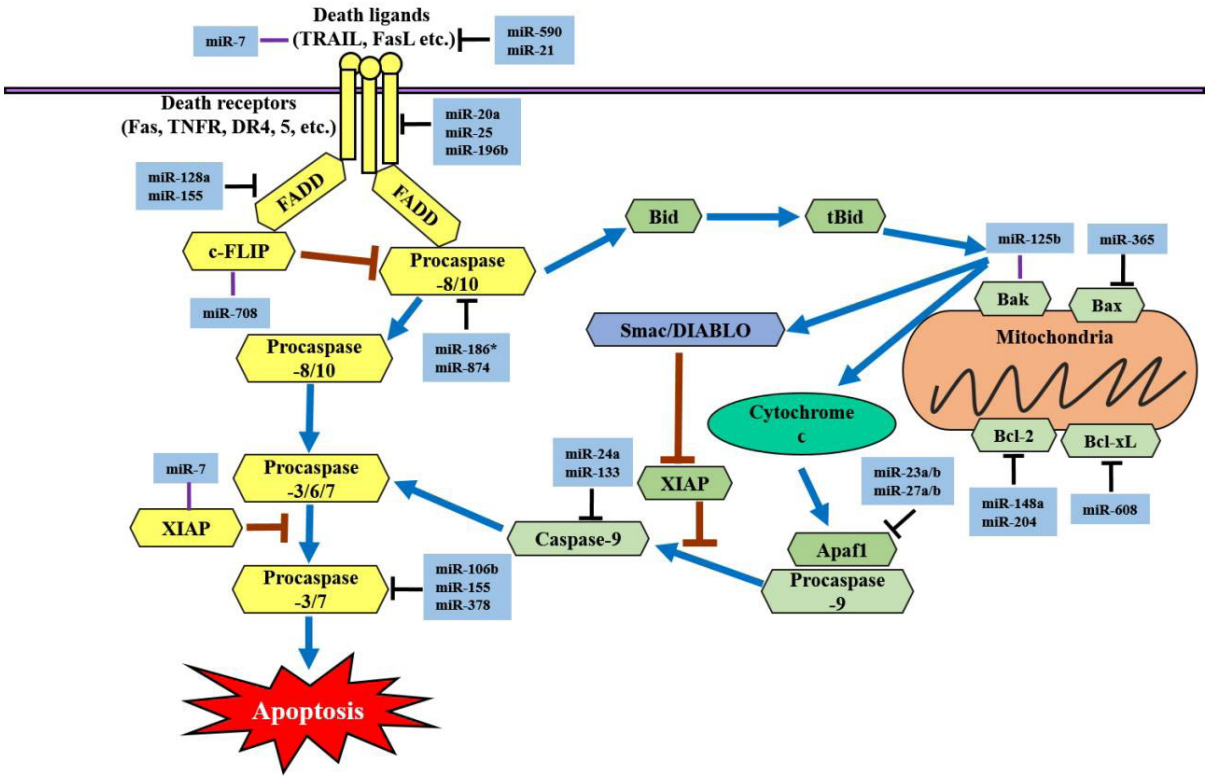

Fig. 1. MicroRNAs (miRs) that regulate the apoptotic signaling pathways. The yellow box indicates the components of the extrinsic apoptotic signaling pathway. When a death ligand binds to a death receptor (DR), an exogenous pathway is initiated. The light green box indicates the components of the intrinsic pathway. Activation of the intrinsic pathway or mitochondrial pathway releases cytochrome c into the cytoplasm. TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand; FasL, Fas ligand; TNFR, TNF receptor 1; FADD, Fas-associated death domain protein; c-FLIP, cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; Bid, BH3 interacting-domain death agonist; tBid, truncated Bid; Smac, second mitochondria-derived activator of caspases, also referred to as DIABLO; Bak, Bcl-2 homologous antagonist killer; Bax, Bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; XIAP, X-linked inhibitor of apoptosis; Apaf1, apoptotic protease activating factor 1.

translation of proapoptotic caspase-2 [61]. ER stress-induced apoptosis is mediated via caspase-2, which is also regulated by IRE1α [62]. PERK-dependent expression of miR-30c-2p inhibits X box-binding protein 1 (XBP1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and overexpression of miR-30c-2-3p exerts a proapoptotic effect by reducing the translation of XBP1 under ER stress conditions [63]. CHOP controls miR-708 transcription during prolonged ER stress [64]. miR-211 is an antiapoptotic miRNA that regulates CHOP expression in a PERK- and ATF4-dependent manner [65] (Fig. 2).

The role of microRNAs in necroptotic cell death pathways

Necroptosis is a programmed form of necrosis or inflammatory cell death. Even if necroptosis inhibits caspase activity, cell suicide occurs in a caspase-independent manner. When caspases are inactivated in cells, receptor-interacting protein (RIP) 1 is phosphorylated by TNF-α and then interacts with RIP3 to induce necroptosis [66]. In this signaling pathway, when TNF-α stimulates TNFR1, TNFR1-associated DD protein (TRADD) and TNF receptor-associated factor 2 (TRAF2) send signals to receptor-interacting serine/threonine-protein kinase (RIPK) 1, finally recruiting RIPK3 to form a necrosome. The RIP1 inhibitor necrostatin-1 (nec-1) has been demonstrated to prevent the death of TNF-α-treated FADD-deficient Jurkat cells [67,68]. Apoptosis-inducing factor (AIF) is transferred from the mitochondria to the cytoplasm and nucleus and induces caspase-independent chromatinolysis [69]. Necroptosis is not only associated with diseases but also with inflammatory diseases such as pancreatitis and Crohn disease [70].

Several miRNAs are known to regulate necroptosis signaling pathways. Deubiquitinase cylindromatosis (CYLD) is an important deubiquitinating enzyme involved in apoptosis or necroptosis signaling pathways. CYLD is directly targeted by miR-181b-1 and miR-19, which leads to inflammation and tumor progression [71,72]. Moreover, miR-874 and miR-512-3p have been reported

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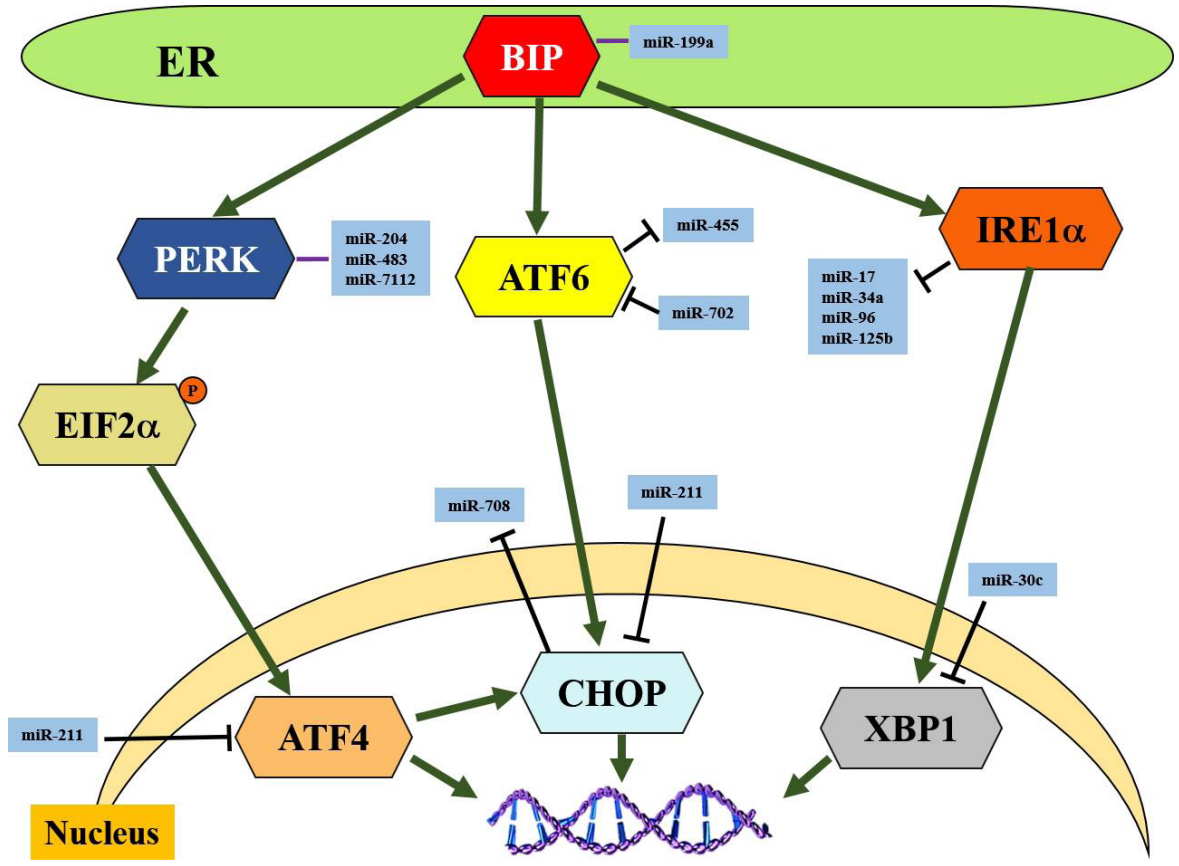

Fig. 2. MicroRNAs (miRNAs or miRs) that regulate the endoplasmic reticulum (ER) stress pathways. Various miRNAs play a role in survival or apoptosis under ER stress conditions. A critical step in unfolded protein response (UPR) signaling is the initial detection of ER stress. PERK, ATF6, and IRE1α possess UPR sensors that are activated by ER stress. BIP, binding immunoglobulin protein, also known as GRP78; PERK, protein kinase RNA-like ER kinase; ATF, activating transcription factor; IRE1α, inositol-requiring enzyme 1 alpha; EIF2α, eukaryotic initiation factor 2 alpha; CHOP, CCAAT-enhancer-binding protein homologous protein; XBP1, X box-binding protein 1.

to regulate necroptosis by targeting caspase-8, which is involved in the transition between apoptosis and necroptosis [73,74]. miR-128a and miR-155 regulate the activity of the adapter protein FADD [37,75]. miR-21 has been shown to act as a pro-necroptosis oncogene through the regulation of RIP1/3-mediated necroptosis [76]. miR-92a-3p is known to be involved in apoptosis or necrosis, which is a member of the miR-17-92 cluster. In addition, miR-92a-3p has been shown to significantly increase cell growth and colony formation in renal cancer cells [77] (Fig. 3).

The role of microRNAs in autophagy pathways

Autophagy is a basic catabolic process that occurs in response to starvation or other stressful conditions. Autophagy encloses dysfunctional, misfolded, or aggregated proteins and damaged cellular components (e.g., mitochondria, ER, and peroxidants) in double-membrane vesicles called autophagosomes, which eventually digest them by lysosomal enzymes and use them for cellular metabolism again [78]. Autophagy involves several key steps for the final degradation of cellular components in lysosomes; sequestration, transport to lysosomes, degradation, and utilization of degradation products. Each step is tightly regulated by evolutionarily conserved autophagy-related (ATG) genes [79].

Autophagy regulates intracellular homeostasis through the cytoplasmic turnover of proteins and organelles. In some cases, autophagy dysfunction can have various pathological consequences, including cancer, neurodegeneration, cardiovascular disorders, and microbe infection. Impaired autophagic signaling pathways are frequently observed in cancer patients. In cancer cells, autophagy has been referred to as a 'double-edged sword' because it increases apoptotic cell death [80] and maintains tumor cell survival in response to metabolic stress *in vitro* [81]. Since the mechanisms that regulate dual opposed survival-supporting and death-promoting roles of autophagy are still far from resolution, it seems necessary to understand the mechanisms that precisely regulate each step of

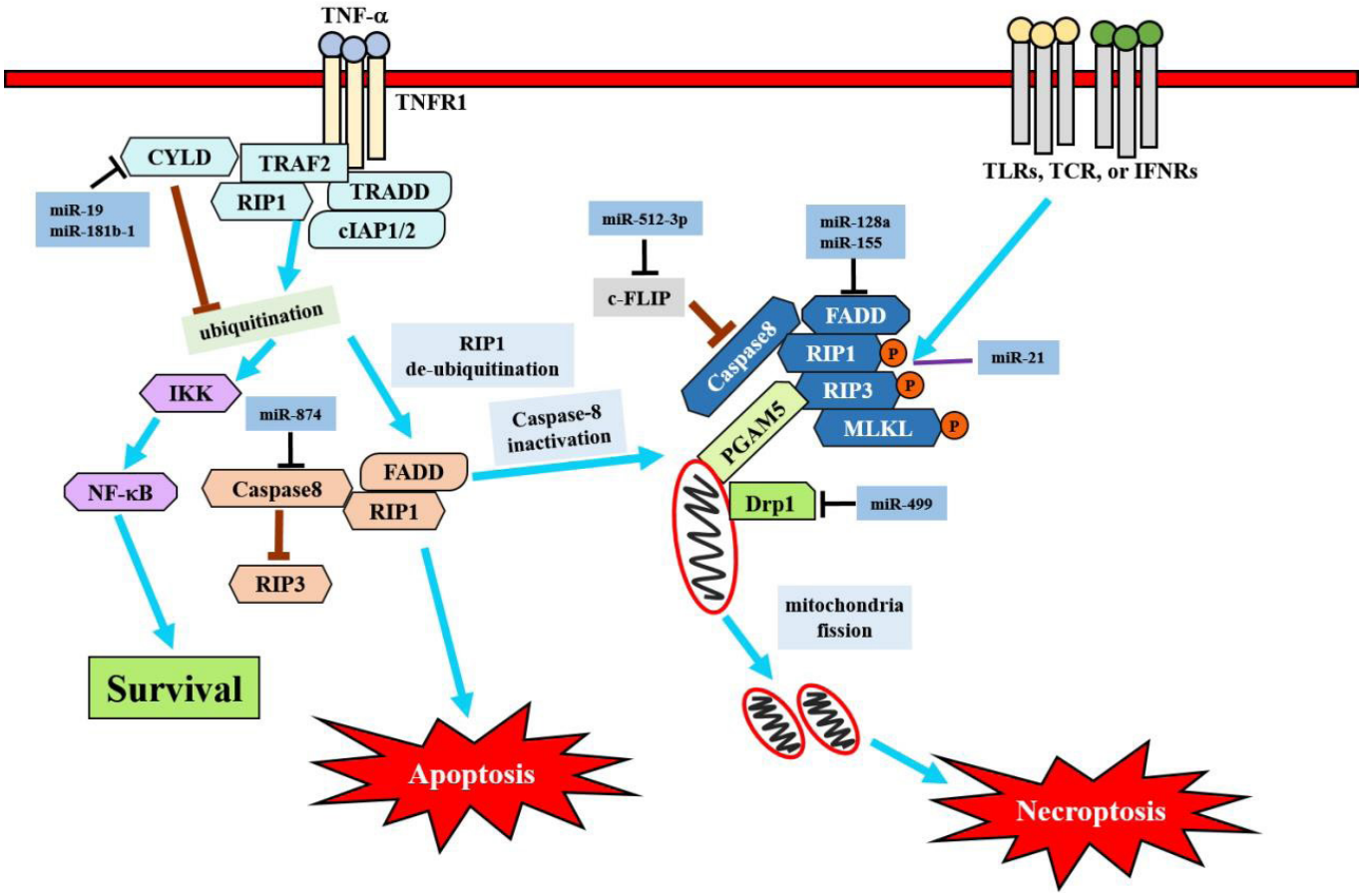

Fig. 3. MicroRNAs (miRs) that regulate necroptotic signaling pathways. Necroptosis is stimulated by TLR, IFNR, and TCR, which are members of the tumor necrosis factor (TNF) receptor superfamily. Extrisic stimili such as cellular stress, damage, and infection activated TNFR1, which can lead to cell survival, apoptosis, or necroptosis. cIAP1 and cIAP2 ubiquitinate RIP1, whereas CYLD deubiquitinates RIP1. MLKL is a critical substrate of RIP3 during the induction of necroptosis. TNFR1, TNF-α receptor 1; CYLD, cylindromatosis; TRAF2, TNF receptor-associated factor 2; RIP1, receptor-interacting protein kinase 1; TRADD, TNFR1-associated death domain protein; c-IAP1/2, cellular inhibitor of apoptosis protein 1/2; IKK, IκB kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; FADD, Fas-associated protein with death domain; TLRs, toll-like receptors; TCR, T-cell receptor; IFNRs, interferon receptors; c-FLIP, cellular FLICE (FADD-like interleukin-1β-converting enzyme) inhibitory protein; MLKL, mixed lineage kinase domain-like; PGAM5, phosphoglycerate mutase 5; Drp1, dynamin-related protein 1.

autophagy to design novel intervention strategies against cancers.

One of the key downstream effectors of autophagy is the mammalian target of rapamycin (mTOR) that coordinates eukaryotic cell growth and metabolism in the presence of growth factors and abundant nutrients [82]. mTOR is well known to regulate cell growth, proliferation, metastasis, and transcription factors. It is associated with two distinct protein complexes, mTOR complex (mTORC) 1/2 [83]. The three important elements of mTORC1 are mTOR, regulatory-associated protein of mTOR (Raptor), and mammalian lethal with Sec13 protein 8 (mLST8), also known as GßL. In addition, mTORC1 contains two inhibitory elements; proline-rich Akt substrate of 40 kDa (PRAS40) and DEP domain-containing mTOR interacting protein (DEPTOR). mTORC2 contains rapamycin-insensitive companion of mTOR (Rictor), a protein that performs similar functions in mTORC2 instead of Raptor. mTORC2 also contains DEPTOR and inhibitory elements mSin1 and Protor1/2. It has been found that the rapamycin complex directly inhibits mTORC1, but mTORC2 is unresponsive to rapamycin treatment [83,84]. Since the mTOR signaling pathway is activated in various cancers, specifically targeting the mTOR pathway via miRNA is a cancer treatment strategy. It is possible to search for various miRNAs that inhibit mTOR signaling in cancer cells, increase the effectiveness of mTORC1/2 inhibitors, and improve the effectiveness of cancer treatment.

miR-99a targets mTOR, which reduces tumorigenesis in lung cancer cells [85]. miR-193a-5p directly targets phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3) and mTOR to inactivate the AKT/mTOR signaling pathway and suppress NSCLC

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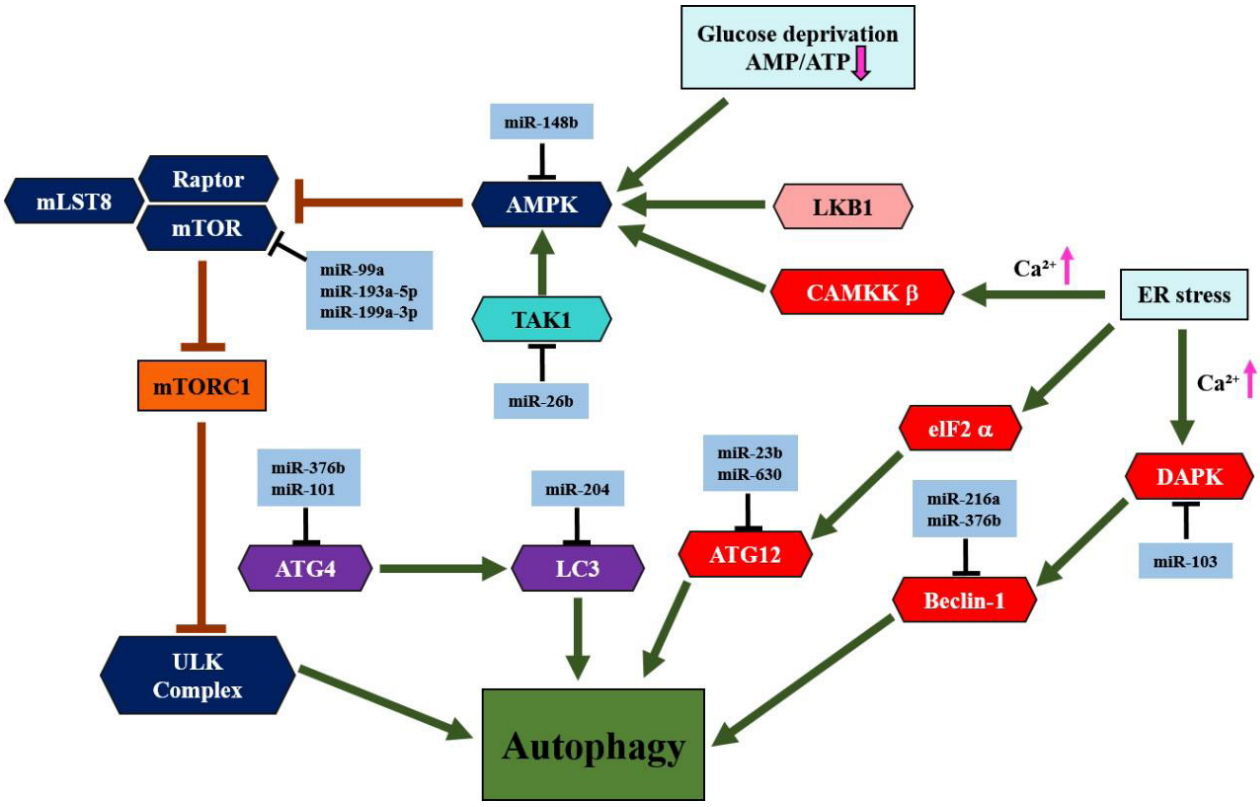

Fig. 4. miRNAs involved in the autophagy pathways. Autophagy occurs under a variety of conditions, such as cell growth signaling, glucose deficiency, hypoxia, genotoxicity, and endoplasmic reticulum (ER) stress, and activates signaling pathways that initiate or inhibit the autophagy cascade. The mTOR and AMPK proteins are important regulators of the autophagy pathway. mLST8, mammalian lethal with Sec13 protein 8, also referred to as GβL; mTOR, mammalian target of rapamycin; Raptor, regulatory-associated protein of mTOR; mTORC1, mTOR complex 1; ULK, Unc-51-like kinase; AMPK, AMP-activated protein kinase; TAK1, transforming growth factor β-activated kinase 1; ATG4, autophagy-related 4 cysteine peptidase; LC3, microtubule-associated proteins 1A/1B light chain 3B; AMP, adenosine monophosphate; ATP, adenosine triphosphate; LKB1, liver kinase B1; CAMKKβ, calcium/calmodulin kinase kinase beta; eIF2α, eukaryotic initiation factor 2 alpha; DAPK, death-associated protein kinase.

metastasis [86]. Moreover, miR-199a-3p regulates mTOR and c-Met to inhibit invasion and enhance doxorubicin sensitivity in hepatocarcinoma cells [87]. Downregulation of miR-148b is associated with poor survival in NSCLC [88]. In pancreatic cancer, it has been observed that miR-148b is a direct target of adenosine monophosphate-activated protein kinase (AMPK) α1 that inhibits cell proliferation and invasion, and enhances chemosensitivity [89]. miR-26b directly suppresses transforming growth factor β-activated kinase 1 (TAK1) and other factors to enhance chemosensitivity [90]. ATG4C, an ATG4 family member, has been observed to decrease the expression of miR-376b [91]. Moreover, miR-101 directly targets ATG4D, an ATG4 family member, which acts as a potential inhibitor of rapamycin- or etoposide-induced autophagy [92]. miR-204 interferes with autophagy and inhibits the growth of renal clear cell carcinoma [93]. In addition, miR-204 directly targets ATF2 to suppress cell proliferation and autophagy and induce apoptosis of NSCLC [94]. In pancreatic cancer cells, ATF12 expression is inhibited by miR-23b, which decreases autophagic activity and suppresses radio-resistance [95]. Additionally, miR-630 is considered to be a target of ATG12 [96]. Beclin-1, the main component of the class III phosphatidylinositol 3-kinase (PI3K-III) complex, is negatively regulated by miR-376b, miR-30a, and miR-216a, which leads to decreased autophagic activity [91,97-99]. Death-associated protein kinase (DAPK) is a well-known proapoptotic and suppressor of metastasis. DAPK is a direct target of miR-103 that promotes colorectal cancer metastasis [100] (Fig. 4).

Conclusion

In this review, we have summarized and discussed how miRNAs regulate apoptosis, ER stress, necroptosis, and autophagy by targeting a wide range of components of these pathways and documented the aberrant expression of miRNAs in cancer and the oncogenic or tumor-suppressor roles of miRNAs. miRNAs discussed in this review could be used as promising diagnostic and prognostic

biomarkers as well as effective therapeutic targets for various cancers. However, further studies are needed to improve knowledge about the mechanisms and functions of miRNAs in various programmed cell death pathways in cancer cells. In addition, it is necessary to determine the best formulation and precise drug delivery system to target cancerous tissues while avoiding unwanted miRNA effects that can result from targeting important genes in other healthy tissues. Finally, the selected miRNAs should have the potential to intervene and modify cell physiology and behavior in many human pathologies, including the deregulation of the cell death machinery.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: all authors; Funding acquisition, Project administration, Validation: TJL; Investigation: JHJ; Writing-original draft: JHJ; Writing-review & editing: TJL.

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A study on evaluator factors affecting physician-patient interaction scores in clinical performance examinations: a single medical school experience

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Background: This study is an analysis of evaluator factors affecting physician-patient interaction (PPI) scores in clinical performance examination (CPX). The purpose of this study was to investigate possible ways to increase the reliability of the CPX evaluation.
Methods: The six-item Yeungnam University Scale (YUS), four-item analytic global rating scale (AGRS), and one-item holistic rating scale (HRS) were used to evaluate student performance in PPI. A total of 72 fourth-year students from Yeungnam University College of Medicine in Korea participated in the evaluation with 32 faculty and 16 standardized patient (SP) raters. The study then examined the differences in scores between types of scale, raters (SP vs. faculty), faculty specialty, evaluation experience, and level of fatigue as time passes.
Results: There were significant differences between faculty and SP scores in all three scales and a significant correlation among raters' scores. Scores given by raters on items related to their specialty were lower than those given by raters on items out of their specialty. On the YUS and AGRS, there were significant differences based on the faculty's evaluation experience; scores by raters who had three to ten previous evaluation experiences were lower than others' scores. There were also significant differences among SP raters on all scales. The correlation between the YUS and AGRS/HRS declined significantly according to the length of evaluation time.
Conclusion: In CPX, PPI score reliability was found to be significantly affected by the evaluator factors as well as the type of scale.

Keywords: Clinical competence; Medical students; Physician-patient relations

Introduction

Establishing major competencies and training for clinical performance in medical education has been prevalent in Korea for only the last 15 years. This is due to the clinical skills test that was added to the paper-based Korean Medical Licensing Examination (KMLE) in 2009. This crucial change in the KMLE has strengthened clinical performance in Korean medical schools.

Yeungnam University has also conducted regional consortiums in training and its evaluation of clinical performances bi-annually. The consortium is primarily intended for educational feedback, so after conducting a similar evaluation of the KMLE, not only individual student feedback but also school feedback will be obtained.

The clinical skills test is consisting of the objective structured clinical examination (OSCE) and clinical performance examina-

tion (CPX). In evaluating communication skills and attitude by the standardized patient (SP), Yeungnam University employs five to six items that are the same as the physician-patient interaction (PPI) scales on the KMLE. These items include effective questioning, careful listening, a patient-centered attitude, using words precisely, and rapport building. In the physical examination station, another item has been included to assess a good manner during physical examination. Even though the six items of the PPI evaluation are based on global rating forms, the assessment guidelines and evaluation criteria for each question are quantitative rather than qualitative. They endeavor to establish an objective evaluation according to the checklist developed for this purpose. Faculty raters evaluate technical skills; SP raters evaluate PPI for the same students. This evaluation process is based on multiple studies conducted on the accuracy of information provided by trained SP raters and derived from SP assessments [1-3].

In general, the degree of agreement between faculty and SP scoring is 80% to 100%. However, research has shown inconsistencies in SP evaluations in Korea for 2,000, although SP score are higher than faculty scores. For example, in the study of Park et al. [4], the degree of agreement among the evaluations was 71% to 82%; the correlation among those evaluations appeared to have a 36% to 42% reliability, and the actual correlation itself was 0.60 to 0.65. The study of Kim et al. [5] regarding 14 evaluation items shows a significant difference between faculty and SP evaluations. In other studies, the correlation between faculty raters and SP raters for PPI was 0.54, which was lower than that in other regions [6,7]. Numerous researchers agree that the differences among the raters are due to a lack of explicit criteria and training experience, the rater's level of fatigue, and the number of items and rating scales [8,9].

Since 2010, however, there has not been enough exploratory research into the characteristics of these assessors or their reliability. This is the primary reason for the current study—to remedy evaluation methods, assessment skills, and training for raters. To accomplish reliable PPI evaluations, we compared faculty evaluations using the Yeungnam University Scale (YUS), analytic global rating scale (AGRS), and holistic rating scale (HRS) [10] with SP evaluation scores. In addition, research was conducted on the differences in faculty specialty and rater's experiences, as well as the rater's level of fatigue as time passes.

The research problems of this study are as follows: are there any differences in PPI scores between faculty raters and SP raters; what are the differences in PPI scores based on the faculty raters' specialty? What are the differences in PPI scores according to the raters' evaluation experience? Are the scores consistent from beginning to end during long evaluation times?

Materials and methods

1. Procedure and participants

The present study protocol was reviewed and approved an exemption of informed consent by the Institutional Review Board of Yeungnam University Hospital (IRB No: 7002016-E-2015-001).

For this study, we analyzed the PPI evaluation in the CPX that was conducted among third-year students at Yeungnam University College of Medicine in 2013. The evaluation was conducted on December 16 and 17. In total, 72 students were enrolled; there were 51 males (70.8%) and 21 females (29.2%) whose average age was 22.45 years. The group was subdivided randomly into 12 teams consisting of six members each. A total of 12 stations were set up to evaluate the CPX over 2 days; two copies of six stations were assigned each morning and afternoon.

To assess the reliability of the evaluation process, faculty raters and SP raters conducted the PPI evaluation simultaneously in each station; 48 faculty raters and 24 SP raters took part in the evaluations. Before the examination, all raters were trained for 2 hours on the general assessment process and the criteria for scoring assigned stations. We analyzed the evaluation results of eight stations, excluding four stations that did not have a complete scoring process. Consequently, we analyzed the final data based on evaluations conducted by 32 faculty and 16 SP raters. Of the 32 faculty raters, 12 evaluated stations related to their specialty while the other 20 evaluated stations out of their specialty. Nine had majored in basic medical science and 23 in clinical medicine. On average, faculty raters had participated in evaluation 5.13 times, while the average evaluation experience of SP raters was 7.44 times. Finally, the eight stations we examined included: jaundice, antenatal care, adult immunization, drinking problems, low back pain, micturition disorder, convulsion in childhood, and mastodynia/breast mass.

2. Research instruments

For this study, three rating scales were employed. The first scale, the YUS, was developed by the Daegu-Gyeungbuk regional consortium in Korea and revised by the Yeungnam University College of Medicine. The YUS consists of six items worth four points each; effective questioning, careful listening, patient-centered attitude, using words precisely, rapport building, and a good manner during physical examination. Also, the uniqueness of this rating scale is that it is similar to the global rating; however, it has been developed as a quantitative criterion to ensure evaluation objectivity. Table 1 shows an example of YUS. As a second scale, we employed four questions from AGRS developed by Hodges and

McIlroy [10]. The AGRS consists of the following four items worth five points each; response to patient's feelings and needs, degree of coherence in the interview, verbal expression, and non-verbal expression. This scale used qualitative criteria to assess the above items. Finally, the one-item HRS was employed as an additional question for the overall assessment of the knowledge and skills. Table 2 shows an example of AGRS and HRS.

3. Analysis

Regarding the 72 students' clinical performance, we compared differences in final scores using the rater's assessment expertise, rating experience, and the level of fatigue. Initially, all test items used T-score as a standard; the scores of YUS, AGRS, and HRS were compared with the average scores of the overall test items. In addition, we compared the faculty rater's scores with those of the SP raters for each of the evaluations. We also compared scores of the faculty raters who assessed stations related to their specialty with the scores of those who assessed stations out of their specialty and the differences between basic medical science and clinical medicine specialties. We proceeded with comparing score differences based on rater evaluation experience divided into three categories; less than three times, three to 10 times, and more than 10 times.

Furthermore, we examined the correlation coefficient based on the SP rater's level of fatigue. To test these group differences, the T-test and F-test were used. To verify differences based on SP rater fatigue, we compared the results of SPs who were assigned during the morning or afternoon with those who participated all day. Moreover, we looked at the correlation differences among all scales.

Table 1. An example of evaluation standards of Yeungnam University Scale

Item	Standard
1. He (or she) asked me something well and effectively	· Effective questions: open questions, confirmation questions, summary of the dialogues
	· Avoid questions: leading question, double meaning questions
	4. Excellent: asked all effective questions without any avoid questions
	3. Good: asked 2 effective questions and avoid questions
	2. Normal: asked 1 effective question or not asked any effective and avoid questions
	1. Not sufficient: not asked any effective question and asked avoid questions
2. He (or she) listened carefully	· Verbal response, listening attitude, eye contact, not take any speaking
	4. Excellent: used 4 actions very well
	3. Good: used 2 or 3 actions of all
	2. Normal: used 1 action or not used any actions and not used any opposite actions
	1. Not sufficient: used 4 opposite actions

Results

A comparison of raters' scores based on the evaluation tools for each item and the inter-rater correlation coefficient are shown in Table 3 and Fig. 1. The results show significant differences in scores between faculty and SP raters according to the evaluation tools. The scores of SP raters were significantly higher than those of the faculty raters; YUS ($t=-18.23$, $p<0.001$), AGRS ($t=-10.24$, $p<0.001$), and HRS ($t=-3.20$, $p<0.01$), respectively. Correlation coefficients between the faculty and SP raters were the following: YUS, 0.49 ($p<0.001$); AGRS, 0.34 ($p<0.01$); and HRS, 0.40 ($p<0.001$), respectively. These results indicate a significant correlation among the raters' scores based on each evaluation tool.

The results of the score differences according to the major congruence of the raters who assessed items related to their specialty and those who assessed items out of their specialty are in Table 4. There was a significant difference between the YUS ($t=-3.61$, $p<0.001$) and the AGRS ($t=-2.73$, $p<0.01$). The scores of the raters who assessed stations related to their specialty were lower than those of the raters who assessed stations out of their area of specialty. In the case of HRS, there was no significant difference.

Table 5 shows the results of score differences according to raters' evaluation experiences. In the YUS and AGRS, significant dif-

Table 2. An example of evaluation standards of analytic global rating scale and holistic rating scale

Example	Rating scale				
	1	2	3	4	5
Response to patient's feelings and needs (empathy)	Does not respond to obvious patient cues (verbal and non-verbal) and/or responds inappropriately		Responds to patient's needs and cues, but not always effectively		Responds consistently in a perceptive and genuine manner to the patient's needs and cues
Degree of coherence in the interview	No recognizable plan to the interaction; the plan does not demonstrate cohesion or the patient must determine the direction of the interview		Organizational approach is formulaic and minimally flexible and/or control of the interview is inconsistent		Superior organization, demonstrating command of cohesive devices flexibility, and consistent control of the interview

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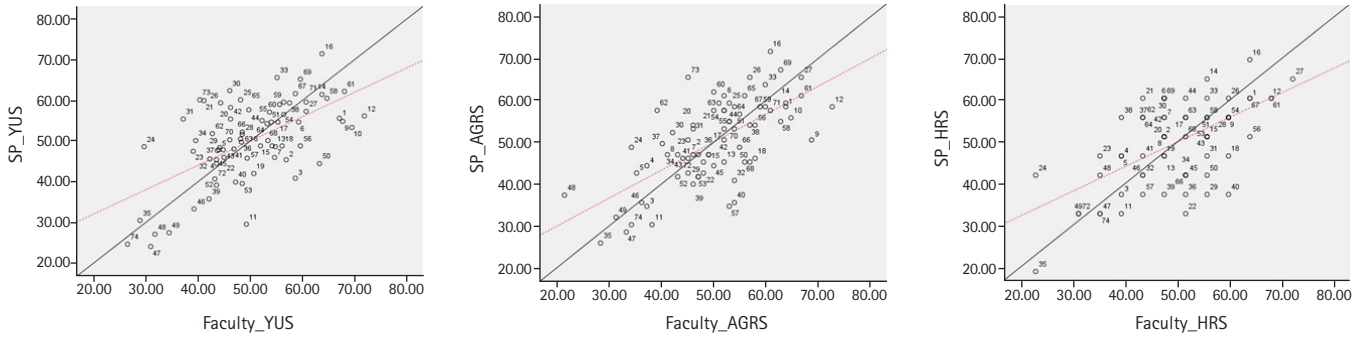

Fig. 1. X-Y scatter plot with scores of faculty and standardized patient. SP, standardized patient; YUS, Yeungnam University Scale; AGRS, analytic global rating scale; HRS, holistic rating scale.

Table 3. Comparisons of rating scales and Pearson's correlation coefficient of raters

Case	Rating scale	Rater						*t*	Pearson's correlation coefficient
		Faculty (n = 32)		SP (n = 16)		Total (n = 48)			
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
A	YUS	4	50.39 (8.41)	2	56.33 (2.53)	6	53.42 (6.82)	−5.70[c]	0.34[b]
	AGRS	4	49.81 (9.34)	2	55.49 (7.79)	6	52.71 (9.01)	−3.98[c]	−0.34[b]
	HRS	4	51.79 (10.50)	2	54.29 (9.28)	6	53.06 (9.94)	−1.51	−0.28[a]
B	YUS	4	43.98 (8.33)	2	53.20 (6.15)	6	48.63 (8.63)	−7.62[c]	0.26[a]
	AGRS	4	45.48 (5.96)	2	47.44 (12.35)	6	46.47 (9.73)	−1.23	0.12
	HRS	4	49.13 (9.45)	2	46.22 (12.90)	6	47.67 (11.37)	1.56	0.32[b]
C	YUS	4	45.34 (7.48)	2	50.24 (7.59)	6	47.85 (7.90)	−3.91[c]	0.36[b]
	AGRS	4	45.77 (7.36)	2	48.28 (10.30)	6	47.05 (9.04)	−1.70	0.27[a]
	HRS	4	45.89 (9.30)	2	46.66 (11.00)	6	46.28 (10.17)	−0.45	0.39[c]
D	YUS	4	46.32 (9.73)	2	53.61 (4.48)	6	50.50 (8.03)	−5.16[c]	−0.11
	AGRS	4	46.71 (10.35)	2	51.54 (6.47)	6	49.48 (8.65)	−3.05[b]	−0.09
	HRS	4	47.79 (10.50)	2	47.75 (7.21)	6	47.76 (8.73)	0.02	0.06
E	YUS	4	47.61 (6.58)	2	55.35 (3.96)	6	51.64 (6.61)	−8.39[c]	0.26[a]
	AGRS	4	49.48 (6.53)	2	55.19 (6.27)	6	52.46 (6.99)	−5.31[c]	0.21
	HRS	4	51.21 (9.84)	2	55.37 (7.09)	6	53.38 (8.74)	−2.87[b]	0.32[b]
F	YUS	4	45.19 (5.67)	2	54.93 (3.12)	6	50.09 (6.68)	−12.88[c]	0.35[b]
	AGRS	4	47.59 (7.27)	2	56.85 (4.78)	6	52.25 (7.68)	−9.11[c]	0.03
	HRS	4	48.03 (9.10)	2	58.43 (4.07)	6	53.26 (8.74)	−8.91[c]	0.14
G	YUS	4	41.50 (8.64)	2	49.77 (4.44)	6	45.09 (8.21)	−7.05[c]	0.23
	AGRS	4	43.21 (8.62)	2	49.73 (5.35)	6	46.04 (8.04)	−5.27[c]	0.24
	HRS	4	45.38 (10.73)	2	46.84 (7.35)	6	46.01 (9.41)	−0.92	0.45[c]
H	YUS	4	49.22 (6.31)	2	54.24 (3.56)	6	51.87 (5.62)	−5.69[c]	0.17
	AGRS	4	51.91 (5.19)	2	54.61 (3.98)	6	53.34 (4.77)	−3.42[c]	0.18
	HRS	4	53.41 (8.84)	2	51.02 (8.10)	6	52.14 (8.51)	1.67	0.06
Total	YUS	4	46.13 (8.12)	2	53.57 (5.18)	6	49.93 (7.73)	−18.23[c]	0.29[c]
	AGRS	4	47.44 (8.08)	2	52.48 (8.38)	6	50.01 (8.61)	−10.24[c]	0.14[b]
	HRS	4	49.05 (10.09)	2	50.95 (9.78)	6	50.02 (9.98)	−3.20[b]	0.20[c]

SP, standardized patients; SD, standard deviation; YUS, Yeungnam University Scale; AGRS, analytic global rating scale; HRS, holistic rating scale; A, jaundice; B, antenatal; C, adult immunization; D, drinking problem; E, low back pain; F, micturition disorder; G, convulsion in childhood; H, mastodynia, breast mass.
[a] $p<0.05$. [b] $p<0.01$. [c] $p<0.001$.

ferences based on the faculty's evaluation experience were observed. It was observed that the scores from those who had participated 3–10 times group were lower than those from the other two groups. In all scales, there were significant differences among the SP raters. However, for the SP raters, scores from those who had participated 3–10 times were higher than those from the other groups.

The reviewed correlation between three rating scales in each group of raters is shown in Table 6. In the results of the correlation between the rating scales, the following were observed; 0.66 to 0.83 in faculty ($p < 0.001$) and 0.68 to 0.82 in SP ($p < 0.001$).

To find the impact of the raters' level of fatigue on evaluation outcome, we compared the scores given by SP raters in the morning and afternoon. The results are shown in Table 7. The correlation between the YUS and AGRS and between the YUS and HRS were significantly lower in the afternoon than in the morning.

Discussion

Analyzing the differences between the evaluation results of the three assessment tools and the raters' characteristics, we have explored factors that may affect PPI scores. This study was conducted to minimize the effects of co-factors to secure fairness. Therefore, this study tried to find out the difference between evaluation results according to the characteristics of evaluators and evaluation tools and discuss the implications of each result.

The result of this study showed that there was a slight difference in PPI scores between faculty raters and SP raters. In general, when there was a significant difference, the evaluation scores of SPs were significantly higher than that of the faculty. These results were similar to previous studies due to the SP role, which was not primarily for evaluation purposes but rather for constructive educational feedback. Hence, SPs are not comfortable with giving low scores. However, faculty raters deal with subjects with which they are familiar; consequently, they can be better focused and stricter in their evaluation [11-13]. In addition, concerning the YUS, AGRS, and HRS scores, Pearson's correlation coefficient between the faculty and SP raters was 0.34 to 0.49. In the study of Kwon et al. [6], the results of the CPX concerning technical skill items-history taking, physical examination, and patient education-showed correlation coefficient from 0.69 to 0.91. In contrast, the correlation for the patient-doctor relationship was somewhat low; 0.09 to 0.51. The reasons for these results could be found in ambiguous applied standards, the level of raters' fatigue, and lack of training [6-9,14]. For additional improvement of the evaluation process, this study recommends periodic evaluation of raters and further training tasks.

The SPs involved in this study had participated in PPI evaluations using the YUS an average of 7.44 times and had at least 3 to 12 hours of training according to the training guidelines set by the consortium. However, in the training for the AGRS and HRS, the instruction portion involved less than three hours of training. Furthermore, the raters' fatigue from having to assess on all three scales could affect the evaluation outcome. In the case of faculty raters, even though they had an average of 5.13 evaluation experi-

Table 4. Comparisons of scores according to the congruence of the raters' specialty

Rating scale	Specialty		Total (n = 32)	*t*
	Congruence (n = 12)	Incongruence (n = 20)		
YUS	44.36 (5.94)	46.74 (8.68)	46.13 (8.12)	−3.61[a]
AGRS	46.00 (6.91)	47.95 (8.39)	47.44 (8.08)	−2.73[b]
HRS	48.61 (10.26)	49.20 (10.05)	49.05 (10.09)	−0.60

Values are presented as mean (standard deviation).
YUS, Yeungnam University Scale; AGRS, analytic global rating scale; HRS, holistic rating scale.
[a] $p < 0.001$. [b] $p < 0.01$.

Table 5. Comparisons of scores between evaluation experiences of faculty raters and standardized patients

Rating scale	Rater	Evaluation experience (time)						Total		F	Scheffé
		< 3		3–10		> 10					
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
YUS	Faculty	6	48.49 (7.48)	20	44.35 (7.64)	6	49.03 (8.83)	32	46.13 (8.12)	19.78[a]	3,1 > 2
	SP	3	48.57 (5.09)	7	55.57 (3.71)	6	51.89 (5.84)	16	53.57 (5.18)	39.68[a]	2 > 1,3
	Total	9	49.68 (6.81)	27	49.37 (8.33)	12	50.94 (7.09)	48	49.93 (7.73)	4.39[b]	3 > 2
AGRS	Faculty	6	51.66 (7.83)	20	46.04 (7.26)	6	50.49 (9.55)	32	47.44 (8.08)	14.11[a]	3,1 > 2
	SP	3	51.22 (6.00)	7	55.29 (6.69)	6	49.78 (9.87)	16	52.48 (8.38)	30.19[a]	2 > 1,3
	Total	9	47.29 (7.20)	29	50.18 (8.38)	10	50.01 (9.76)	48	50.01 (8.61)	0.4	
HRS	Faculty	6	49.96 (10.30)	20	48.18 (10.08)	6	50.87 (9.69)	32	49.05 (10.09)	3.25[b]	
	SP	3	49.80 (7.18)	7	53.48 (8.90)	6	49.64 (10.88)	16	50.95 (9.78)	19.25[a]	2 > 1,3
	Total	9	48.54 (9.15)	27	50.55 (9.92)	12	50.04 (10.50)	48	50.02 (9.98)	3.17[b]	2 > 1

SD, standard deviation; YUS, Yeungnam University Scale; SP, standardized patient; AGRS, analytic global rating scale; HRS, holistic rating scale.
[a] $p < 0.001$. [b] $p < 0.05$.

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Table 6. Comparisons of correlation between three rating scales in each group of raters

Pearson's correlation coefficient	Faculty (n = 32)	Standardized patient (n = 16)	Total (n = 48)
YUS-AGRS correlation	0.83[a]	0.77[a]	0.80[a]
AGRS-HRS correlation	0.75[a]	0.82[a]	0.77[a]
YUS-HRS correlation	0.66[a]	0.68[a]	0.62[a]

YUS, Yeungnam University Scale; AGRS, analytic global rating scale; HRS, holistic rating scale.
[a] $p < 0.001$.

Table 7. Comparisons of correlations between morning and afternoon in standardized patient raters

Pearson's correlation coefficient	Morning (n = 16)	Afternoon (n = 16)	Total (n = 32)	*t*
YUS-AGRS correlation	0.82 (0.08)	0.71 (0.10)	0.76 (0.11)	3.32[a]
AGRS-HRS correlation	0.80 (0.12)	0.76 (0.13)	0.78 (0.12)	0.75
YUS-HRS correlation	0.72 (0.14)	0.59 (0.10)	0.65 (0.14)	2.74[b]

Values are presented as mean (standard deviation).
YUS, Yeungnam University Scale; AGRS, analytic global rating scale; HRS, holistic rating scale.
[a] $p < 0.01$. [b] $p < 0.05$.

ences, their previous experience was limited only to evaluating technical skills; thus, they did not have proper training in conducting PPI evaluations. Since the pre-evaluation training for this study was completed in only one hour, overall training for the evaluation process was insufficient. There is another possibility that the raters' fatigue level was high because we conducted the technical skill and PPI evaluations together. The fact that the reliability among the scales evaluated in the afternoon is lower than that in the morning can be interpreted as an increase in the fatigue of the evaluator and a decrease in concentration. Therefore, it is necessary to arrange evaluators separately in the afternoon or provide sufficient rest time.

There were significant differences in the scores related to the raters' specialty and in scores between basic medical science and clinical medicine. Regarding the evaluation experience, the scores showed significant differences among each faculty and SP group. In the case of the faculty, the scores of evaluators with 3–10 evaluation experiences were significantly lower than those with less than three or more than 10 evaluation experiences. However, in the case of SPs, the evaluation scores of evaluators with 3–10 experiences were significantly higher than those with less than three or more than 10 evaluation experiences. These results are the same for all YUS, AGRS, and HRS evaluations.

According to these results, it was found that the faculty members were more thoroughly assessed if their majors matched, or if they had more than three or less than 10 evaluation experiences. However, SPs appeared to be less thorough, as they became accustomed to evaluation and became more involved when they had three to 10 evaluation experiences. To offset these differences and increase reliability, we need to strengthen the rater's competences through systematic strategies during their training and feedback. In addition, it is necessary to systematically apply a statistical method to offset the score difference between evaluators. Accordingly, in medical schools, it is necessary to train or acquire evaluation experts or analysis experts, and it is necessary to secure an evaluation system or an evaluation support team that is capable of systematic evaluation support.

Besides, in Korea, technical skills are assessed by faculty, but humanistic skills are assessed by SPs. The faculty raters tend to over-emphasize the importance of technical skills and, thus, evaluate them more strictly. However, they are inclined to be laxer and more generous when evaluating humanistic skills because they would feel awkward doing otherwise [15]. Moreover, Park et al. [7] reported lower PPI scores from SP evaluators through comparative studies on the accuracy of scoring by faculty and SPs on the CPX, confirming that there are also differences between evaluators who are simply observant or participatory. This means that it may also depend on the extent of the evaluator's subjective intervention, and therefore, accurate feedback on humanistic skills can be hindered in the process of evaluation feedback and retraining. Hence, faculty raters need to recognize the importance of humanistic skills and feedback for their results. Separate sessions of technical and humanistic skills on the CPX needs to be examined closely; both adequacy and reliability should be reviewed.

This study also tried to explore the appropriateness of the evaluation tool. Numerous previous studies on the subject report that the global rating is similar to the checklist or even superior in validity and reliability. Furthermore, to evaluate students' performance, they recommend using the checklist and the global rating scale together [11,16-18]. The checklist is primarily known for the evaluation of technical skills, including procedural performance. However, the global rating scale is known as an efficient tool to measure a student's attitudes and PPI, communication skills, and possible expertise [16,18-23]. Therefore, as far as humanistic skills are concerned, it is appropriate to employ the global rating scale for the PPI.

The worksheet has been developed as a checklist, although the PPI evaluation scales include global rating scale items at the Yeungnam University College of Medicine. This is because the checklist is superior in apparent objectivity and ease of use [24]. However, the checklist form of the worksheet may be more appropriate for the technical skills station, and the global rating form may be more appropriate for attitudes in the PPI station [25]. Generally, raters who use the checklist are inclined to give the same scores to

the students whether they performed well [26]. In this study, one of the SPs reported that there were students who were not satisfied with the overall physician-patient relationship, although she gave high scores for a lack of demerit factors according to the checklist.

In addition, students tend to memorize the checklist rather than practice technical skills in the process of preparing for the OSCE [27]. In this context, the phenomenon diminishes the value of education; specifically, it reduces the validity of assessing students' competence [12]. It is therefore imperative that we provide improved assessment tools for students so that the skills are embodied rather than a simple recitation of a memorized PPI checklist. Furthermore, it is necessary that students internalize the correct attitude in their practice. Thus, we propose a further study on how to improve evaluation tools and standards as a form of the AGRS.

In this study, SP assesses an average of six students at one station. We compared the correlations among the individual assessment scales, dividing the process into two different time periods-morning and afternoon-to find out the potential impact that raters' fatigue can have on the scores. We found a significant difference in the correlation between YUS and AGRS, and between YUS and HRS. Scores given in the afternoon session were lesser reliable than those given in the morning, which is statistically significant. Indeed, it is hard to stay focused on evaluations for a long time. The rater's fatigue, caused by the multitude of evaluation items and the number of students to evaluate, is responsible for the failure to maintain consistency [28-30]. To enhance the degree of consistency among raters, a strategy to lengthen the training period but reduce the time that raters spend on assessments could be proposed. Furthermore, specific ways could be proposed to use professional SPs more efficiently. As described above, SP evaluators received 3 to 12 hours of pre-training for CPX evaluation whereas faculty members received only one hour of pre-training. The reason for the low correlation between evaluation scores between faculty members and SP evaluators may also be because the standardized evaluator education was not conducted equally. It is suggested that systematic training is required for all evaluators to increase the reliability of evaluation scores.

This study based on one CPX assessment conducted at a school, and it is focused on the evaluation of the patient-doctor relationship rather than the clinical performance process. Due to temporal and financial limitations in the actual evaluation, two SPs participated in one clinical item evaluation, while four professors participated in the same evaluation. Therefore, the decrease in reliability for the evaluation tools of SP evaluators in the afternoon may be due to the increased fatigue.

Although the correlation was a little low, it was considered that the correlation between faculty and SP evaluators was higher when YUS was used than when AGRS or HRS were used. In the actual evaluation situation, ease of evaluation is considered as an important factor, and the evaluation tools with high validity and reliability with a few evaluation items are preferred. It is recommended to use HRS for the ease of evaluation, but it can be seen that the use of AGRS or YUS that comprises four to six items may be more appropriate to compensate for the limitations regarding single-item measurement. The most appropriate evaluation tool should be suitable in the form and number of evaluation items, and both evaluation validity and reliability must be satisfied. Therefore, it is necessary to continuously study which evaluation tools are useful for evaluating according to various evaluation situations and clinical presentations.

The limitations of this study are as follows: First, this cannot be generalized because it based on the experience of a single school. Second, it is a retrospective study, not a study designed to identify only the factors that affect PPI scores. Third, this is a separate analysis of the PPI scores only, which are parts of the station for CPX. Therefore, it did not reflect the impacts of the characteristics (e.g., difficulty level, etc.) of each station. Finally, it did not reflect the personal characteristics (e.g., beliefs, emotional state, fatigue level, etc.) of raters on the day of assessment.

In conclusion, the reliability of PPI scores on the CPX was found to be significantly affected by evaluator factors as well as the type of scale used. There is a need for a further study to establish guidelines for evaluating PPI on the CPX and to offer appropriate assessment tools, an ideal number of items, raters' qualification, and ideal length of evaluation time.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization and Validation: all authors; Project administration: KSL, YHL; Funding acquisition: YHL; Data curation and Formal analysis: KHC, YSP; Writing-original draft: YSP, KSL; Writing-review & editing: all authors.

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The relationship between disability and clinical outcomes in maintenance dialysis patients

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Background: Dialysis patients are prone to having disabilities. We aimed to evaluate the association between disability and various clinical outcomes in Korean dialysis patients.
Methods: This study consisted of 1,615 dialysis patients from 27 centers. We evaluated disability by using four questions on the activities of daily living (ADLs) concerning whether help was needed for feeding, dressing/undressing, getting in/out of bed, or taking a bath/shower. We divided the patients into three groups: no disability (Non-D, none of the four ADL domains required help; n = 1,312), mild disability (Mild-D, one ADL domain required some/full help; n = 163), or moderate to severe disability (MS-D, two or more ADL domains required some/full help; n = 140). We evaluated falls, frailty, health-related quality of life (HRQoL), mortality, and hospitalization.
Results: The numbers of participants with a fall during the last 1 year were 199 (15.2%), 42 (25.8%), and 44 (31.4%) in the Non-D, Mild-D, and MS-D groups, respectively ($p < 0.001$). The numbers of participants with frailty in the Non-D, Mild-D, and MS-D groups were 381 (29.0%), 84 (51.5%), and 93 (66.4%), respectively ($p < 0.001$). In both univariate and multivariate analyses, the physical component scale and mental component scale scores decreased as the grade of disability increased ($p < 0.001$ for both scores). Hospitalization-free survival rate at 500 days was 64.2%, 56.7%, and 51.1% in the Non-D, Mild-D, and MS-D, respectively ($p = 0.001$ for trend). Patient survival rate at 500 days was 95.3%, 89.5%, and 92.3% in the Non-D, Mild-D, and MS-D, respectively ($p = 0.005$ for trend).
Conclusion: Disability was associated with falls, frailty, HRQoL scales, and survival trends in Korean dialysis patients.

Keywords: Dialysis; Disabled persons; Quality of life; Treatment outcome

Introduction

Patients with end-stage renal disease require renal replacement therapy, which includes dialysis and kidney transplantation. Although kidney transplantation is the best option for renal replacement therapies, most patients undergo dialysis. In the United States, 124,114 patients were diagnosed with incident end-stage renal disease; among them, 87.8% underwent hemodialysis (HD) and 9.6% underwent peritoneal dialysis (PD) [1]. Dialysis patients have poor survival and clinical outcomes compared with the general population. Many researchers have tried to identify risk factors for poor prognosis in dialysis patients. However, the prognosis remains poor, and studies about new risk factors are ongoing.

According to the World Health Organization (WHO), disability can be defined as an umbrella term, which includes impairment, activity limitation, and participation restrictions [2]. Disability is associated with poor clinical outcomes in the general population, due to inaccessibility to health care services, and vulnerability to

infection. Many comorbid conditions lead to the development of disability, and end-stage renal disease is associated with many comorbid conditions such as diabetes mellitus (DM), hypertension, and uremia. Therefore, dialysis patients are prone to having disabilities. Jassal et al. [3] analyzed dialysis outcomes and practice patterns in a cohort of 7,226 patients from 12 countries, and showed that disability is associated with low health-related quality of life (HRQoL) and poor survival. Additionally, Yazawa et al. [4] used a Japanese national registry of 7,664 HD patients, and showed an association between disability and mortality. However, previous studies have included limited ethnicities and only focused on survival or HRQoL. Regional and national differences must be considered. Hence, we aimed to evaluate the association between disability and various clinical outcomes in Korean dialysis patients.

Materials and methods

This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2016-06-022). Informed consent was obtained from all individual participants included in the study.

1. Study population

We used data from a previous study [5]. Briefly, a total of 2,737 study participants underwent maintenance dialysis and were enrolled from 27 dialysis centers between July and December 2012. Patients were excluded for the following reasons: age < 20 years (n = 12), dialysis vintage < 6 months (n = 164), a history of hospitalization in the prior 3 months for any other than an HD vascular access (n = 351), inability to walk with or without an assistive device (n = 79), inability to communicate with the interviewer (n = 149), refusal to provide informed consent (n = 254), or insufficient data (n = 113). Finally, a total of 1,615 patients were recruited into our study (Fig. 1; 1,249 and 366 patients underwent HD and PD, respectively). The participants were recruited between July and December 2012; the follow-up ended in March 2014. During the follow-up period, transfer to other hospitals, change of dialysis modality, kidney transplantation, or follow-up loss was considered as censored data.

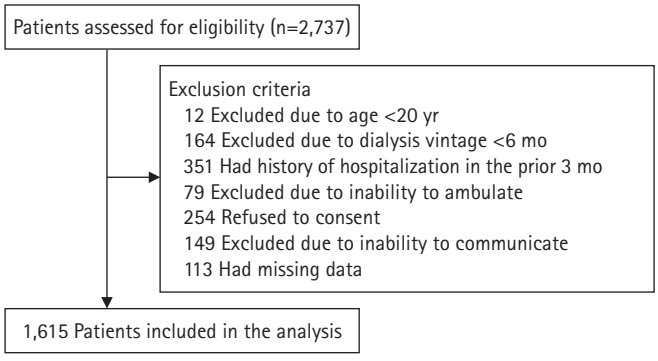

Fig. 1. Study flow chart.

2. Study variables

In our study, all variables except patient survival and hospitalization rates were defined using findings at the enrollment. Our study examined age, sex, body mass index (BMI, kg/m^2), DM, coronary artery disease (CAD), cerebrovascular disease (CVD), dialysis vintage, and education level, as well as hemoglobin (mg/dL), serum albumin (g/dL), blood urea nitrogen (BUN, mg/dL), creatinine (mg/dL), calcium (mg/dL), phosphorus (mg/dL), total cholesterol (mg/dL), high-sensitivity C-reactive protein (hs-CRP, mg/dL), and intact-parathyroid hormone (i-PTH, pg/mL) levels. DM was defined as a self-reported history and medical record of its diagnosis, or a fasting glucose level of ≥ 126 mg/dL. CAD was defined as a self-reported history and medical record of angina, myocardial infarction, or congestive heart failure. CVD was defined as a self-reported history and medical record of stroke.

3. Assessment of disability and clinical outcomes

We evaluated disability by using four questions on activities of daily living (ADLs) concerning whether help was needed for feeding, dressing/undressing, getting in/out of bed, or taking a bath/shower [6]. Each question required one of three responses: no help, some help, or full help. We divided the patients into three groups: Non-D, (non-disabled, none of the four ADL domains required help), Mild-D (mildly disabled, one ADL domain required some or full help), or MS-D (moderate to severely disabled, two or more ADL domains required some or full help).

All data on mortality and hospitalization rates were retrieved from medical records up to March 2014 (mean follow-up duration, 484 ± 113 days). If a patient with HD was admitted for a vascular access-related problem, the hospitalization was not considered as a significant one. We evaluated exhaustion using the vitality (VT) component in HRQoL scales, which consist of four questions: "Did you feel full of pep?", "Did you have a lot of energy?", "Did you feel worn out?", and "Did you feel tired?" Exhaustion was defined as mean vital score < 5 on four questions [5]. We defined a fall as an event that resulted in a participant coming to rest unintentionally on the ground or a lower level with or without losing consciousness during the last 1 year. Serious falls were defined as head injury requiring hospitalization, joint dislocations, severe sprains, or a laceration requiring sutures [7]. We identified numbers of participants with fall history and total numbers of falls and/or numbers of serious falls.

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Exercise was classified using the WHO definition [8]. Physical activity was defined as the presence of regular exercise during leisure time for the past 3 months. Exercise was defined as engaging in moderate activity for > 30 minutes/day for 5 days a week or at a high intensity for > 20 minutes/day for 3 days a week. Frailty was defined using modified criteria from the study by Johansen et al. [9]. Johansen's criteria include four components (slowness/weakness, 2 points for physical functioning scale < 75; poor endurance/exhaustion, 1 point for VT scale < 55; physical inactivity, 1 point for physically active < 1 day/week during their leisure time for the past 3 months; and unintentional weight loss, 1 point for unintentional body weight loss > 4.5 kg or 5% of baseline value over the past year). A summed score ≥ 3 is defined as frailty.

4. Health-related quality of life assessment

The Kidney Disease Quality of Life-Short Form (KDQOL-SF) Korean version 1.3 was used to evaluate HRQoL [10]. This questionnaire includes the 36-Item Short Form Health Survey (SF-36) with eight domains (physical functioning, role limitations due to physical health problems, body pain, general health, VT, social functioning, role limitations due to emotional problems, and mental health) and an overall health rating. It also includes a kidney disease-specific scale with 11 items (symptom/problems [SP], effects of kidney disease [EKD], burden of kidney disease [BKD], work status [WS], cognitive function [CF], quality of social interaction [QSI], sexual function [SeF], sleep, social support [SS], patient satisfaction [PS], and dialysis staff encouragement [DSE]). Each domain was scored from 0 to 100. The physical component scale (PCS) and mental component scale (MCS) scores were also calculated from the SF-36 scale [11].

5. Statistical analyses

IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) was used for analyses. Our data were expressed as the mean ± standard deviation (SD) or standard error (SE) for continuous data and as numbers (percentage) for categorical data. Pearson chi-square test was used to analyze categorical data. One-way analysis of variance, followed by a *post-hoc* Tukey comparison, was used to analyze continuous data. The Kaplan-Meier log-rank test and Cox regression analysis were used to compare survival estimates. Multivariate methodology was used for the analysis of covariance or Cox regression analysis. The covariates included age, sex, BMI, DM, CAD, CVD, dialysis vintage, dialysis modality, education level, and levels of hemoglobin, serum albumin, BUN, serum creatinine, calcium, phosphorus, i-PTH, total cholesterol, and hs-CRP. Logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), which were then used to determine the correlation between falls and the groups. The level of statistical significance was set at $p < 0.05$.

Results

1. Clinical characteristics

The numbers of participants in the Non-D, Mild-D, and MS-D groups were 1,312, 163, and 140, respectively (Table 1), and the prevalence of disability was 18.8% in our cohort. Patients in the MS-D group were the oldest among those in the three groups. The proportion of those with comorbidities (DM, CAD, and CVD) increased as the grade of disability increased. The Non-D group had the highest proportion of those on HD. Serum albumin, creatinine, and phosphorus levels in the MS-D group were lower than those in the Non-D group. The mean follow-up duration was 484 ± 113 days. The trend showed lesser follow-up duration in the Mild-D group than in the other groups ($p = 0.046$ for trends; $p = 0.037$ for Non-D vs. Mild-D; $p = 0.998$ for Non-D vs. MS-D; $p = 0.161$ for Mild-D vs. MS-D).

2. Evaluation of falls, frailty, and exhaustion according to disability

The numbers of participants who had a fall during the past 1 year were 199 (15.2%), 42 (25.8%), and 44 (31.4%) in the Non-D, Mild-D, and MS-D groups, respectively ($p < 0.001$). In addition, the numbers of participants who had a serious fall during the past 1 year were 35 (2.7%), 5 (3.1%), and 6 (4.3%) in the Non-D, Mild-D, and MS-D groups, respectively ($p < 0.001$). The total numbers of falls during the past 1 year were 0.30 ± 1.51, 0.42 ± 0.84, and 0.57 ± 1.01 in the Non-D, Mild-D, and MS-D groups, respectively ($p = 0.075$).

Univariate logistic regression analysis showed that the ORs of falls in the Mild-D and MS-D groups were 1.94 (95% CI, 1.33–2.85; $p = 0.001$) and 2.62 (95% CI, 2.62–3.85; $p < 0.001$), respectively, relative to the Non-D group. The OR of falls in the MS-D group was 1.35 (95% CI, 0.82–2.22; $p = 0.238$), relative to the Mild-D group. Multivariate logistic regression analysis showed that the ORs of falls in the Mild-D and MS-D groups were 1.62 (95% CI, 0.97–2.70; $p = 0.066$) and 2.03 (95% CI, 1.18–3.49; $p = 0.011$), respectively, relative to the Non-D group. The OR of falls in the MS-D group was 1.38 (95% CI, 0.68–2.81; $p = 0.369$), relative to the Mild-D group.

The numbers of participants with frailty in the Non-D, Mild-D, and MS-D groups were 381 (29.0%), 84 (51.5%), and 93 (66.4%), respectively ($p < 0.001$). Additionally, the numbers of participants with exhaustion in the Non-D, Mild-D, and MS-D groups were 844 (64.3%), 112 (68.7%), and 114 (81.4%), respectively

Table 1. Clinical characteristics

Characteristic	Non-D (n = 1,312)	Mild-D (n = 163)	MS-D (n = 140)	*p*-value[a]
Age (yr)	55.0 ± 12.7	57.9 ± 13.5	61.1 ± 13.1[b),c)]	< 0.001
Male sex	736 (56.1)	92 (56.4)	75 (53.2)	0.795
Body mass index (kg/m^2)	22.4 ± 3.2	22.3 ± 3.1	22.4 ± 3.4	0.967
Diabetes mellitus	496 (37.8)	66 (40.5)	77 (54.6)	0.001
Coronary artery disease	193 (14.7)	25 (15.3)	36 (25.5)	0.004
Cerebrovascular disease	103 (7.9)	19 (11.7)	22 (15.6)	0.004
Dialysis vintage (yr)	5.1 ± 4.4	5.4 ± 4.5	5.0 ± 4.9	0.729
Education level				0.579
≤ 6th grade	278 (21.2)	41 (25.2)	34 (24.3)	
7th–12th grade	259 (19.7)	35 (21.5)	26 (18.6)	
> 12th grade	775 (59.1)	87 (53.4)	80 (57.1)	
Hemoglobin (mg/dL)	10.5 ± 0.9	10.4 ± 0.9	10.4 ± 1.1	0.546
Serum albumin (mg/dL)	3.9 ± 0.4	3.8 ± 0.4	3.8 ± 0.4[b)]	< 0.001
BUN (mg/dL)	60.6 ± 15.0	57.6 ± 15.6	57.5 ± 14.1	0.007
Creatinine (mg/dL)	10.6 ± 3.0	10.1 ± 2.9	9.6 ± 3.0[b)]	< 0.001
Calcium (mg/dL)	8.72 ± 0.83	8.64 ± 0.76	8.58 ± 0.84	0.085
Phosphorus (mg/dL)	5.37 ± 1.36	5.06 ± 1.35	4.79 ± 1.18[b),c)]	< 0.001
Total cholesterol (mg/dL)	153.5 ± 36.7	156.1 ± 38.6	156.2 ± 40.9	0.551
i-PTH (pg/mL)	283.8 ± 345.1	277.5 ± 378.2	216.8 ± 254.9	0.087
hs-CRP (mg/dL)	0.68 ± 1.63	0.76 ± 1.93	0.62 ± 1.29	0.837
Dialysis modality (HD)	1,053 (80.3)	103 (63.2)	94 (66.7)	< 0.001
Follow-up (day)	487 ± 114	463 ± 125[b)]	487 ± 82[c)]	0.046

Values are presented as mean±standard deviation for continuous variables and number (%) for categorical variables.
Non-D, non-disabled group; Mild-D, mildly disabled group; MS-D, moderate to severely disabled group; BUN, blood urea nitrogen; i-PTH, intact-parathyroid hormone; hs-CRP, high-sensitivity C-reactive protein; HD, hemodialysis.
[a)] *p*-values were tested by using one-way analysis of variance, followed by a *post-hoc* Tukey comparison, for continuous variables, and Pearson chi-square test for categorical variables. [b)] $p < 0.05$ vs. the Non-D group. [c)] $p < 0.05$ vs. the Mild-D group. There was no significant difference in variables between groups without superscripts, such as [b)] or [c)].

($p < 0.001$). The numbers of participants who performed exercise in the Non-D, Mild-D, and MS-D groups were 313 (23.9%), 30 (18.4%), and 20 (14.3%), respectively ($p = 0.023$).

3. Evaluation of health-related quality of life scales, hospitalization, and survival according to disability

Table 2 shows differences in the HRQoL scales according to disability. On both univariate and multivariate analyses, the PCS and MCS scores decreased as the grade of disability increased. Among kidney disease-specific scales, SP, EKD, BKD, WS, CF, QSI, sleep, and PS were associated with the grade of disability on both univariate and multivariate analyses.

Kaplan-Meier analysis showed that those in the Mild-D and MS-D groups had poor first-hospitalization-free survival compared with those in the Non-D group (Fig. 2A). The Non-D group had better patient survival compared with the Mild-D group, but there were no significant differences in survival between the Non-D and MS-D groups or the Mild-D and MS-D groups (Fig. 2B). The total numbers of deaths during follow-up in the Non-D, Mild-D, and MS-D groups were 59 (4.5%), 16 (9.8%), and 11 (7.9%), respectively ($p = 0.007$), which was lower in the Non-D group than in the other groups. The most common cause of deaths in the Non-D and Mild-D groups was CAD (15 [25.4%] in Non-D group and 4 [25.0%] in Mild-D group), which that in the MS-D group was infection (5 [45.5%]). Multivariate Cox regression analysis showed that the Mild-D group had a higher hazard ratio relative to the Non-D group (Table 3). Although statistical significance was not observed, the MS-D group also had a higher hazard ratio relative to the Non-D group. Trends for first-hospitalization-free survival rate were similar to those for patient survival.

Discussion

The proportion of participants with falls, frailty, and exhaustion increased as the grade of disability increased. Participants with disabilities had low physical activity. Both univariate and multivariate analyses showed an inverse association between the grade of disability and the PCS or MCS. In addition, SP, EKD, BKD, WS, CF,

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Table 2. Comparison of quality-of-life scales according to disability

Scale	Univariate (mean ± SD)				Multivariate (mean ± SE)			
	Non-D	Mild-D	MS-D	*p*-value	Non-D	Mild-D	MS-D	*p*-value
SF-36 scale								
PF	78.4 ± 20.0	62.2 ± 26.3[a]	49.2 ± 31.9[a,b]	< 0.001	76.6 ± 0.8	64.4 ± 1.8[a]	51.4 ± 2.1[a,b]	< 0.001
RP	69.5 ± 39.6	49.3 ± 41.8[a]	38.7 ± 43.9[a,b]	< 0.001	69.9 ± 1.5	55.4 ± 3.7[a]	35.4 ± 4.2[a,b]	< 0.001
BP	80.1 ± 24.1	70.5 ± 27.3[a]	61.4 ± 28.2[a,b]	< 0.001	79.8 ± 0.9	74.2 ± 2.3[a]	59.7 ± 2.6[a,b]	< 0.001
GH	46.0 ± 22.3	39.2 ± 21.9[a]	35.1 ± 21.9[a]	< 0.001	46.0 ± 0.9	40.8 ± 2.1[a]	33.3 ± 2.4[a]	< 0.001
VT	46.5 ± 20.8	39.4 ± 20.6[a]	34.6 ± 22.2[a,b]	< 0.001	46.6 ± 0.8	41.6 ± 2.0[a]	34.7 ± 2.2[a]	< 0.001
SF	78.1 ± 26.7	66.6 ± 27.8[a]	60.9 ± 31.6[a]	< 0.001	77.9 ± 1.1	67.8 ± 2.6[a]	59.6 ± 3.0[a]	< 0.001
RE	75.1 ± 39.6	55.3 ± 44.6[a]	49.2 ± 45.9[a]	< 0.001	76.6 ± 1.6	63.2 ± 3.8[a]	41.9 ± 4.3[a,b]	< 0.001
MH	60.8 ± 19.7	52.7 ± 20.0[a]	48.3 ± 22.7[a]	< 0.001	62.0 ± 0.8	55.0 ± 1.9[a]	46.7 ± 2.2[a,b]	< 0.001
OHR	39.0 ± 25.4	33.7 ± 28.9	27.8 ± 25.7[a,b]	< 0.001	37.4 ± 1.0	34.9 ± 2.4	27.4 ± 2.7[a,b]	0.003
PCS	64.1 ± 18.9	52.1 ± 21.1[a]	43.8 ± 23.2[a,b]	< 0.001	63.8 ± 0.7	55.3 ± 1.8[a]	42.9 ± 2.0[a,b]	< 0.001
MCS	61.3 ± 19.5	50.7 ± 20.3[a]	45.6 ± 22.5[a,b]	< 0.001	61.8 ± 0.8	53.7 ± 1.8[a]	43.2 ± 2.1[a,b]	< 0.001
KD-specific scale								
SP	81.9 ± 13.5	74.5 ± 17.1[a]	70.6 ± 18.9[a,b]	< 0.001	82.4 ± 0.6	77.3 ± 1.3[a]	69.3 ± 1.5[a,b]	< 0.001
EKD	75.2 ± 17.9	66.3 ± 20.8[a]	60.6 ± 22.3[a,b]	< 0.001	76.6 ± 0.7	67.6 ± 1.7[a]	57.6 ± 1.9[a,b]	< 0.001
BKD	36.8 ± 26.2	27.4 ± 25.3[a]	27.7 ± 26.6[a]	< 0.001	37.2 ± 1.0	27.3 ± 2.4[a]	25.2 ± 2.8[a]	< 0.001
WS	29.9 ± 37.1	21.2 ± 32.3[a]	16.7 ± 29.1[a]	< 0.001	29.3 ± 1.3	21.3 ± 3.3[a]	23.9 ± 3.8	0.049
CF	88.1 ± 15.2	80.3 ± 20.9[a]	73.2 ± 24.3[a,b]	< 0.001	88.9 ± 0.6	82.7 ± 1.5[a]	70.7 ± 1.8[a,b]	< 0.001
QSI	77.5 ± 20.6	69.2 ± 21.9[a]	62.7 ± 26.3[a,b]	< 0.001	77.0 ± 0.8	69.8 ± 2.0[a]	58.6 ± 2.3[a,b]	< 0.001
SeF	78.1 ± 25.9	69.3 ± 29.9	77.2 ± 24.0	0.230	77.7 ± 2.2	69.0 ± 6.1	88.5 ± 8.3	0.155
Sleep	65.6 ± 21.0	57.4 ± 21.6[a]	56.7 ± 21.0[a]	< 0.001	66.7 ± 0.8	56.8 ± 1.9[a]	55.6 ± 2.2[a]	< 0.001
SS	68.9 ± 26.9	59.2 ± 27.2[a]	66.7 ± 26.3[b]	< 0.001	67.6 ± 1.1	61.5 ± 2.6	65.5 ± 2.9	0.084
PS	66.6 ± 22.7	61.7 ± 24.4	63.1 ± 21.5	0.013	66.5 ± 0.9	60.3 ± 2.1	63.2 ± 2.4	0.019
DSE	86.2 ± 18.1	84.7 ± 20.5	87.9 ± 18.5	0.310	88.3 ± 0.7	85.6 ± 1.6	86.6 ± 1.8	0.260

p-values were determined by using Student's t-test for univariate analysis and analysis of covariance for multivariate analysis. The multivariate analysis was adjusted for age, sex, body mass index, dialysis modality, diabetes mellitus, cerebrovascular disease, coronary artery disease, dialysis vintage, education level, levels of hemoglobin, serum albumin, blood urea nitrogen, serum creatinine, calcium, phosphorus, total cholesterol, intact-parathyroid hormone, and high-sensitivity C-reactive protein.

SD, standard deviation; SE, standard error; Non-D, non-disabled group; Mild-D, mildly disabled group; MS-D, moderate to severely disabled group; SF-36, 36-Item Short Form Health Survey; PF, physical functioning; RP, role limitations due to physical health problems; BP, body pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; OHR, overall health rating; PCS, physical component scale; MCS, mental component scale; KD, kidney disease; SP, symptom/problems; EKD, effects of kidney disease; BKD, burden of kidney disease; WS, work status; CF, cognitive function; QSI, quality of social interaction; SeF, sexual function; SS, social support; PS, patient satisfaction; DSE, dialysis staff encouragement.

[a] $p < 0.05$ vs. the Non-D group. [b] $p < 0.05$ vs. the Mild-D group. There was no significant difference in variables between groups without superscripts, such as [a] or [b].

QSI, sleep, and PS were associated with the grade of disability in both univariate and multivariate analyses. Although the statistical significance was weak, the trend was favorable for the first-hospitalization-free and patient survival rates in the Non-D group. However, there were no significant differences in these rates between the Mild-D and MS-D groups.

Disability was defined as an umbrella term for impairments, activity limitations, and participation restrictions [2]. Social, medical, or psychological problems lead to functional or intellectual disability, which is associated with inaccessibility to health care services or vulnerability to diseases such as sore or urinary tract infection. Disability can be diagnosed using a medical, functional, or social model, with the functional model (using ADL) being the most commonly used one [12]. Katz et al. [13] first published a model using 6 ADLs (bathing, dressing, toileting, transfer, continence, or feeding). Modified scales using 4 or 5 ADLs were introduced after the original version [6,14,15]. We evaluated disability using a model with 4 ADLs [6].

Dialysis patients are at a high risk of falls and these are associated with adverse outcomes. In addition, previous studies have shown an association between frailty/exhaustion and cardiovascular disease or mortality, in dialysis and nondialysis populations [16,17]. Therefore, we aimed to identify the association between disability and these variables. First, we analyzed cross-sectional data at en-

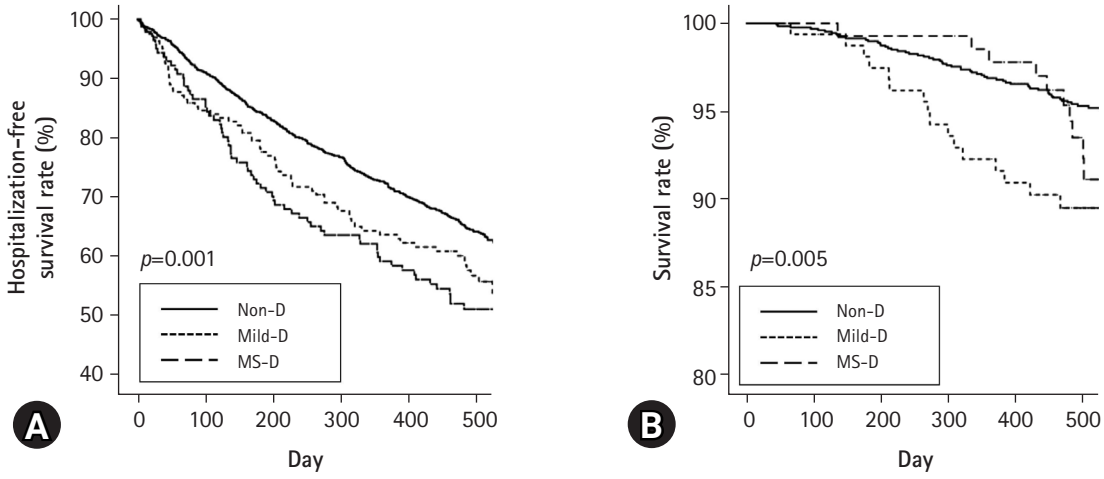

Fig. 2. Kaplan-Meier curves of hospitalization-free survival and patient survival. (A) Hospitalization-free survival rate at 500 days (Non-D, 64.2%; Mild-D, 56.7%; MS-D, 51.1%; $p=0.001$ for trends, $p=0.023$ for Non-D vs. Mild-D, $p=0.001$ for Non-D vs. MS-D, and $p=0.445$ for Mild-D vs. MS-D). (B) Patient survival rate at 500 days (Non-D, 95.3%; Mild-D, 89.5%; MS-D, 92.3%; $p=0.005$ for trends, $p=0.003$ for Non-D vs. Mild-D, $p=0.088$ for Non-D vs. MS-D, and $p=0.434$ for Mild-D vs. MS-D). Non-D, non-disabled group; Mild-D, mildly disabled group; MS-D, moderate to severely disabled group.

Table 3. Cox regression analyses according to disability

Variable	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Patient survival				
Non-D (ref)	-	-	-	-
Mild-D	2.32 (1.34–4.03)	0.003	2.15 (1.08–4.30)	0.030
MS-D	1.73 (0.91–3.29)	0.095	1.26 (0.55–2.87)	0.583
Mild-D (ref)	-	-	-	-
MS-D	0.74 (0.34–1.59)	0.436	0.58 (0.21–1.56)	0.277
First HFS				
Non-D (ref)	-	-	-	-
Mild-D	1.34 (1.04–1.72)	0.025	1.33 (0.98–1.81)	0.064
MS-D	1.52 (1.18–1.97)	0.001	1.23 (0.89–1.71)	0.210
Mild-D (ref)	-	-	-	-
MS-D	1.14 (0.81–1.60)	0.445	0.80 (0.52–1.23)	0.303

Multivariate analysis was adjusted for age, sex, body mass index, dialysis modality, diabetes mellitus, cerebrovascular disease, coronary artery disease, dialysis vintage, education level, and levels of hemoglobin, serum albumin, blood urea nitrogen, serum creatinine, calcium, phosphorus, total cholesterol, intact-parathyroid hormone, and high-sensitivity C-reactive protein.
CI, confidence interval; Non-D, non-disabled group; Mild-D, mildly disabled group; MS-D, moderate to severely disabled group; ref, reference; HFS, hospitalization-free survival.

rollment and found that the presence of disability was associated with falls. Although a causal relationship between the two variables was not clear, we suggested that patients with disabilities would be at risk of falls and those who have had falls would be prone to having disabilities. Second, our study showed an association between disability and frailty/exhaustion. Frailty is defined as a medical syndrome with multiple etiologies that is associated with decreased strength, endurance, and physical function [17]. Sense of exhaustion is defined as a combination of fatigue, lack of energy, feelings of hopelessness, loss of libido, or increased irritability [16]. In our study, frailty was evaluated based on physical function/performance, VT, and unintentional weight loss. Exhaustion was evaluated using VT component in HRQoL scales. Therefore, frailty focused on physical function and exhaustion focused on subjective sense. Although the two variables closely overlap or correlate, they are different. Our study showed that disability was associated with these two variables (frailty and exhaustion).

Disability was associated with falls, frailty, and exhaustion, all of

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which can in turn lead to disability; exercise or rehabilitation may be helpful to prevent or decrease these vicious cycles. El-Khoury et al. [18] performed a meta-analysis for the effect of the exercise program on fall-induced injuries in an elderly population and showed that exercise results in a decrease in all injurious falls. Desai et al. [19] evaluated the favorable effect of pedaling exercise on a 6-minute walking test and handgrip and pinch strengths in HD patients. A Korean study evaluated the positive effect of intradialytic exercise on daily physical activity, and it was found to improve physical activity [20]. Additionally, Lorenz et al. [21] showed a favorable result of a protocolized exercise program in kidney transplant candidates with advanced chronic kidney disease. However, our results showed that exercise decreased as the grade of disability increased. Education and encouragement of active exercise or rehabilitation would lead to improvement and prevention of adverse outcomes in participants with disabilities or those prone to having disabilities.

We evaluated the effect of disability on HRQoL scales in dialysis patients. Jassal et al. [3] investigated the association between disability scores and HRQoL. However, they evaluated HRQoL using SF-36 alone and only focused on the PCS and MCS among data for the SF-36 scales. In addition, they performed multivariate analyses adjusted by age and country alone. We evaluated HRQoL using the KDQOL-SF and examined the scores for each of the 22 components, including the PCS and MCS. Various covariates were adjusted in our study. Our results showed that all 11 scores in SF-36 including the PCS and MCS were associated with disability, which is consistent with previous study findings. Among kidney disease-specific scales, SP, EKD, BKD, WS, CF, QSI, and sleep were associated with disability. However, SeF, SS, PS, and DSE were not associated with disability; among these, SS, PS, and DSE would be more influenced by social factors such as quality of health care or medical insurance than by medical or functional status in each participant.

A prospective study showed the positive association between the presence of disability and mortality in dialysis patients [22]. A multicenter study using the Dialysis Outcomes and Practice Pattern Study cohort enrolled 7,226 HD patients and showed that mortality increased and HRQoL decreased as functional dependency increased [3]. A Japanese study divided the 7,664 HD patients into three groups according to the severity of disability, and a positive association between the grade of disability and early death or all-cause death was observed [4]. In addition, previous studies showed that multi-domain interventions including nutritional, physical, or cognitive treatment were effective in improving physical or emotional function in the elderly population [23,24].

Our results were similar to those from previous studies. This study showed that the Mild-D group had poor patient survival compared with the Non-D group. The MS-D group had poor patient survival compared with the Non-D group, but there was no statistical significance. Additionally, there was no significant difference in patient survival rates between the Mild-D and MS-D groups. The first hospitalization-free survival trend was similar to that of patient survival. The Mild-D group had the poorest survival, possibly because of two factors. First, the use of a subjective method using questionnaires and the lack of consensus for the assessment of the severity of disability are associated with a nonlinear trend between the severity of disability and prognosis. This study did not show poor prognosis in the MS-D group compared to the Mild-D group, and this may be caused by the two aforementioned factors. The presence of disability is associated with high morbidity and mortality. Some studies have shown the association between the severity of disability and prognosis, but there were differences in the methods defining disability and cut-off value for severity [25,26]. In addition, Son et al. [25] showed that the presence of disability was associated with poor prognosis, but prognosis did not differ between mild and severe disability. In our study, disability was defined using questionnaires for ADL, which is a highly subjective method. The patients in the MS-D group had significantly lower scores for body pain, MCS, SP, and QSI than those in the Mild-D group. These revealed that the severity of disability can lead to low HRQoL scores, but measuring the severity of disability using a subjective method can be influenced by low HRQoL scores. Second, the short-term follow-up duration and high patient survival rates in our study may not achieve statistical significance. In addition, the numbers of deaths by CAD, infection, or others, respectively, were 15, 13, and 31 in the Non-D group, four, three, and nine in the Mild-D group, and none, five, and six in the MS-D group. The absolute number of deaths was different among the three groups, but there was no statistically significant difference in the distribution of the cause of death among them ($p = 0.271$). Further investigations, using a method combined with objective indicators such as handgrip strength or gait speed and data with greater number of deaths during long-term follow-up, would be helpful to identify the difference in prognosis and cause of death according to the severity of disability.

Our study included both HD and PD patients and showed that the number of HD patients decreased as the grade of disability increased. Differences in disability and HRQoL according to modality are additional important issues. There were conflicting results regarding the association between disability/HRQoL and dialysis modality. Although our study did not include these data, a previous study using this cohort evaluated the impact of disability by dialysis modality [27]. The study showed that disability was more

common in PD patients; additionally, MCS and PCS were higher in HD patients than in PD patients.

Malnutrition is associated with a loss of muscle mass, which can lead to disability. Serum albumin and creatinine are well-known indicators of nutritional or muscle mass status, and serum phosphorus is highly associated with protein intake. Therefore, malnourished patients with low serum albumin, creatinine, or phosphorus levels are prone to the development of disability. In our study, the Non-D group had trend for higher serum albumin, creatinine, and phosphorus than the other groups. The trend in these variables would be an extension of the high prevalence of malnutrition in patients with disabilities.

This study has a few limitations. First, our study design was retrospective, and we used a data set from a previous study [5]. Second, we did not evaluate disability by using questionnaires with traditional measurements, such as those used by Katz et al. [15]. Questionnaires for five ADLs are most commonly used to define disability [28]. However, our study evaluated disability using four items (meal, dress/undress, get in or out of bed, and take a bath or shower) among the five to six traditional items. Validity of the use of four items has not been evaluated. However, due to limited effort and time commitments, two similar questions such as those for toileting or bathing can be combined into one question. Third, our study did not include data on dialysis adequacy. Fourth, there was a large difference in the numbers among the groups. The numbers in the Non-D group were greater than those in the other groups. The difference in numbers among the groups is common in studies using diseases with low prevalence and this is associated with selection bias. Studies for two groups may be overcome using statistical methods, such as propensity score matching. However, there was little evidence for propensity score matching methods in studies of three or more groups. Future prospective studies with long-term follow-up and additional parameters such as dialysis adequacy are needed to overcome these limitations.

In conclusion, disability was associated with poorer outcomes, which include falls, frailty, and exhaustion in Korean dialysis patients. Most HRQoL scales and survival trends were poorer in participants with disabilities than those without a disability.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization and Funding acquisition: SHK; Data acquisition, SHK, JYD, JCK; Formal analysis and Data interpretation: SHK, JCK; Writing-original draft: SHK, JCK; Writing-review & editing: all authors.

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Analysis of the risk factors of acute kidney injury after total hip or knee replacement surgery

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Background: Postoperative acute kidney injury (AKI), which increases the risk of postoperative morbidity and mortality, poses a major concern to surgeons. We conducted this study to analyze the risk factors associated with the occurrence of AKI after orthopedic surgery.
Methods: This was a retrospective study that included 351 patients who underwent total hip or knee replacement surgery at Inje University Haeundae Paik Hospital between January 2012 and December 2016.
Results: AKI occurred in 13 (3.7%) of the 351 patients. The patients' preoperative estimated glomerular filtration rate (eGFR) was 66.66±34.02 mL/min/1.73 m^2 in the AKI group and 78.07±21.23 mL/min/1.73 m^2 in the non-AKI group. The hemoglobin levels were 11.21±1.65 g/dL in the AKI group and 12.39±1.52 g/dL in the non-AKI group. Hemoglobin level was related to increased risk of AKI (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.02–0.68; p=0.016). Administration of crystalloid or colloid fluid alone and the perioperative amount of fluid did not show any significant relationship with AKI. Further analysis of the changes in eGFR was performed using a cutoff value of 7.54. The changes in eGFR were significantly related to decreased risk of AKI (OR, 0.74; 95% CI, 0.61–0.89; p=0.002).
Conclusion: Renal function should be monitored closely after orthopedic surgery if patients have chronic kidney disease and low hemoglobin level. Predicting the likelihood of AKI occurrence, early treatment of high-risk patients, and monitoring perioperative laboratory test results, including eGFR, will help improve patient prognosis.

Keywords: Acute kidney injury; Orthopedic procedures; Postoperative complications; Risk factors

Introduction

Postoperative acute kidney injury (AKI), which increases the risk of postoperative morbidity and mortality, poses a major concern to surgeons [1,2]. Previous studies reported a 9.1% risk of AKI after elective or emergency orthopedic surgical procedures [3,4]. According to a study conducted in patients who underwent any type of inpatient operative procedure in the United States, hospital mortality showed a high correlation with postoperative AKI. In patients with AKI, the lengths of stays in the intensive care unit (6 days vs. 2 days) and hospital (12 days vs. 5 days) were longer and the risk-adjusted average cost of care was higher than those in patients without AKI (US dollar [USD] 42,600 vs. USD 26,700) [5].

Several perioperative risk factors are associated with the development of AKI. The major perioperative risk factors include underlying chronic kidney disease (CKD), diabetes, and congestive heart failure during cardiac surgery [6]. However, little is known about the occurrence of postoperative AKI after orthopedic surgery. Patients undergoing orthopedic surgery are expected to have

a high probability of renal dysfunction because of comorbidities, potential high volume of blood loss, and development of perioperative infection. Recently, the number of orthopedic surgeries being performed has been increasing [7] along with the aging of the Korean population [8], which leads to a high number of high-risk Korean patients. Thus, we conducted this study to analyze the risk factors associated with the occurrence of AKI after orthopedic surgery to provide ample information that will aid the effective management of patients, such as elderly patients who have undergone orthopedic surgery.

Materials and methods

1. Patients

This study was approved by the Institutional Review Board (IRB) of the Inje University Haeundae Paik Hospital (IRB No: 2020-08-018). Written informed consent was obtained from the study subjects. This retrospective study included 351 patients who underwent total hip or knee replacement surgery in Inje University Haeundae Paik Hospital between January 2012 and December 2016. Age, sex, preoperative glomerular filtration rate (GFR), postoperative GFR, drugs used (nonsteroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors, and statins), number of prescribed drugs (total number of drugs prescribed and taken at the hospital before surgery), albumin level (g/dL), hemoglobin level (g/dL), pro-B-type natriuretic peptide level (pg/mL), ejection fraction, and perioperative amount of fluid (the total amount of fluid administered in 3 days, including the day before surgery), types of fluid administered during surgery, presence of diabetes and hypertension, and presence of CKD were assessed.

2. Definition

AKI was defined as a postoperative creatinine level of ≥ 0.3 mg/dL [9], and CKD was defined as a GFR of < 60 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [10]. The postoperative estimated GFR (eGFR) was based on value obtained on the third day after surgery. The change in eGFR from baseline was indicated as ΔeGFR.

3. Statistical analyses

The study data are presented as frequencies with percentages for categorical variables and means ± standard deviations for continuous variables. The effect of the independent variables on the response variables was analyzed using multivariate logistic regression, and the statistically significant variables were selected using a backward elimination method with a 0.05 alpha level. Differences in the characteristics of the study participants were compared across subgroups by using the chi-square or Fisher exact test for categorical variables and the independent *t*-test or Mann-Whitney *U*-test for continuous variables. The Shapiro-Wilk test was used to check if the data distribution was normal. Univariate and multivariate analyses were performed using logistic regression to identify prognostic factors that are independently related to AKI. A receiver-operating characteristic curve was used to assess the sensitivity and specificity of the change in eGFR from baseline. Positive and negative predictive values were also calculated. All statistical analyses were performed using the IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 11.6.0 software (MedCalc Software Ltd., Ostend, Belgium). A p-value of < 0.05 was considered statistically significant.

Results

The baseline characteristics of the study patients are shown in Table 1. Overall, AKI occurred in 13 (3.7%) of the 351 patients. The mean ages of the study participants in the AKI and non-AKI groups were 67.92 ± 13.49 years and 66.34 ± 11.03 years, respectively. Of the study population, 269 patients (76.6%) were women, and 66 (18.8%) had CKD. The patients' preoperative eGFR was 66.66 ± 34.02 mL/min/1.73 m^2 in the AKI group and 78.07 ± 21.23 mL/min/1.73 m^2 in the non-AKI group. The albumin level was 3.31 ± 0.32 g/dL in the AKI group and 3.67 ± 0.42 g/dL in the non-AKI group. The hemoglobin level was 11.21 ± 1.65 g/dL in the AKI group and 12.39 ± 1.52 g/dL in the non-AKI group. The ΔeGFR was significantly related to decreased risk of AKI (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.61–0.89; $p = 0.002$); Hemoglobin level showed statistically significant results with acute renal injury (OR, 0.13; 95% CI, 0.02–0.68; $p = 0.016$). Lower hemoglobin level was associated with more acute renal injury. Regarding the administration of perioperative fluid therapy, eight (3.7%) of the 219 patients in the crystalloid group and five (3.8%) of the 132 patients in the colloid group developed AKI. Administration of crystalloid or colloid fluid alone did not show any significant association with the development of AKI. The perioperative amount of fluid was 1,330.77 ± 606.06 mL in the AKI group and 1,539.85 ± 942.03 mL in the non-AKI group, showing no statistically significant difference (Table 1).

The multivariate analysis revealed that the other variables were not related to AKI, although some variables showed significance after the univariate analysis. The ΔeGFR was further analyzed using a cutoff value of 7.54. The sensitivity, specificity, false-negative rate, false-positive rate, positive predicted value, and negative predicted value of ΔeGFR for predicting AKI were 100%, 89.64%, 0.00%, 10.36%, 27.08%, and 100%, respectively. The concordance

Table 1. Patients' demographic and clinical variables across groups

Variable	Acute kidney injury			Univariate logistic regression		Multivariate logistic regression[a]	
	Yes (n = 13)	No (n = 338)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (yr)	67.92 ± 13.49	66.34 ± 11.03	0.280[b]	1.01 (0.96–1.07)	0.614	-	-
Sex							
Male	3 (23.1)	79 (23.4)	> 0.999[c]	0.98 (0.26–3.66)	0.980	-	-
Female	10 (76.9)	259 (76.6)				-	-
Diabetes mellitus							
Yes	2 (15.4)	66 (19.5)	> 0.999[c]	0.75 (0.16–3.46)	0.712	-	-
No	11 (84.6)	272 (80.5)		1.00		-	-
Hypertension							
Yes	11 (84.6)	182 (53.8)	0.029[d]	4.71 (1.03–21.59)	0.046	-	-
No	2 (15.4)	156 (46.2)		1.00		-	-
CKD							
Yes	9 (69.2)	57 (16.9)	< 0.001[c]	11.09 (3.30–37.26)	< 0.001	-	-
No	4 (30.8)	281 (83.1)		1.00		-	-
ACEi							
Yes	4 (30.8)	110 (32.5)	> 0.999[c]	0.88 (0.27–2.94)	0.842	-	-
No	9 (69.2)	219 (64.8)		1.00		-	-
NSAIDs							
Yes	2 (15.4)	50 (14.8)	> 0.999[c]	1.01 (0.22–4.72)	0.985	-	-
No	11 (84.6)	279 (82.5)		1.00		-	-
Anesthesia							
Spinal	11 (84.6)	267 (79.0)	> 0.999[c]	1.46 (0.32–6.75)	0.626	-	-
General	2 (15.4)	71 (21.0)		1.00		-	-
During operative bleeing (mL)	155.77 ± 149.41	227.57 ± 260.51	0.558[b]	1.00 (1.00–1.00)	0.325	-	-
Operation time (min)	173.08 ± 25.78	186.88 ± 41.10	0.267[b]	0.99 (0.97–1.01)	0.231	-	-
Type of surgery							
Total knee replacement	9 (69.2)	229 (67.8)	1.000[c]	1.07 (0.32–3.55)	0.911	-	-
Total hip replacement	4 (30.8)	109 (32.2)		1.00		-	-
Preoperative GFR (mL/min/1.73 m^2)	66.66 ± 34.02	78.07 ± 21.23	0.043[b]	0.97 (0.95–1.00)	0.058	-	-
ΔeGFR	−29.47 ± 18.10	10.89 ± 14.93	< 0.001[e]	0.82 (0.75–0.90)	< 0.001	0.74 (0.61–0.89)	0.002
Albumin (g/dL)	3.31 ± 0.32	3.67 ± 0.42	0.001[b]	0.13 (0.03–0.49)	0.003	-	-
Hemoglobin (g/dL)	11.21 ± 1.65	12.39 ± 1.52	0.015[b]	0.61 (0.43–0.88)	0.008	0.13 (0.02–0.68)	0.016
Postopeative CRP (mg/L)	13.73 ± 8.09	13.39 ± 7.18	0.786[b]	1.01 (0.93–1.09)	0.870	-	-
Total CO_2 (mmol/L)	24.28 ± 2.82	26.53 ± 3.22	0.019[b]	0.78 (0.64–0.95)	0.013	-	-
Ejection fraction (%)	65.04 ± 6.99	64.66 ± 4.09	0.354[b]	1.02 (0.87–1.19)	0.788	-	-
Hospital stay (day)	24.82 ± 6.59	23.55 ± 12.14	0.104[b]	1.01 (0.96–1.06)	0.731	-	-
No. of prescribed drug	7.36 ± 3.93	4.11 ± 3.47	0.006[b]	1.23 (1.07–1.43)	0.005	-	-
proBNP (ng/L)	248.57 ± 274.08	235.01 ± 409.40	0.511[b]	1.00 (1.00–1.00)	0.954	-	-
Fluid therapy							
Crystalloid	8 (61.5)	211 (62.4)	1.000[c]	1.00		-	-
Colloid	5 (38.5)	127 (37.6)		1.04 (0.33–3.24)	0.948	-	-
Perioperative amount of fluid (mL)	1,330.77 ± 606.06	1,539.85 ± 942.03	0.479[b]	1.00 (1.00–1.00)	0.425	-	-

Values are presented as mean ± standard deviation or number (%).
CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; eGFR, estimated glomerular filtration rate; ΔeGFR, change in eGFR at postoperative from baseline; CRP, C-reactive protein; proBPN, pro-B-type natriuretic peptide.
[a]In a multivariate logistic regression, the statistically significant variables in the univariate analyses were included. Then, categorical variables that have less frequency in a certain subgroup such as hypertension and CKD were excluded since the estimated odds ratio goes infinity and is not estimable. Finally, the statistically significant variables were selected in a backward elimination method with 0.05 alpha level.
The *p*-values were derived from [b]Mann-Whitney *U*-test, [c]Fisher exact test, [d]chi-square test, and [e]independent *t*-test. Shapiro-Wilk test was employed for test of normality assumption.

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between a ΔeGFR of −7.54 and the occurrence of AKI was good (316/351, 90.03%) (Table 2, Fig. 1).

Discussion

This study involved the analysis of the risk factors for AKI in patients who underwent major orthopedic surgery in our hospital for over 5 years. The incidence of renal insufficiency after orthopedic surgery has been reported to be up to 9.1% [3,4]. The incidence also differs according to the surgical site. According to a study by the Scottish Arthroplasty Project, the prevalence of AKI after total hip arthroplasty increased from 0.47% to 0.78%, and the prevalence of AKI after total hip arthroplasty increased from 0.39% to 0.75% between 2004 and 2013 [11]. In the present study, the incidence of AKI was 3.7%, which is low as compared with those recorded in previous studies. The incidence of AKI varies among studies depending on the type of surgery performed [12-14].

In the present study, preoperative hemoglobin levels were found to influence the occurrence of AKI, which is consistent with previous studies [7], thereby suggesting that preoperative general conditions may affect the postoperative clinical course.

In another study, for patients with severe sepsis in the surgical intensive care unit, a lower AKI incidence rate was recorded for a crystalloid group than for a hydroxyethyl starch group [15]. Adequate fluid management with consideration of fluid type is important to maintain hemodynamic stability in patients undergoing surgery. Insufficient fluid administration results in renal hypoperfusion but may cause pulmonary congestion when performed excessively. In the present study, however, we found no statistically significant differences related to the type and amount of fluid administered.

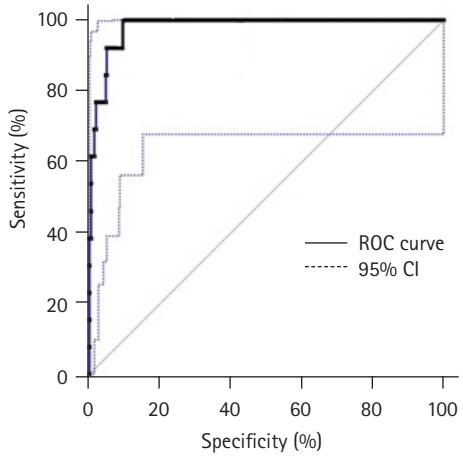
The definition of AKI has been constantly revised and supplemented [16]. We, therefore, sought to identify patients with additional risk of developing AKI according to their ΔeGFR. A cutoff of 7.54 had a high sensitivity and specificity (100% and 89.64%, respectively). Therefore, if the ΔeGFR is >7.54, management is required but still depending on the case. In clinical practice, after checking only creatinine levels, if the change is within the normal range even if the ΔeGFR is significant, it is often skipped unremarkably. In our study, 73.3% of the patients with significant ΔeGFR had changes in creatinine level that were within the normal range (0.7–1.2 mg/dL). Clinicians should check patients' eGFR because if the change is significant, careful monitoring is required particularly for changes in renal function in patients with AKI. These data will help establish the treatment direction and improve prognosis, particularly in older patients, because their treatment can be challenging owing to the difficulty in estimating the accurate renal function using creatinine levels (because of age-related reduction of muscle mass) and other factors [17].

One study showed that blood transfusion, hepaticojejunostomy, and oliguria are the strongest predictors of AKI after liver resection, although their findings could not be applied to orthopedic research because of the specificity of the field [18]. In a cohort study that assessed age, male sex, presence of diabetes, low GFR, use of

Table 2. Comparison of efficacies of ΔeGFR for detecting the acute kidney injury

Variable	Cut-point value of ΔeGFR	
	≤−7.54	>−7.54
Acute kidney injury		
Yes	13	0
No	35	303
AUC (*p*-value)	0.98 (<0.001)	
Sensitivity (%)	13/13 (100)	
Specificity (%)	303/338 (89.64)	
FNR, 100%–sensitivity	0/13 (0)	
FPR, 100%–specificity	35/338 (10.36)	
PPV (%)	13/48 (27.08)	
NPV (%)	303/303 (100)	

ΔeGFR, change in estimated glomerular filtration rate at postoperative from baseline; AUC, area under the curve; sensitivity, proportion of patients with acute kidney injury who had a lower than −7.54 for ΔeGFR; specificity, proportion of patients without acute kidney injury who had a higher than −7.54 for ΔeGFR; FNR, false-negative rate; FPR, false-positive rate; PPV, positive predicted value; NPV, negative predicted value.
Concordance between ΔeGFR with −7.54 and acute kidney injury was good (316/351, 90.03%).



AUC	0.980
SE	0.009
95% CI	0.960–0.992
Z-Statistic	51.029
p-value (H_0: area=0.05)	<0.001

Fig. 1. Efficacy rates of changes in estimated glomerular filtration rate (ΔeGFR) for detecting acute kidney injury. AUC, area under the receiver-operating characteristic (ROC) curve; SE, standard error; CI, confidence interval.

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, the number of prescriptions, and the American Society of Anesthesiologists grade during surgery for orthopedic patients in Scotland, acute renal injury was identified as a predictor of and confirmed to be associated with increased long-term mortality [19]. In our study, the risk factors considered in previous studies did not show a statistically significant relationship with acute renal injury, and the difference in these results was that the incidence of AKI was lower in our study than in other studies. This could be because our study was conducted in a single race or local area; hence, its main limitation resulted in a selection bias.

This study has some limitations. First, because the study was conducted in a single institution, it was conducted in patients of a single race or from a local area, and a selection bias may be associated with this. Therefore, the results of our study can be applied to domestic patients but will be difficult to apply to various races. Further multicenter studies are needed to augment the information generated from the present study. The second limitation is that it is a retrospective study. Whether the statistically significant variables had a causal relationship with AKI was difficult to confirm, and the association alone could be confirmed. Because the data we used were from patients not recruited for research, new AKI-related risk factors may exist among the variables that we did not consider. Thus, additional prospective studies are needed. The third limitation is a problem because of the small number of patients with AKI as compared with the total number of patients. Owing to the small number of patients, securing statistical significance was difficult. Thus, further studies with larger numbers of patients are needed.

Renal function should be monitored closely after orthopedic surgery if the patient has CKD or low hemoglobin levels, which should be stabilized before the procedure. In addition, clinicians should check the eGFR because a significant change in eGFR requires careful monitoring based on the occurrence of AKI. In elderly patients whose renal functions are difficult to accurately assess on the basis of creatinine levels, more attention should be paid to eGFR changes. Predicting the likelihood of AKI occurrence, early treatment of high-risk patients, and monitoring perioperative laboratory test results, including eGFR, will help improve patient prognosis.

Acknowledgments

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: YWK; Writing-original draft: YJL; Writing-review & editing: YWK, BSP, SP, JHP, IHK, JK.

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Association between cystographic anastomotic urinary leakage following retropubic radical prostatectomy and early urinary incontinence

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Background: This study was performed to investigate the association between cystographic anastomotic urinary leakage (UL) after retropubic radical prostatectomy (RRP) and early urinary incontinence (UI).

Methods: The medical records of 53 patients who had undergone cystography after RRP at our institution between January 2015 and December 2018 were retrospectively analyzed. Cystography was performed 7 to 10 days after surgery. The duration of catheterization depended on the degree of UL, which was classified as mild, moderate, or severe. The study subjects were divided into the non-UL group and the UL group. Continence was defined as the use of no pads. The prostate was dissected in an antegrade fashion, and urethrovesical anastomosis was performed with a continuous suture.

Results: Incontinence rates at 1 and 3 months postoperatively were significantly higher in the UL group than the non-UL group (83.3% vs. 52.2%, $p=0.014$ and 76.7% vs. 47.8%, $p=0.030$, respectively); however, those at 6 and 12 months were not significantly different (23.3% vs. 17.4%, $p=0.597$ and 4.3% vs. 10.0%, $p=0.440$, respectively). The severity of UL was not found to influence the duration of incontinence. The presence of cystographic anastomotic UL was found to be predictive of UI during the first 3 postoperative months (odds ratio, 3.3; $p=0.045$).

Conclusion: The presence of anastomotic UL on cystography was associated with higher rates of UI in the early postoperative periods. However, incontinence rates in patients with or without anastomotic UL immediately after RRP equalized at 6 months and the severity of UL did not affect the duration of postoperative UI.

Keywords: Anastomotic leak; Prostatectomy; Urinary incontinence

Introduction

Retropubic radical prostatectomy (RRP) is now established as the gold standard surgical management for localized prostate cancer [1,2]. However, the role of RRP has become more complex because a greater focus has been placed on patient- and cancer-specific considerations, especially those related to the balance between oncologic and functional outcomes. Unfortunately, the majority of patients who undergo RRP for prostate cancer experience treatment-related complications, especially postprostatectomy urinary incontinence (PPUI), which has a significant impact on patient quality of life [3].

RRP involves removal of the prostate and formation of a new connection between the urethra and bladder. Prostate removal is achieved by antegrade or retrograde processing, and anastomosis between the urethra and bladder is performed using a continuous

or interrupted suture. In the case of open RRP, an interrupted suture is usually used, but the widespread use of laparoscopy has contributed to the proportion of procedures conducted using a continuous suture [4].

In general, cystography is performed between 1 and 2 weeks after RRP to confirm urinary leakage (UL) at the anastomosis site. One of the most common short-term complications of RRP is UL [5]. In several studies, the incidence of UL has been reported to be as high as 10% [6]. The consensus opinion is that UL does not seem to affect long-term PPUI, but early continence may be delayed due to UL, and patients with anastomotic leakage have a higher incidence of PPUI [7,8]. However, it remains unclear how the degree of UL affects urinary incontinence after RRP, and no reports on this relationship have been published in Korea.

We retrospectively analyzed the incidence and severity of UL in 53 patients who had undergone RRP at our center. These patients were divided into two groups based on the presence or absence of anastomotic UL immediately after surgery and compared with respect to possible factors responsible for UL. Moreover, the association between UL and PPUI was investigated.

Materials and methods

1. Study design and patient enrollment

After the approval of the Institutional Review Board (IRB) and Ethics Committee of Dongguk University College of Medicine (IRB No: 1107-201903-HR-03-02), 53 consecutive patients with a diagnosis of prostate cancer who had undergone RRP at our institution between January 2015 and December 2018 were enrolled in this study. Informed consent was waived by the IRB.

2. Variables inspected

Data were obtained by retrospective chart review. The variables analyzed included age, body mass index (BMI), prostate volume, operative time, estimated blood loss, duration of catheter indwelling, presence or absence of UL on postoperative cystography, and pathologic variables (i.e., preoperative prostate-specific antigen [PSA] level, postoperative Gleason score, and pathologic stage).

Cystography was performed 7 to 10 days after surgery. Normal saline (up to 200 mL) was injected to check for UL. The duration of catheterization depended on the degree of UL, which was classified as mild, moderate, or severe. UL was defined as mild when leakage was observed after injecting 200 mL, moderate if observed after injecting 100 mL, and severe if leakage occurred before injecting 100 mL normal saline (Fig. 1).

In cases of mild UL, the catheter was removed after 3 days, and for moderate UL, it was removed after 7 days [9]. In cases of severe UL, cystography was repeated at 7-day intervals with the catheter *in situ* until the UL ceased. The 53 study subjects were divided into two groups; the non-UL group (n=23) and the UL group (n=30).

3. Definition and assessment of continence

Continence was defined as no pad usage, as determined by patient response. Patients were asked the following question; "How many pads or adult diapers have you used daily to control leakage during the past 4 weeks?" Continence recovery was evaluated routinely at 1, 3, 6, and 12 months after RRP.

4. Surgical technique

RRP was performed in the supine position. The superficial dorsal vein was coagulated by bipolar ablation, and periprostatic fat was removed. Before disassembling the bladder and prostate, both lat-

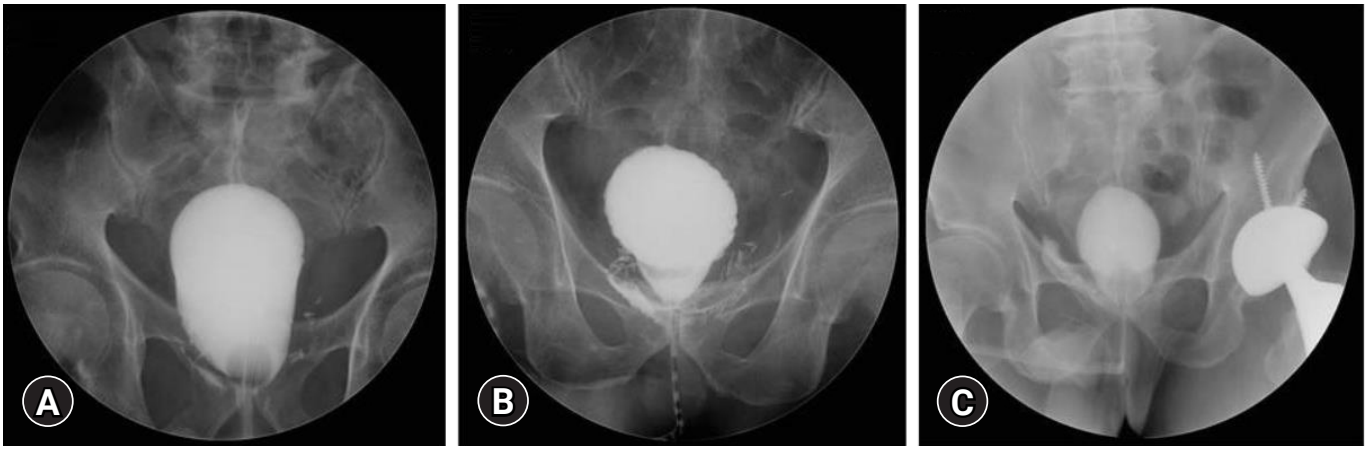

Fig. 1. Cystography findings and classification of urinary leakage (UL). (A) Mild UL (UL developed after bladder filling with 200 mL normal saline). (B) Moderate UL (UL developed after bladder filling with 100 mL normal saline). (C) Severe UL (UL developed before bladder filling with 100 mL normal saline).

eral outer borders of the bladder and prostate were dissected and a cut was placed along the imaginary bladder-prostate borderline. After dissecting vas deferens and seminal vesicles, the prostate was dissected in an antegrade fashion while preserving the bilateral nerves, and hemostasis was conducted carefully. A double-stranded running suture was then placed bidirectionally from 6 o'clock to 3 and 9 o'clock and then from 3 o'clock to 9 and 12 o'clock while maintaining tension at the posterior anastomosis site to achieve anastomosis with a Monosyn 3.0 (Aesculap, Melsungen AG, Germany) suture. A catheter was then inserted, and a 120-mL saline filling test was conducted to confirm the absence of leakage.

5. Statistical analysis

The chi-square test and the Mann-Whitney test were used to analyze the demographics and perioperative outcomes. Incontinence rates at 1, 3, 6, and 12 months after surgery were analyzed using the chi-square test. Logistic regression analysis was used to identify factors that independently affected incontinence. PASW Statistics version 18.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. For all comparisons, *p*-values of < 0.05 were considered statistically significant.

Results

Fifty-three patients who had undergone RRP were included in the study. The mean patient age was 68.8 years (range, 67–70 years), mean BMI was 24.5 ± 2.9 kg/m^2, and mean prostate size was 40.1 ± 18.6 mL. Six patients (11.3%) had a preoperative PSA > 20 ng/mL, and pathological organ-confined disease was observed in 31 patients (58.5%).

UL was detected during postoperative cystography inspections in 30 patients (56.6%); six had mild, 12 had moderate, and 12 had severe leakage. The longest period of catheterization was 38 days, which was observed in three patients. These three patients were evaluated for incontinence 1 month after removal of the Foley catheter. The mean catheterization periods for mild, moderate, and severe UL were 13.0, 17.0, and 20.1 days, respectively.

Times to catheter removal were significantly different between UL and non-UL groups (9.7 ± 0.9 vs. 20.6 ± 7.5, $p = 0.001$) (Table 1). However, other perioperative characteristics and outcomes were similar. Furthermore, no significant intergroup difference was observed for pathologic data, including pathologic stage, mean Gleason score, and positive surgical margin (Table 1).

Incontinence rates at 1 and 3 months postoperatively were significantly different between UL and non-UL groups (83.3% vs. 52.2%, $p = 0.014$ and 76.7% vs. 47.8%, $p = 0.030$, respectively), but no significant difference was observed at 6 months (Table 2). The degree of UL was not found to influence the duration of incontinence (Table 2). In patients with severe UL, the incontinence rate at 12 months was 16.7%.

By logistic regression analysis, anastomotic UL was found to be the only significant predictor of urinary incontinence (odds ratio,

Table 1. Perioperative characteristics and outcomes between urinary leakage (UL) and non-UL group

Characteristic	UL group (n = 30)	Non-UL group (n = 23)	*p*-value
Age (yr)	69.1 ± 4.8	68.4 ± 5.9	0.649
Body mass index (kg/m^2)	25.1 ± 2.9	23.6 ± 2.6	0.059
Prostate volume (mL)	41.0 ± 21.5	39.0 ± 14.4	0.709
Preoperative PSA (ng/mL)	10.4 ± 9.0	9.8 ± 9.2	0.830
Mean operative time (min)	218.6 ± 33.5	193.1 ± 43.8	0.088
Estimated blood loss (mL)	284.7 ± 129.8	268.2 ± 143.0	0.664
Catheterization (day)	20.6 ± 7.5	9.7 ± 0.9	0.001
Pathologic stage			0.152
T2	15 (50.0)	7 (30.4)	
T3	15 (50.0)	16 (69.6)	
Pathologic Gleason score			0.615
6	0	2 (8.7)	
7	14 (46.7)	12 (52.2)	
8	7 (23.3)	2 (8.7)	
9	9 (30.0)	6 (26.1)	
10	0	1 (4.3)	
Positive surgical margin	8 (26.7)	8 (34.8)	0.524

Values are presented as mean±standard deviation or number (%).
PSA, prostate-specific antigen.

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3.3; 95% confidence interval, 0.973–11.207; $p=0.045$) (Table 3). There were no significant factor of PPUI at 6 and 12 months (Tables 4, 5).

Discussion

PPUI is a major complication of RRP and has a substantial impact on patient's quality of life because it affects physical activity and social well-being. The reported incidence of PPUI varies from 4% to 69% [9,10], depending on multiple factors such as age, preoperative voiding status, sphincteric functional competence, perioperative bladder function, and operative factors [10-13].

The pathophysiology of PPUI is not fully understood, although several studies have suggested that intrinsic bladder sphincter deficiency, underactivity, neural injury [14,15], defects in urethral support [16], shortening of membranous urethral length, and venous sealing effects underlie the condition [17,18]. Research efforts have resulted in several surgical advances, especially the nerve-saving technique, which was recently evaluated in a large European patient cohort [19].

Although UL does not seem to affect long-term incontinence, it has been associated with early PPUI [7,8]. Consistently, in this study, the incontinence rates were significantly higher in the UL group compared to the non-UL group during the first 3 postoperative months; however, no significant intergroup difference was observed at 6 months postoperatively. Furthermore, anastomotic UL was identified as a significant prognostic factor of urinary incontinence in the early postoperative period following RRP. These findings indicate that given the absence of UL through a defective anastomotic site, adequate urinary drainage after RRP is essential to promote healing of the vesicourethral anastomosis.

In the current study, the proportion of cases with UL after RRP (56.6%) was higher than has been previously reported [20,21]. At our center, in cases of UL post-RRP, the Foley catheter is removed at 1 to 2 weeks postoperatively, depending on the degree of UL.

Table 2. Incontinence rates between urinary leakage (UL) and non-UL group from 1 to 12 months and comparison of incontinence rates based on the degree of leakage

Variable	Incontinence rate			
	1 Mo	3 Mo	6 Mo	12 Mo
Group				
Non-UL group (n = 23)	12 (52.2)	11 (47.8)	4 (17.4)	1 (4.3)
UL group (n = 30)	25 (83.3)	23 (76.7)	7 (23.3)	3 (10.0)
p-value	0.014	0.030	0.597	0.440
Degree of leakage[a]				
Mild (n = 6)	4 (66.7)	4 (66.7)	3 (50.0)	0
Moderate (n = 12)	11 (91.7)	10 (83.3)	1 (8.3)	1 (8.3)
Severe (n = 12)	10 (83.3)	9 (75.0)	3 (25.0)	2 (16.7)
p-value[b]	0.066	0.157	0.209	0.519

Values are presented as number (%).
[a]Mild, leakage occurred after injecting 200 mL normal saline (NS); moderate, leakage occurred after injecting 100 mL NS; severe, leakage occurred before injecting 100 mL NS. [b]Non-UL group, Mild, Moderate and Severe UL group were analyzed by chi-square test.

Table 3. Multivariate logistic regression analysis for factors of postprostatectomy urinary incontinence at 3 months

Variable	OR (95% CI)	*p*-value
Age	1.044 (0.925–1.179)	0.483
Body mass index	1.250 (0.955–1.637)	0.105
Prostate-specific antigen	1.019 (0.939–1.105)	0.655
Pathologic T stage	1.204 (0.293–4.945)	0.796
Gleason score	1.160 (0.585–2.298)	0.671
Prostate size	1.006 (0.970–1.043)	0.754
Duration of catheterization	1.317 (0.733–2.366)	0.357
Degree of leakage	1.213 (0.105–8.551)	0.111
Urinary leakage	3.301 (0.973–11.207)	0.045

OR, odds ratio; CI, confidence interval.

Table 4. Multivariate logistic regression analysis for factors of PPUI at 6 months

Variable	OR	95% CI	*p*-value
Age	1.080	0.908–1.284	0.386
Body mass index	1.098	0.843–1.431	0.486
PSA	0.965	0.868–1.072	0.506
Pathologic T stage	5.730	0.753–43.626	0.092
Gleason score	0.409	0.133–1.252	0.117
Prostate size	1.018	0.981–1.056	0.344
Duration of catheterization	1.211	0.937–1.565	0.143
Degree of leakage	0.082	0.003–2.577	0.155
Urinary leakage	0.107	0.008–1.425	0.091

PPUI, postprostatectomy urinary incontinence; OR, odds ratio; CI, confidence interval; PSA, prostate specific antigen.

Table 5. Multivariate logistic regression analysis for factors of PPUI at 12 months

Variable	OR	95% CI	*p*-value
Age	1.015	0.702–1.466	0.939
Body mass index	2.111	0.832–5.359	0.116
PSA	1.101	0.877–1.381	0.407
Pathologic T stage	2.985	0.094–94.440	0.535
Gleason score	2.743	0.267–28.200	0.396
Prostate size	0.862	0.636–1.168	0.339
Duration of catheterization	0.696	0.293–1.652	0.412
Degree of leakage	570.906	0.003–7.853	0.178
Urinary leakage	600.972	0.042–2.647	0.177

PPUI, postprostatectomy urinary incontinence; OR, odds ratio; CI, confidence interval; PSA, prostate specific antigen.

Thus, sphincter function at the anastomosis site is likely to be abnormal during the early period. All of our patients received continuous anastomosis, and thus, approximation was more precise than that achieved using interrupted sutures. Leakage is more likely in incompletely sutured regions when interrupted sutures are used but may also occur due to loosening of the approximation with continuous anastomosis. If the Foley catheter indwelling period is sufficient, contracture is less likely during healing, and the healing period is reduced. However, when continuous suturing is performed using an open approach, the distance between 5 and 7 o'clock in the posterior anastomosis area tends to be greater than that in the anterior anastomosis area. This might have contributed to the higher prevalence of UL after RRP in the present study. Since RRP cases were performed by a single surgeon with less than 60 cases of experience, it was also considered a very important cause.

There were 12 patients with severe UL, and 2 (16.7%) of them experienced mild incontinence 1 year after RRP. These patients used only one pad per day and had no obstructive symptoms, such as a weak urine stream or hesitancy, which are the main symptoms of bladder neck contracture. Despite a short follow-up period, we were able to conclude that serious UL did not necessarily cause bladder neck contracture.

This study is limited by its retrospective, single-center design, and relatively small sample size. In fact, many factors affect PPUI, including the length of the preserved urethra after surgery, preservation of the bladder neck, sphincter injury, and preoperative voiding status. However, our study shows that postoperative cystographic UL does not develop into long-term incontinence and that in this era of robotic surgery, a continuous anastomosis suture procedure can be adopted during open RRP. No association has been previously reported between incontinence and urethrovesical anastomosis leakage in Korea.

Cystographically detected anastomotic UL was associated with higher rates of early urinary incontinence. However, continence rates were much improved 6 months after RRP in patients with anastomotic UL after surgery and the severity of UL did not affect the duration of postoperative UI.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Pudendal nerve entrapment syndrome caused by ganglion cysts along the pudendal nerve

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Pudendal nerve entrapment (PNE) syndrome refers to the condition in which the pudendal nerve is entrapped or compressed. Reported cases of PNE associated with ganglion cysts are rare. Deep gluteal syndrome (DGS) is defined as compression of the sciatic or pudendal nerve due to a non-discogenic pelvic lesion. We report a case of PNE caused by compression from ganglion cysts and treated with steroid injection; we discuss this case in the context of DGS. A 77-year-old woman presented with a 3-month history of tingling and burning sensations in the left buttock and perineal area. Ultrasonography showed ganglion cystic lesions at the subgluteal space. Magnetic resonance imaging revealed cystic lesions along the pudendal nerve from below the piriformis to the Alcock's canal and a full-thickness tear of the proximal hamstring tendon. Aspiration of the cysts did not yield any material. We then injected steroid into the cysts, which resolved her symptoms. Steroid injection into a ganglion cyst should be considered as a treatment option for PNE caused by ganglion cysts.

Keywords: Corticosteroids; Ganglion cysts; Nerve entrapment; Pudendal nerve

Introduction

Pudendal neuralgia is a neuropathic pain that presents in the distribution of pudendal nerve. The pudendal nerve emerges from the sacral plexus nerves (S2 to S4) and carries sensory fibers to genitalia such as the penis, scrotum, clitoris, and labia, and to the motor fibers of the perineum and pelvic floor muscles. Although pudendal neuralgia can be suspected in the presence of perineal pain, it is difficult to determine a cause in the absence of organic lesions on imaging tests [1]. Pudendal nerve entrapment (PNE) syndrome refers to the condition in which the pudendal nerve is entrapped or compressed [2]. Previous studies have reported that most cases of PNE are related to iatrogenic mechanical insult, such as gynecologic or hip surgery, or from incorrect seating position while cycling [3-5]. Only a few cases of organic lesions associated with PNE have been reported [1,2]. Furthermore, there has only been one published report of PNE related to ganglion cysts; this case was successfully treated with ultrasound-guided aspiration of the cysts [2].

Pudendal neuralgia caused by PNE presents with unilateral pelvic pain. This pain is typically aggravated by a seated position because the pudendal nerve is compressed between the sacrospinous and sacrotuberous ligaments and relieved by sitting on the toilet seat [1]. PNE may also cause pain in the posterior hip, the buttocks while seated, or in the medial thigh; referred sciatic pain has also been reported [1]. Recently, the concept of deep gluteal syndrome (DGS) has been introduced and defined as compression of the sciatic or pudendal nerve due to a non-discogenic pelvic lesion [6]. Thus, PNE can be considered to be part of the DGS spectrum.

In this report, we present a case of PNE caused by ganglion cysts that was successfully treated with steroid injections. We discuss this case in the context of DGS.

Case

This case report was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No: 2020-06-037). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

A 77-year-old woman presented to our clinic with a 3-month history of tingling and burning sensations in the left buttock and perineal area. The pain was aggravated in the sitting position and relieved while standing or in a supine position. She had no sphincter dysfunction such as urination or defecation and no history of trauma or pelvic surgery. On physical examination, passive external rotation and abduction of her hip joint produced the inguinal and buttock pain. There was a tenderness over the ischial tuberosity and piriformis area. There was no weakness of the lower extremities except for the left knee flexor (Medical Research Council grade IV). Deep tendon reflexes of the lower limbs were normal. There was no sensory impairment in the left lower extremity or the S4 and S5 dermatomes. Her pedal pulses were normal. We performed an ultrasound to identify the cause of her buttock and perineal pain. Ultrasonography revealed cystic lesions at the subgluteal space and a near full-thickness tear of the proximal hamstring tendons at the ischial tuberosity (Fig. 1). Pelvis magnetic resonance imaging showed ganglion cystic lesions along the pudendal nerve from below the piriformis to the Alcock's canal (Figs. 2, 3). In addition, we noted fluid collection related to the tear of the hamstring origin sites around the ischial tuberosity (Figs. 2, 3). Based on the proximity of the ganglion cysts to the pudendal nerve, we determined that the cysts caused the PNE. Aspiration of the cysts under ultrasound guidance did not produce material. We then injected steroid (triamcinolone acetonide 20 mg+1% lidocaine 3 mL) into the cysts, which resolved her burning sensations.

Discussion

The prevalence of pudendal neuralgia caused by PNE has not been established, mostly due to the fact that it is often underdiagnosed. Kaur and Singh [7] and Spinosa et al. [8] reported an incidence of 1% in the general population and it is also known to be more common in females than males. While PNE can significantly impair patients' quality of life, owing to its rarity and difficulty of diagnosis, it is often inappropriately treated [7]. Further, the mean time to diagnosis is 4 years and there is no specific diagnostic test [9]. The 'Nantes criteria,' created to facilitate the diagnosis of PNE, include (1) pain in the anatomical territory of the pudendal nerve, (2) pain that is worsened by sitting, (3) the patient is not woken at night by the pain, (4) there is no objective sensory loss on clinical examination, and (5) pain relief provided by an anesthetic pudendal nerve block [10]. In our case, the patient met the first four diagnostic criteria.

The pudendal nerve originates from the S2, S3, and S4 sacral nerve roots and courses between the piriformis and ischiococcygeus muscles, leaving the pelvis through the greater sciatic foramen. It then crosses the sacrospinous ligament and re-enters the pelvis through the lesser sciatic foramen. After re-entrance, it courses anterosuperiorly through the Alcock's canal. The nerve divides into three branches as it exits the canal. The Alcock's canal lies on the medial surface of the obturator internus muscle and the medial aspect of ischial tuberosity above the falciform ridge [7,11]. In our patient, ganglion cysts were observed along the pudendal nerve from below the piriformis to the Alcock's canal. Cystic lesions observed along the pudendal nerve should be distinguished from extraneural or intraneural ganglion cysts. Because our patient did not receive an exploratory operation or high-resolution magnetic resonance neurography, the characteristics of the cysts were not identified in detail.

DGS encompasses a variety of conditions including piriformis, gemelli-obturator internus, ischiofemoral impingement, and proximal hamstring syndromes. The presenting symptoms can be localized in the perineal, perianal and posterior areas, with the specific location depending on which nerve is compressed or irritated. Previous studies of DGS have mainly discussed involvement of the sciatic nerve rather than of the pudendal nerve. Hamstring tears around the ischial tuberosity can also be a cause of DGS. Further, proximal hamstring tendon pathologies can cause a ganglion cyst that irritates or compresses the adjacent nerves [6]. In our case, ganglion cysts along the pudendal nerve seemed to be associated with a full-thickness tear of the proximal hamstring tendon. We consider our patient's symptoms to fit into the category of DGS.

Ganglion cysts have been reported in most joints, tendons, and, rarely, in bone. On average, they have a 50% spontaneous resolution rate. While the management of ganglion cysts ranges from nonsurgical to surgical treatments, aspiration is the mainstay of nonsurgical treatment [12]. Lee et al. [2] reported the first case of PNE caused by a ganglion cyst and suggested ultrasound-guided aspiration as a treatment option to alleviate pain. However, the recurrence rate of cysts treated with aspiration alone is more than 50% [12]. To decrease recurrence after simple aspiration, steroid injections have been used [13]. In our patient's case, aspiration of the cysts was non-productive but an injected steroid was successful in alleviating her pain. Considering that aspiration of the cyst did not produce material, the injected steroid might spread to the

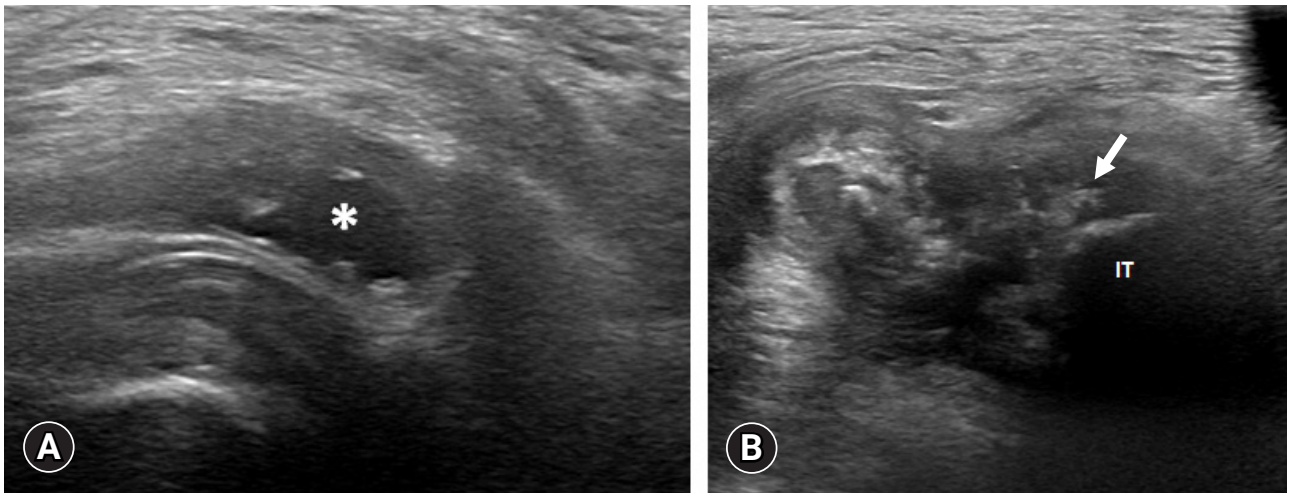

Fig. 1. Ultrasonographic findings. (A) A 2.6x1.2 cm-sized ganglion cystic lesion (asterisk) at the subgluteal space. (B) Full-thickness tear (arrow) of the proximal hamstring tendon at the ischial tuberosity (IT).

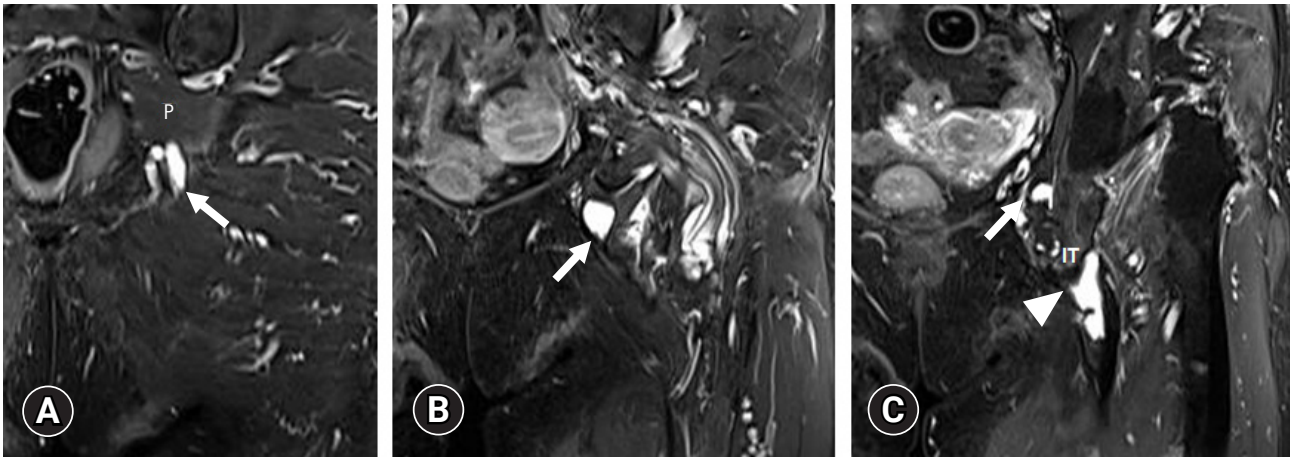

Fig. 2. Coronal fat-suppressed T2-weighted images of ganglion cyst courses along the pudendal nerve. (A) A 2.0x0.8 cm-sized ganglion cyst (arrow) below piriformis (P). (B) A 1.8x1.4 cm-sized ganglion cyst (arrow) at the entrance of the Alcock's canal. (C) A 1.0x0.75 cm-sized ganglion cyst (arrow) within the Alcock's canal and full-thickness tear (arrowhead) of the proximal hamstring tendon at the ischial tuberosity (IT).

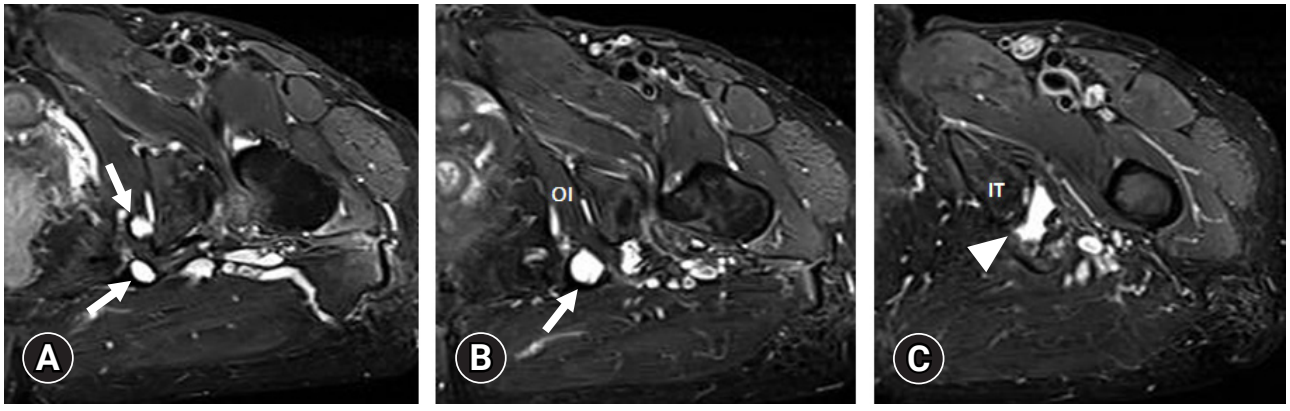

Fig. 3. Axial fat-suppressed T2-weighted images of ganglion cyst courses along the pudendal nerve. (A) A 1.0x0.8 cm-sized and 1.2x1.3 cm-sized ganglion cysts (arrows) around the Alcock's canal. (B) A 1.3x1.5 cm-sized ganglion cyst (arrow) medial to the obturator internus (OI) muscle. (C) A full-thickness tear (arrowhead) of the proximal hamstring tendon at the ischial tuberosity (IT).

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pudendal nerve and lead to a significant improvement, such as perineural steroid injection in PNE patients without ganglion cyst [9]. Steroids might suppress ectopic nerve activity from damaged peripheral nerve fibers and stabilize the nerve's membrane [14]. This suggests that steroid injection should be considered as a treatment option for patients with PNE in whom aspiration of ganglion cysts to alleviate the pain has failed.

In conclusion, in patients with unilateral perineal and buttock area pain, PNE should be considered as a possible cause of the pain. We suggest steroid injections as a treatment option for PNE associated with ganglion cysts, particularly when aspiration is unsuccessful.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Formal analysis, Supervision, and Writing-review & editing: DHK; Data curation, Writing-original draft: YJK.

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Diplopia developed by cervical traction after cervical spine surgery

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Diplopia is a rare complication of spine surgery. The abducens nerve is one of the cranial nerves most commonly related to diplopia caused by traction injury. We report a case of a 71-year-old woman who presented with diplopia developing from abducens nerve palsy after C1–C2 fixation and fusion due to atlantoaxial subluxation with cord compression. As soon as we discovered the symptoms, we suspected excessive traction by the instrument and subsequently performed reoperation. Subsequently, the patient's symptoms improved. In other reported cases we reviewed, most were transient. However, we thought that our rapid response also helped the patient's fast recovery in this case. The mechanisms by which postoperative diplopia develops vary and, thus, remain unclear. We should pay attention to the fact that the condition is sometimes an indicator of an underlying, life-threatening condition. Therefore, all patients with postoperative diplopia should undergo thorough ophthalmological and neurological evaluations as well as careful observation by a multidisciplinary team.

Keywords: Abducens nerve; Cranial nerve diseases; Diplopia; Spinal fusion

Introduction

Perioperative ocular complications are rare yet important. The American Society of Anesthesiologists (ASA) Closed Claims database was initiated in 1984 to analyze anesthesia malpractice and improve patient safety. Data from the ASA Closed Claims have shown that intraoperative eye injuries account for 4% of medico-legal claims, indicating that eye care is an important part of anesthesia-related care [1]. Diplopia can rarely present after spine surgery. As a result, there have been a few investigations on this condition, and the mechanism by which diplopia develops following spine surgery remains unknown [2]. The current report summarizes the current literature and presents a case of postoperative diplopia that developed following cervical spine surgery. We hope that this report will lead to a better understanding of postoperative diplopia and how best to manage patients with the condition.

Case

This study was approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (IRB No: 2018-09-016). Written informed consent was obtained from the patient for

publication of this case report and accompanying images.

A 71-year-old woman (height, 149 cm; weight, 62 kg) was admitted in the outpatient department. The patient complained of pain and tightness on the side of her neck and an accompanying tingling sensation in both hands that had been ongoing for 3 years. The patient had a 20-year history of hypertension and was taking hypertensive drugs (olmesartan medoxomil, 20 mg; hydrochlorothiazide, 12.5 mg; and cilnidipine, 10 mg). She was diagnosed with atlantoaxial subluxation with cord compression and was treated with a C1–C2 fixation and fusion (Fig. 1A, 1B). The surgical time was 170 minutes and the total anesthesia time was 265 minutes. The patient had perioperative bleeding with an estimated blood loss of 300 mL. As a result, the patient received 1 unit of packed red blood cells intraoperatively, which led to hemodynamic stability. Following surgery, the patient was transferred to a general ward for recovery. One day after surgery, the woman complained of acute horizontal diplopia. Ophthalmologic examination revealed limited lateral gaze (–0.5) in the left eye and esotropia (2 prism diopters [PDs]) in the left eye in primary gaze position with distant fixation, which increased to 5 PDs in left gaze position. Based on these findings, the patient was suspected to have left abducens nerve palsy. Her best corrected visual acuity was 20/25 (plano; Dcyl –2.00, axis 90°) in the right eye and 20/20 (Dsph +1.25, Dcyl –2.25, axis 90°) in the left eye. Anterior segment findings and pupillary reflex were normal in both eyes. No abnormal finding was observed in the eyelid. Neurologic examination including brain magnetic resonance imaging did not provide any specific finding except diplopia. The surmised cause of diplopia was thought to be associated with excessive 6th cranial nerve (CN) due to C1–C2 fixation and fusion. In preoperative cervical spine plain radiography, Powers ratio was 0.80 (Fig. 1A). After the C1–C2 fixation of fusion, Powers ratio was increased to 1.04 (Fig. 1B). We judged this to be an excessive rod distraction. Therefore, rod repositioning was performed to reduce the interspinous distance. After reoperation, Powers ratio decreased to 0.87 (Fig. 1C). However, there was no change in the atlanto-dental interval during perioperative period (Fig. 1). Two days after cervical spine surgery (1 day after nerve traction reduction), the patient reported an improvement in symptoms. Thirty-five days after the initial surgery (34 days after nerve traction reduction), diplopia had resolved completely.

Discussion

Diplopia is a rare complication after spine surgery, but several cases have been reported [2-9]. In non-spine surgery, diplopia has been reported mainly in patients undergoing spinal anesthesia, and only rarely in patients undergoing general anesthesia [10]. In the case presented here, the patient did not complain of postoperative diplopia immediately after spine surgery or during anesthetic recovery. Other reports have described times of onset of diplopia varying from 1 day to several days after operation (Table 1) [2-9]. As a result of its delayed onset, postoperative diplopia is rarely diagnosed by the anesthesiologist. It is very difficult to explain the mechanisms associated with delayed onset of diplopia after spine surgery. We presume that the following factors may contribute to delayed onset of diplopia. Intraoperative dural tear, spinal anesthe-

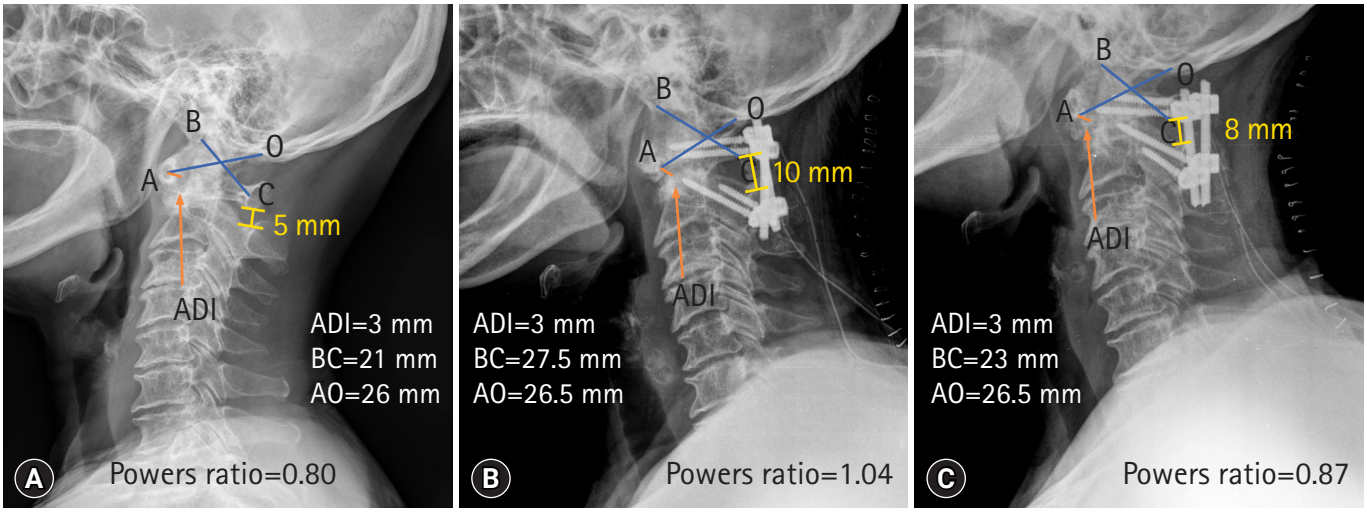

Fig. 1. Pre- and postoperative cervical spine lateral plain radiography. (A) Preoperative, (B) 1st postoperative, and (C) after 2nd postoperative images. ADI, atlanto-dens interval; BC, distance from the basion to the anterior aspect of the posterior arch of C1; AO, distance from the posterior aspect of the anterior arch of C1 to the opisthion; Powers ratio, BC/AO. In cases of Powers ratio >1 in plain radiographs and ADI >3 mm, anterior atlanto-occipital dissociation should be suspected.

Table 1. Reported cases of diplopia after spine surgery

Year	Author	Surgery	Patient sex	Age (yr)	Surgical position	Spine level	Presumed causes of diplopia	Palsy detection (postoperative day)	Treatment	Palsy remission
1999	Barsoum et al. [9]	Laminectomy	Male	59	Prone	Lumbar	Traction	Unknown	Conservative	6 Months
2003	Nakagawa et al. [6]	Spinal tumor resection	Female	22	Prone	Cervical	CSF leakage	3	Conservative	1 Year
2009	Cho et al. [3]	Posterior fusion	Male	61	Prone	Lumbo-sacral	CSF leakage	2	Conservative	5 Weeks
2011	Abd-Elsayed et al. [2]	Fusion	Female	14	Prone	Lumbar	Facial edema	1	Conservative	Few days
		Fusion	Female	34	Prone	Lumbar	Facial edema	1	Conservative	5 Days
		Fusion, discectomy	Female	67	Supine	Cervical	Facial edema	1	Conservative	Few days
		Fusion	Female	18	Lateral	Thoraco-lumbar	Facial edema	1	Conservative	3 Days
2012	Thomas et al. [8]	Discectomy	Male	53	Prone	Lumbar	CSF leakage	7	Dural repair	2 Weeks
2013	Joo et al. [4]	Discectomy	Male	48	Prone	Lumbo-sacral	CSF leakage	3	Dural repair	1 Week
2013	Khurana et al. [5]	Discectomy	Male	48	Prone	Thoracic	CSF leakage	> 21	Dural repair+chest drain	3 Months
		Discectomy	Male	46	Prone	Thoracic	CSF leakage	Unknown	Conservative	5 Months
2016	Sandon et al. [7]	Discectomy	Female	47	Prone	Thoracic	CSF leakage	10	Dural repair+chest drain	1 Month
2020	This report	Fusion	Female	71	Prone	Cervical	Traction	1	Conservative	35 Days

CSF, cerebrospinal fluid.

sia, and primary intracranial hypotension produce cerebrospinal fluid (CSF) leakage, leading to traction of brain with stretching of CNs, such as the abducens nerve, resulting in subsequent diplopia [4-9,11]. Since most patients are usually in the lying position following the operation, the CSF leakage is relatively smaller compared with that in the sitting position; hence, diplopia is relieved [11]. However, when the patient sits or stands a few days after operation, the diplopia worsens due to relatively more CSF leakage compared with that in the lying position [4-8,11]. In addition, during the immediate postoperative period, non-attention by the surgeon, depending on the severity of diplopia, may also contribute to delayed onset of diplopia.

The mechanisms by which diplopia develops are diverse and not well understood, but CN injury is a well-known and obvious cause [2,9]. Extraocular muscles that control eye movement are innervated by CNs, including the oculomotor nerve (CN3), trochlear nerve (CN4), and abducens nerve (CN6) [12,13]. Diplopia occurs due to a malfunction of the extraocular muscles and/or the nervous system components that control them [12,13]. Of all the CNs, CN6 is thin and has a long intracranial course [14,15]. It emerges from the ventral aspect of the brainstem at the pontomedullary junction and runs through Dorello's canal between the dura and skull (Fig. 2) [12,13]. After piercing the dura, the nerve turns sharply forward at the tip of the petrous temporal bone to enter the cavernous sinus (Fig. 2) [12,13]. In the cavernous sinus, CN6 runs laterally to the internal carotid artery and medial to CN3, CN4, and CN5 (the trigeminal nerve) (Fig. 2) [12]. This sudden intracranial spatial alteration and compression of Dorello's canal are the main causes of CN6 injury [12,13]. Also, atherosclerosis and dolichoectasia of vessels can compress the nerve [13]. After continuing forward, CN6 finally leaves the cavernous sinus and enters the orbit through the superior orbital fissure (Fig. 2) [12,13]. At this point, it is encircled by a common tendinous ring. CN6 then innervates the lateral rectus muscle and produces eye abduction (Fig. 2) [12,13]. This long pathway makes CN6 particularly vulnerable to mechanical damage caused by bones and ligaments. Indeed, this was observed in our case, in which diplopia occurred due to excessive traction of the 6th CN. We identified the change in the atlanto-occipital area presented as an increase in Powers ratio after C1–C2 fixation and fusion with the occurrence of diplopia. Diplopia improved with normalization of the Powers ratio after the second surgery. Based on these features, the changes in the atlanto-occipital area after C1–C2 fixation and fusion may be associated with CN6 traction injury as the cause of diplopia. Previously, CN paralysis or damage was reported to occur due to the use of equipment such as Gardner-Wells tongs, halo traction, or halo-pelvic traction [9]. Other nerves, including the glossopharyngeal nerve (CN9), the vagus nerve (CN10), and the hypoglossal nerve (CN1), are most vulnerable to stretching injury because of their vertical or oblique course through the cranium. However, the most commonly injured nerve is CN6, with most cases caused by trauma and perioperative traction [2,13-16]. In addition, CSF leakage, CSF hygroma, face edema and traction, and wrong head position on the head rest may cause diplopia following spine surgery [2-9,17]. Fur-

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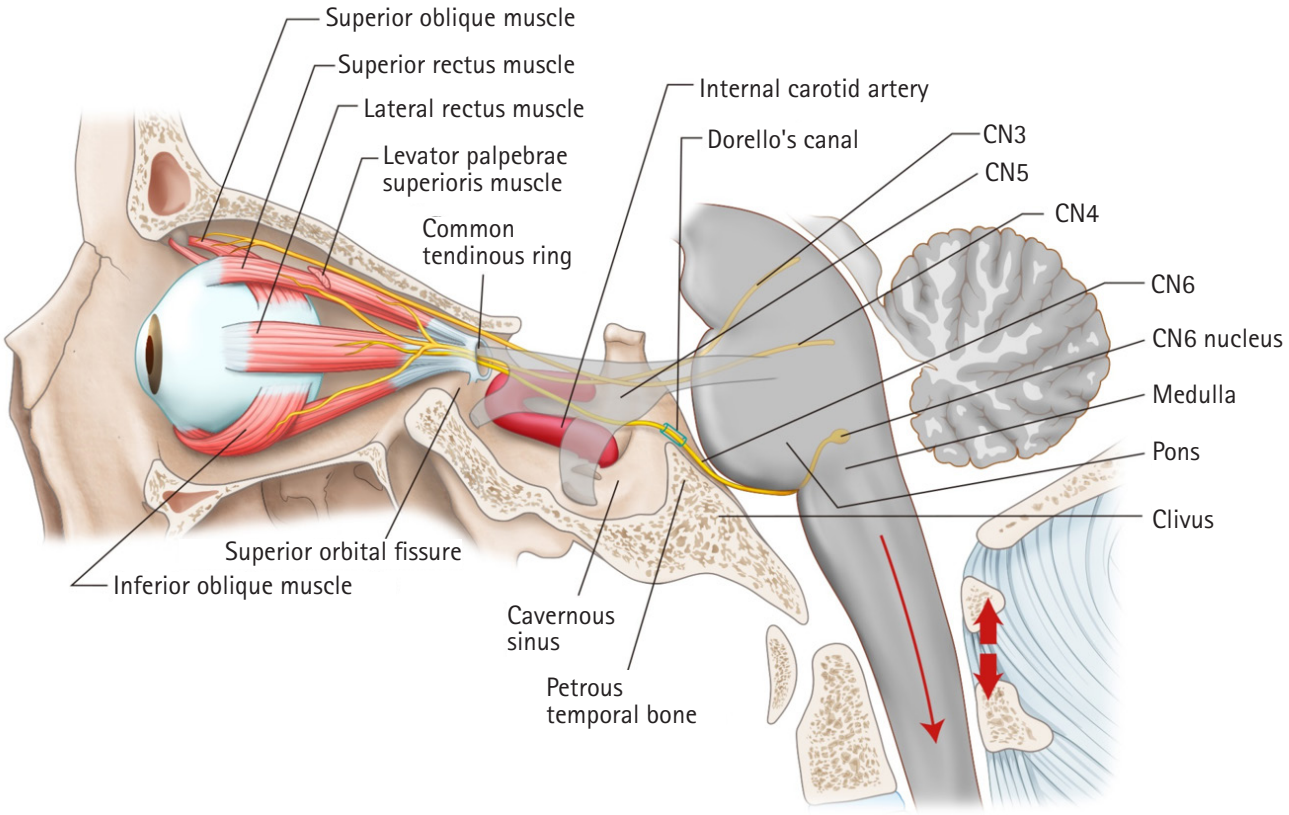

Fig. 2. Anatomy and mechanism by which CN6 palsy develops. The CN6 has a very long intracranial course, making this nerve particularly vulnerable to damage. Operative traction, hyperextension (thick arrows), and downward brain placement (thin arrow) can result in stretch injuries where the abducens nerve enters Dorello's canal. CN3, oculomotor nerve; CN4, trochlear nerve; CN5, trigeminal nerve; CN6 abducens nerve.

thermore, diplopia following spine surgery may indicate a life-threatening situation, which can be associated with subdural hematoma and transtentorial herniation [18]. Therefore, it is recommended to manage patients with diplopia following spine surgery with immediate ophthalmology and neurology consultations. If no pertinent issues are identified, occlusion therapy with patching or prism glasses is the first line of treatment. If there is no improvement after this non-surgical treatment, corrective eye surgery or a botulinum toxin injection into the lateral rectus muscle can be attempted [7]. However, these more invasive therapies are usually not needed, and conservative treatment improves diplopia because most patients spontaneously improve over time (Table 1) [2-9,15].

In conclusion, diplopia is a rare complication of spine surgery that can be caused by perioperative traction, CSF leakage, and facial edema and traction. Fortunately, these patients generally have a good prognosis because other neurologic complications such as perioperative visual loss generally do not occur, and most patients tend to make a full recovery. However, diplopia does require immediate ophthalmological examination, neurological evaluation, and careful observation because it may be a sign of a life-threatening condition, including subdural hematoma.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: JYK; Data curation: SJK, HK, YSL; Investigation and Visualization: SJK, HK; Validation: YSL; Writing-original draft: JYK, HK; Writing-review & editing: HK, JYK, YSL.

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Ultrasonographic and magnetic resonance images of a gluteus maximus tear

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The diagnosis of a gluteal muscle tear or strain is based on clinical findings. However, for an accurate diagnosis, imaging examinations are also needed. Herein, we describe the case of a patient with a gluteus maximus muscle tear confirmed by ultrasonography (US) and magnetic resonance imaging (MRI). A 58-year-old woman complained of dull pain in the left lateral gluteal region that she had been experiencing for 8 days. In the axial US image, retraction of the left gluteus maximus muscle was noted around its insertion site in the iliotibial band. On an MRI, a partial tear in the left gluteus maximus was observed at its insertion site in the left iliotibial band. In addition, fluid infiltration due to edema and hemorrhage was observed. A partial left gluteal muscle tear was diagnosed. The patient was treated with physical therapy at the involved region and oral analgesics. She reported relief from the pain after 1 month of treatment. Based on this experience, we recommend US or MRI for accurate diagnosis of muscle tear or strain.

Keywords: Magnetic resonance imaging; Pain; Skeletal muscle; Sprains and strains; Ultrasonography

Introduction

A gluteal muscle tear or strain frequently occurs during sports activities or while performing running or jumping activities. Its diagnosis is challenging and is often based on non-specific clinical findings [1,2]. In the current report, we describe the case of a patient with a gluteus maximus muscle tear that was confirmed by ultrasonography (US) and magnetic resonance imaging (MRI).

Case

This study was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: 2020-06-066). All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

A 58-year-old woman visited the Department of Physical Medicine and Rehabilitation in our hospital because of dull pain in the left lateral gluteal region that she had been experiencing for 8 days. The pain had started while she was hiking. The numeric rating scale (NRS) score was 8 out of 10. Prior to this event, she had no history of trauma, injury, or surgical operation on the gluteal or pelvic area. On physical examination, the pain was observed to be aggravated upon extension, abduction, and external rotation of the left hip. Deep palpation revealed tenderness along the left lateral gluteal region.

For the evaluation of the gluteal muscles with US (ACUSON S2000; Siemens Korea, Seoul, Korea), a 12-MHz linear probe was placed at the level of the lateral facet of the greater trochanter of the left femur. The axial US image showed a retracted left gluteus maximus muscle and an anechoic defect around its insertion site in the iliotibial band (Fig. 1). On an MRI, a partial tear in the left

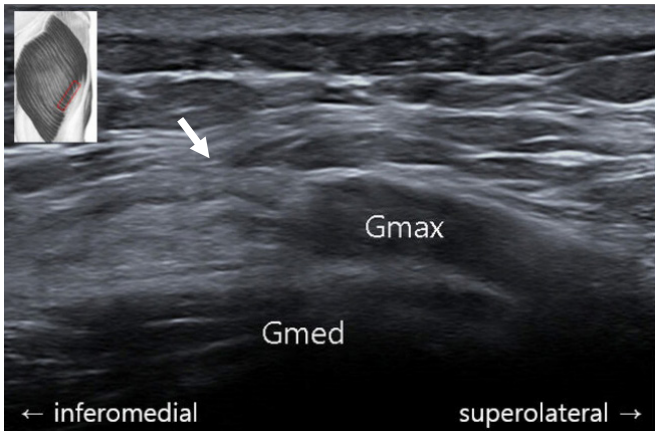

Fig. 1. Axial ultrasound image of the torn left gluteal muscles (arrow). Gmax, gluteus maximus; Gmed, gluteus medius.

gluteus maximus was observed at its insertion site in the left iliotibial band, suggesting grade 2 muscle strain (Fig. 2) [3]. At the area adjacent to the site of the tear, fluid infiltration due to edema and hemorrhage were also noted. No abnormal findings were observed in the left gluteus medius, gluteus minimus, and iliotibial band. Therefore, a partial left gluteal muscle tear was diagnosed. The patient was treated with physical therapy at the involved region and oral analgesics. She reported relief from the pain (NRS score, 2) after 1 month of treatment.

Discussion

This report describes a case in which a diagnosis of a gluteus maximus tear was confirmed with US and MRI. The gluteus maximus is the largest muscle in the gluteal region and plays an important

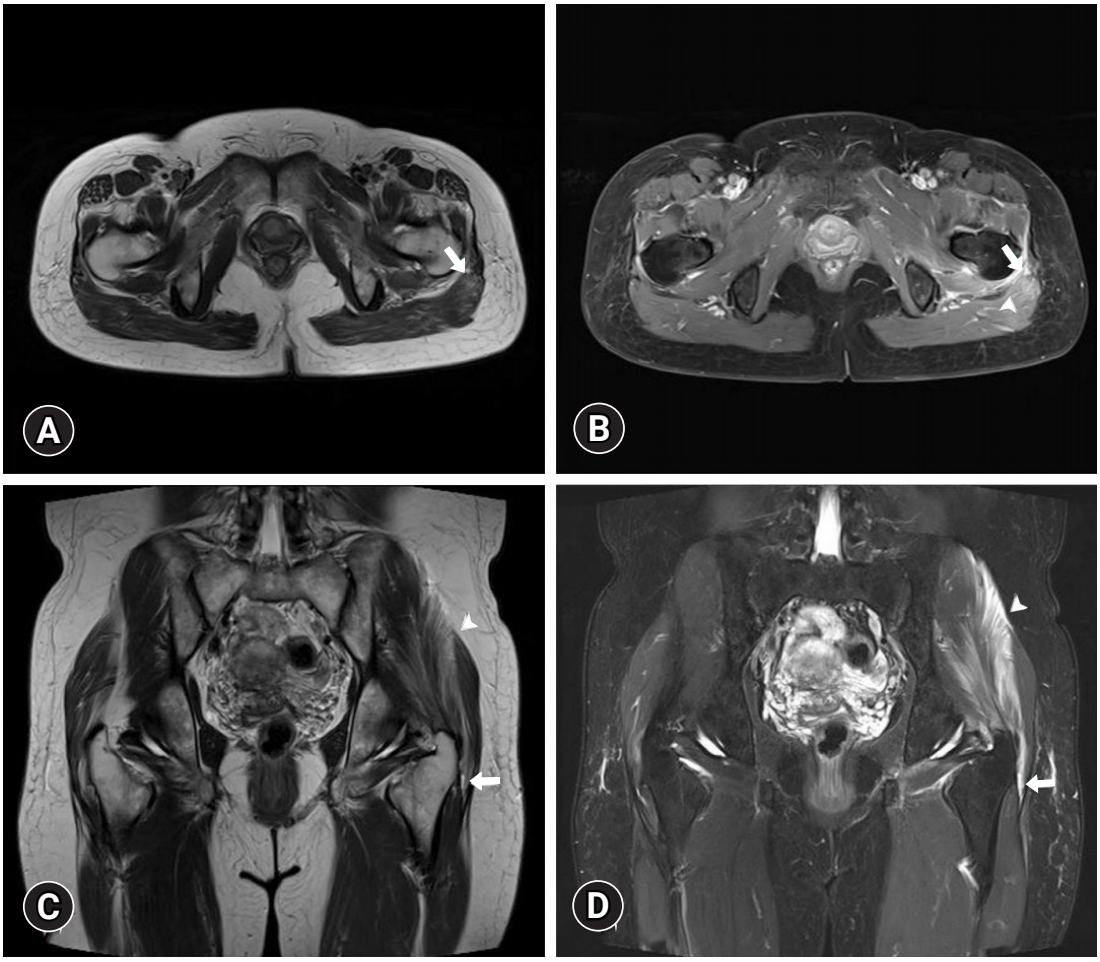

Fig. 2. (A, B) Axial T2- and gadolinium-enhanced fat-suppressed T1-weighted magnetic resonance images (MRIs) at the level of the lateral facet of the greater trochanter of the left femur. A partial tear of the left gluteus maximus muscle at its insertion site in the left iliotibial band is observed (arrows). Fluid infiltration around the site of the tear (arrowhead), suggesting edema or hemorrhage, is also observed. (C, D) Coronal T2- and fat-suppressed T2-weighted MRIs at the level of the lateral facet of the greater trochanter of the left femur. There is a partial tear at the myotendinous junction of the left gluteus maximus and iliotibial band (arrows) with intramuscular feathery fluid infiltration in the left gluteus maximus (arrowheads) suggesting grade 2 muscle strain.

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role in maintaining balance during standing, walking, or running by controlling the hip joint and thigh [4]. Dysfunction of this muscle due to strain limits an individual's daily activities. Clinically, a gluteal strain can be confused with several differential diagnoses, including hamstring strain, sciatic nerve lesion, gluteal tendinopathy, bony fracture in the pelvis, lumbar radiculopathy, lumbar facet pathology, and sacroiliac joint pathology. Therefore, a detailed evaluation is necessary for an accurate diagnosis.

Although clinical examination forms the basis of diagnosis for muscle strain, imaging evaluation is necessary to confirm the clinical diagnosis [1,2]. US and MRI are useful tools for determining the location and extent of the lesion and assessing possible compression of the surrounding structures [1]. US has merits in that it offers real-time images of soft tissues with great convenience. MRI is better in detecting pathological changes in soft tissue and bone and is useful for evaluating the pathology of deep muscles. The combined use of these two diagnostic tools facilitates an accurate diagnosis.

Based on the mechanism of injury, muscle injuries are classified into extrinsic and intrinsic injuries [1]. In the case reported herein, the gluteus maximus tear was not caused by extrinsic injury, and there were no contusions or penetration. Intrinsic injury is caused by contraction or elongation of the muscle, usually resulting in destruction of muscle fibers at the myotendinous junction [1]. In this patient, the gluteal muscle tear seemed to have occurred by intrinsic injury at the myotendinous junction between the gluteus maximus and the iliotibial band.

So far, US or MRI findings of gluteus maximus muscle tears have rarely been reported in the literature. Therefore, this report would be helpful for clinicians in diagnosing gluteus maximus muscle tears.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: JBK, MCC; Data curation, Formal analysis, Investigation, and Supervision: MCC; Methodology: JBK, WL, MCC; Visualization: WL, MCC; Writing-original draft: JBK; Writing-review & editing: MCC.

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A new type of oculocutaneous albinism with a novel *OCA2* mutation

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Oculocutaneous albinism (OCA) is a group of rare genetically heterogeneous disorders, characterized by hypopigmentation of the eyes, skin, and hair, which result in ocular abnormalities and a risk of developing skin cancer. Currently, there is no ophthalmologic procedure or drug that prevents the clinical features of OCA. Here, we report a new type of OCA in two, unrelated Korean families with the same *OCA2* mutation. Affected individuals in this study are different from those of previous reports in two aspects: an inheritance pattern and clinical presentation. All reported patients with OCA have shown an autosomal recessive inheritance pattern, while our patients showed an autosomal dominant inheritance pattern. Small amounts of pigment can be acquired with age in OCA, but there is no substantial variation from adolescence to adulthood in this regard. A case where the patient attained normal pigmentation levels has never been reported. However, our patients displayed completely normal pigmentation in their late twenties. Whole exome sequencing and *in-silico* analysis revealed a novel mutation, *OCA2* c.2338G>A p.(G780S) (NM_000275) with a high likelihood of pathogenicity. Sanger sequencing of p.G780S identified the same mutation in the affected individuals, which was not found in the family members with normal phenotype. We hypothesize that *OCA2* G780S not only acts as a pathogenic variant of OCA but also induces pigmentation by enhancing the melanogenesis gene expression of other modifier genes, such as *SLC45A2* and *TPC2*. These findings may provide further understanding of melanin biosynthesis and new treatment methods for OCA.

Keywords: Mutation; Oculocutaneous albinism; Whole exome sequencing

Introduction

Oculocutaneous albinism (OCA) is a group of rare genetically heterogeneous disorders. OCA is an autosomal recessive disorder associated with mutations in genes which control the biosynthesis of the melanin pigment [1]. The pigmentary system is dependent on the production of melanin, the light-absorbing biopolymer found within ocular, epidermal, and follicular melanocytes [2]. OCA is characterized by hypopigmentation of the eyes, skin and hair, which results in ocular abnormalities and a risk of developing skin cancer. All patients with OCA are accompanied by ocular abnormalities, such as nystagmus, reduced visual acuity, photophobia, strabismus, foveal hypoplasia, hypopigmentation of the iris, and color vision impairment [3]. Currently, there is no ophthalmologic

procedure or drug that prevents the clinical features of OCA. The clinical spectrum of OCA varies, ranging from mild hypomelanosis to complete lack of melanin production, which is mainly associated with tyrosine metabolism [4].

To-date, seven types of OCA (OCA1-7) have been identified, depending on a different genetic defect. *OCA2*, which is the most common type of albinism worldwide [5], is caused by pathogenic variants of *OCA2* gene [6]. The *OCA2* locus maps to chromosome 15q and is the human homolog of the mouse pink-eyed dilution gene encoding the P protein [7-9]. The mutation types causing *OCA2* are variable, including missense/nonsense single nucleotide variations (SNVs), splicing variations, small indels, and large indels. So far, 184 relevant mutations have been reported in Human Gene Mutation Database (HGMD, professional 2019.4). The most common *OCA2* mutation is a 2.7-kb deletion on exon 7, which is found in many affected individuals of sub-Saharan African descent [10]. Other *OCA2* mutations, including missense/nonsense SNVs and small deletions, are more common in other populations (https://ghr.nlm.nih.gov/gene/OCA2).

Prevalence of *OCA2* is approximately 1:38,000 to 1:40,000 in most populations throughout the world. The exception to this is the African population, in which the prevalence is estimated at 1:1,500 to 1:3,900 [10,11]. Here we report a new type of OCA in two unrelated Korean families with the same *OCA2* mutation.

Case

Participants were sourced from two, unrelated Korean families comprising four generations. This study was approved by the Institutional Review Board of the Kyungpook National University Hospital (IRB No: KNUH 2016-06-011). Written informed consents were obtained from the patient's parents for publication of this case report and accompanying images.

A 4-year-old Korean male patient came to seek medical attention for genetic diagnosis of albinism. The patient had ivory skin, medium blond hair, and light brown eyes (Fig. 1A). The father of the patient was also diagnosed with OCA when he was young (Fig. 1B). On ophthalmologic examination, best-corrected visual acuity (BCVA) was 20/50 for both eyes. He presented with esotropia and reduced stereoscopic vision. The iris was hypopigmented, but iris translucency was not evident on slit lamp examination. Fundus examination showed hypopigmented fundi (Fig. 1C). The patient was born with pale white skin and blond hair, both of which had acquired increased pigmentation with age. The color of his eyes, skin and hair gradually became darker and attained normal pigmentation in his late twenties. At the time of the visit, the father showed normal black hair and tan skin (Fig. 1A). The albinism showed an autosomal dominant inheritance pattern through the history of the family: the father, one of his aunts, grandfather, and great-grand mother (Fig. 1D).

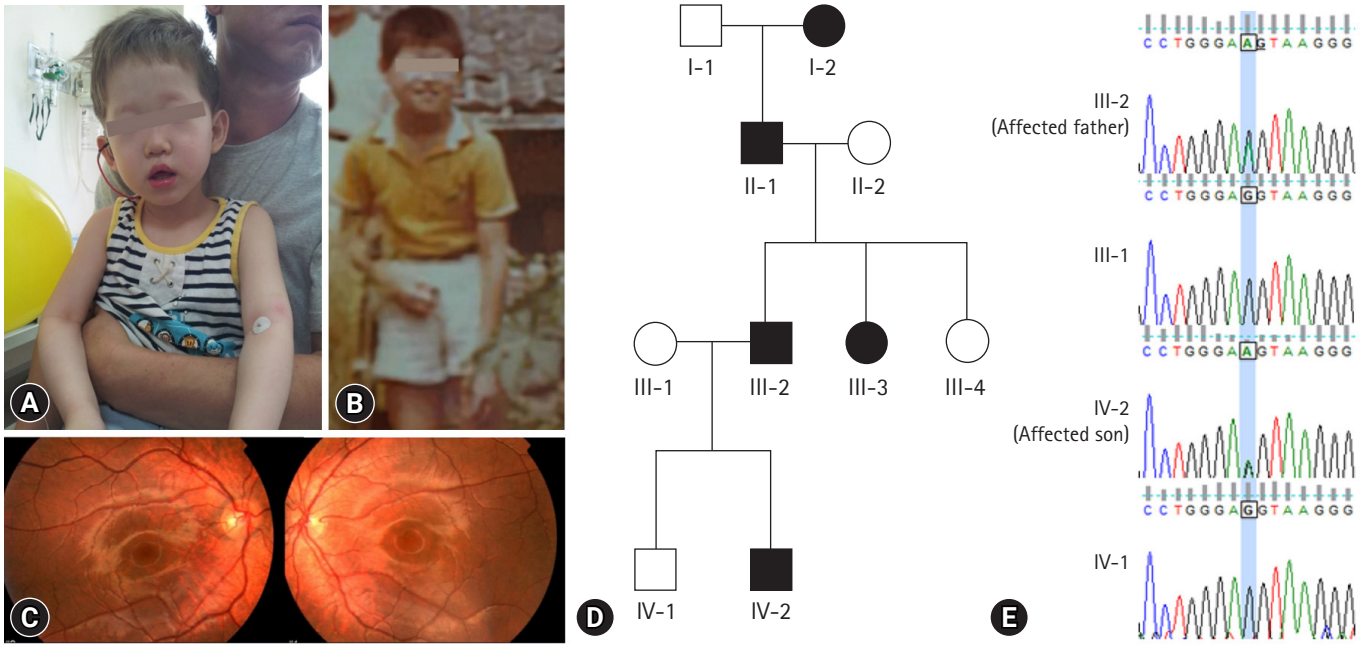

Fig. 1. (A) General appearance of the affected son and the affected father of the first family at the time of visit. (B) The father of the patient also had oculocutaneous albinism when he was young. (C) Hypopigmented fundi of the affected son. (D) The pedigree shows autosomal dominant inheritance. (E) Chromatograms of family members showing the same *OCA2* mutation in the affected individuals.

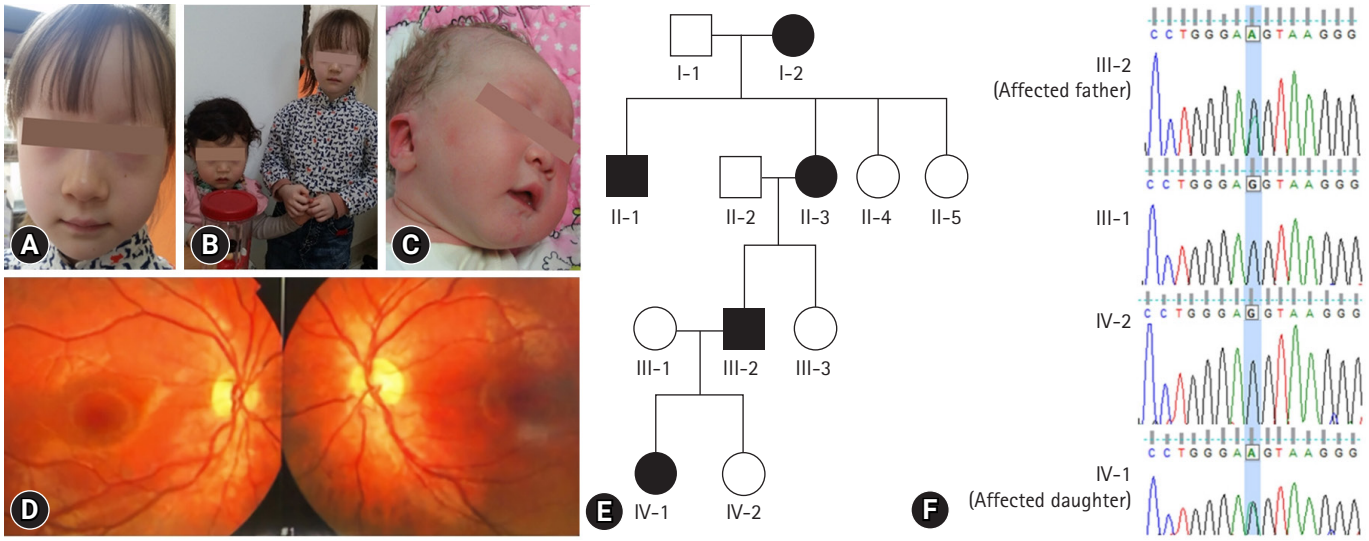

Fig. 2. (A) General appearance of the affected daughter at the time of visit. (B) General appearance of the affected daughter and her unaffected sister. (C) The affected daughter had pale white skin and blond hair when she was just born. (D) Hypopigmented fundi of the affected daughter. (E) The pedigree shows autosomal dominant inheritance. (F) Chromatograms of family members showing the same *OCA2* mutation in the affected individuals.

A 6-year-old Korean female patient was referred for evaluation of hypopigmentation. She had ivory skin, dark blond hair, and light brown eyes (Fig. 2A). Her younger sister had normal pigmentation (Fig. 2B). She had pale white skin and blond hair when she was born (Fig. 2C). On ophthalmologic examination, BCVA was 20/25 for both eyes and fundus examination showed hypopigmented fundi (Fig. 2D). A gradual increase in pigmentation was observed in the color of her eyes, skin and hair compared to the time of her birth. Similar to the father of the male patient described earlier, her father had OCA when he was young, the characteristics of which became darker and attained normal pigmentation in his late twenties. The albinism showed an autosomal dominant inheritance pattern through the father, grandmother, great-granduncle, and great-grandmother (Fig. 2E). The affected individuals had similar characteristics which displayed progressive darkening and completely normal pigmentation by their late twenties.

Whole exome sequencing and *in-silico* analysis revealed a novel mutation, *OCA2* c.2338G > A p.(G780S) (NM_000275). *In-silico* analysis was performed using bioinformatics software programs such as SIFT (http://sift.jcvi.org/), polyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), and phastCons score. Prediction results were deleterious (0.00) in SIFT and damaging (1.00) in polyPhen-2, indicating that the amino-acid substitutions have a high probability of pathogenicity. G780S was extremely conserved in multiple species with phastCons scores of 1.0, and has never been reported in the HGMD, HGMD Professional database, dbSNP, or the 1000 Genomes database with a minor allele frequency of 0. Sanger sequencing of p.G780S validated the same mutation in the affected individuals which was not identified in the family members with normal phenotype (Fig. 1E, 2F).

Discussion

OCA2 encodes a pigment cell-specific, 12-transmembrane domain protein with homology to ion permeases. G780S is located in one of the extracellular topological domains of *OCA2*. Several studies demonstrated the function of *OCA2* as a positive regulator of pH neutralization and melanogenesis promotion [12,13]. *TYR* is the key enzyme for melanogenesis which is solely dependent on neutral pH. Ion transport proteins such as *OCA2*, *SLC45A2*, and *TPC2* function together to promote *TYR* function in a so called "combinational function of ion transport proteins" for the maintenance of pH [14]. *OCA2* induces large outward Cl– conductance which is essential for maintaining neutral pH for melanosomes [14]. *SLC45A2* and *TPC2* act as modifier genes of *OCA2*. Modifier genes are defined as genes that affect the phenotypic properties of other genes. Genetic modifiers can affect penetrance, dominance, expressivity, and pleiotropy. The P protein is not composed of dimers and seems unlikely to have a dominant-negative effect. It might represent a gain-of-function due to other historical genetic factors of melanogenesis in these families.

Known pathogenic mutations of *OCA2* include V443I, P743L, and A481T. Patients with compound heterozygous mutations of V443I and P743L had severe *OCA2* phenotypes [15]. *OCA2* A481T has previously been reported to result in partial function of the P protein [15-17]. Melanin production gradually increased in

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patients with *OCA2* A481T during childhood, but no case had been reported where a patient attained normal pigmentation. The patients with *OCA2* A481T had a compound heterozygous pathogenic *OCA2* mutation in the other allele, and heterozygous carriers of *OCA2* A481T did not show hypopigmentation [18]. Most carriers are normally asymptomatic as pathologic mutation in one copy of the *OCA2* gene does not result in OCA. However, some individuals have been reported to have mild phenotypes, such as a small degree of iris transillumination, or hair and skin hypopigmentation in a heterozygous state [18]. In another study, carriers of N476D of *OCA2* presented with a mild hypopigmentation phenotype, which was particularly obvious at a young age [19].

Affected individuals in this study are different from those previously reported in two aspects: an inheritance pattern and clinical presentation. All reported patients with OCA to-date have shown an autosomal recessive inheritance pattern, while our patients showed an autosomal dominant inheritance pattern. There has never been a reported case of a patient who attained normal pigmentation, while our patients displayed completely normal pigmentation in their late twenties. Individuals with *OCA2* mutation can acquire small amounts of pigment with age, but this does not vary substantially from adolescence to adulthood [20].

In summary, we report a novel *OCA2* gene mutation found in two OCA families. We hypothesize that *OCA2* G780S not only acts as a pathogenic variant of OCA, but also induces pigmentation by enhancing melanogenesis gene expression of other modifier genes, such as *SLC45A2* and *TPC2*. These findings may provide further understanding of melanin biosynthesis and new treatments of OCA.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: SYL, EJL, JCB, SYK, SKH; Data curation: KMJ, SYK, SKH; Formal analysis: KMJ, SKH; Validation: SYL; Methodology, Resources: JCB; Investigation: SYL, EJL; Software: SYK; Supervision: SKH; Writing-original draft: SYL, EJL, SKH; Writing-review & editing: JCB, KMJ, SYK, SKH.

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Delayed treatment-free response after romiplostim discontinuation in pediatric chronic immune thrombocytopenia

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We report the case of a 16-month-old patient with chronic immune thrombocytopenia (ITP) patient who experienced delayed treatment-free response (TFR) after romiplostim treatment. He received intravenous immunoglobulin every month to maintain a platelet count above 20,000/μL for 2 years. Thereafter, he received rituximab and cyclosporine as second-line therapy, with no response, followed by romiplostim. After 4 weeks of treatment, the platelet count was maintained above 50,000/μL. Following 7 months of treatment, he discontinued romiplostim, and the platelet count decreased. His platelet counts remained above 50,000/μL, without any bleeding symptoms, 2 years after romiplostim discontinuation. This is the first report of TFR after romiplostim treatment in pediatric chronic ITP.

Keywords: Child; Immune thrombocytopenia; Idiopathic thrombocytopenic purpura; Romiplostim; Treatment-free response

Introduction

Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children [1]. Chronic ITP lasts for over 12 months after the initial diagnosis. Most patients with chronic ITP cannot achieve remission with conventional treatments (intravenous immunoglobulin [IVIG], corticosteroid, and anti-D immunoglobulin) or experience relapse after remission [2]. Thrombopoietin receptor agonists (TPO-RAs) such as romiplostim and eltrombopag are promising agents against chronic ITP in children and adults [3]. Romiplostim stimulates TPO receptors to increase platelet production in chronic ITP. Romiplostim is approved for use in adults and children [3]. Some patients experience a treatment-free response (TFR) after treatment with TPO-RA [4]. Here we report the case of a delayed TFR after romiplostim treatment in a pediatric patient with chronic ITP.

Case

This study was approved by the Institutional Review Board (IRB) of the Yeungnam University Medical Center (IRB No: 2019-12-024). Written informed consent was obtained from the parent/guardian for publication of this case report and accompanying images.

A 16-month-old boy presented with petechiae, bruises, and ecchymoses of the trunk and extremities. He was diagnosed with acute ITP and was treated with IVIG. He relapsed within a month and was tested for a secondary cause of ITP. The tests were performed to differentiate between viral infections and autoimmune diseases, which can cause secondary ITP. The laboratory findings

were as follows: white blood cell count, 17,980/μL (58% neutrophils); hemoglobin level, 14 g/dL; and platelet count, 3.000/μL. Kidney and liver function test results were unremarkable. Other laboratory findings were as follows: C-reactive protein level, 0.563 mg/dL (range, < 0.5 mg/dL); erythrocyte sedimentation rate, 22 mm/hour (range, 0–20 mm/hour); C3 level, 159.4 mg/dL (range, 90–180 mg/dL); C4 level, 28.2 mg/dL (range, 10–40 mg/dL); CH50 level, 40.8 U/mL (range, 23–46 U/mL); antinuclear antibody, negative; anti-Smith antibody, negative; antiplatelet antibody, negative; and venereal disease research laboratory test, non-reactive. In addition, the bone marrow showed increased numbers of megakaryocytes and non-platelet budding micro-megakaryocytes as well as increased cellularity. Therefore, he was diagnosed with primary ITP.

He was treated with IVIG (1 g/kg/day for 2 days) every 4 to 6 weeks for 2 years to maintain the platelet count above 20,000/μL. His platelet count showed a pattern of a temporary increase to over 100,000/μL after IVIG administration and then decreased to less than 10,000/μL after 2 to 3 weeks. Steroids such as dexamethasone and prednisolone had no effect on the platelet count, which was continuously less than 10,000/μL. Systemic bruising, petechiae, and mucocutaneous bleeding occurred repeatedly when the platelet levels dropped below 20,000/μL. Two years after diagnosis, he was treated with rituximab (375 mg/m^2/day for 4 weeks) and cyclosporine as second-line therapy, but he showed no response. The patient was treated with romiplostim (initial dose, 1 μg/kg/week) at 49 months (i.e., 33 months after diagnosis); the romiplostim dose was later increased to 10 μg/kg/week. Romiplostim was purchased through the Korea Orphan & Essential Drug Center (KOEDC) (Seoul, Korea). After 4 weeks of treatment, his platelet counts increased (Fig. 1). During the 7 months of romiplostim treatment, he showed no bleeding symptoms and required no additional IVIG or steroid treatment. No adverse effects of romiplostim such as headache, skeletal pain, abdominal pain, or thromboembolism were observed. After 7 months of romiplostim therapy, he discontinued romiplostim due to the economic burden, and his platelet count decreased again while he continued IVIG treatment. However, the frequency of annualized IVIG treatment gradually decreased after romiplostim treatment (Fig. 2).

Two years after romiplostim discontinuation, his platelet count remained above 50,000/μL, and he achieved TFR for over 36 months with no treatment. In addition, no bleeding symptoms were observed.

Discussion

ITP is an autoimmune-mediated acquired bleeding disorder characterized by isolated thrombocytopenia, which is defined as a peripheral blood platelet count below 100×10^3/μL, with no obvious initiating and/or underlying cause. ITP affects patients of all ages, genders, and races; age-specific incidence is the greatest in children and the elderly [5].

The mechanism underlying platelet count reduction in ITP

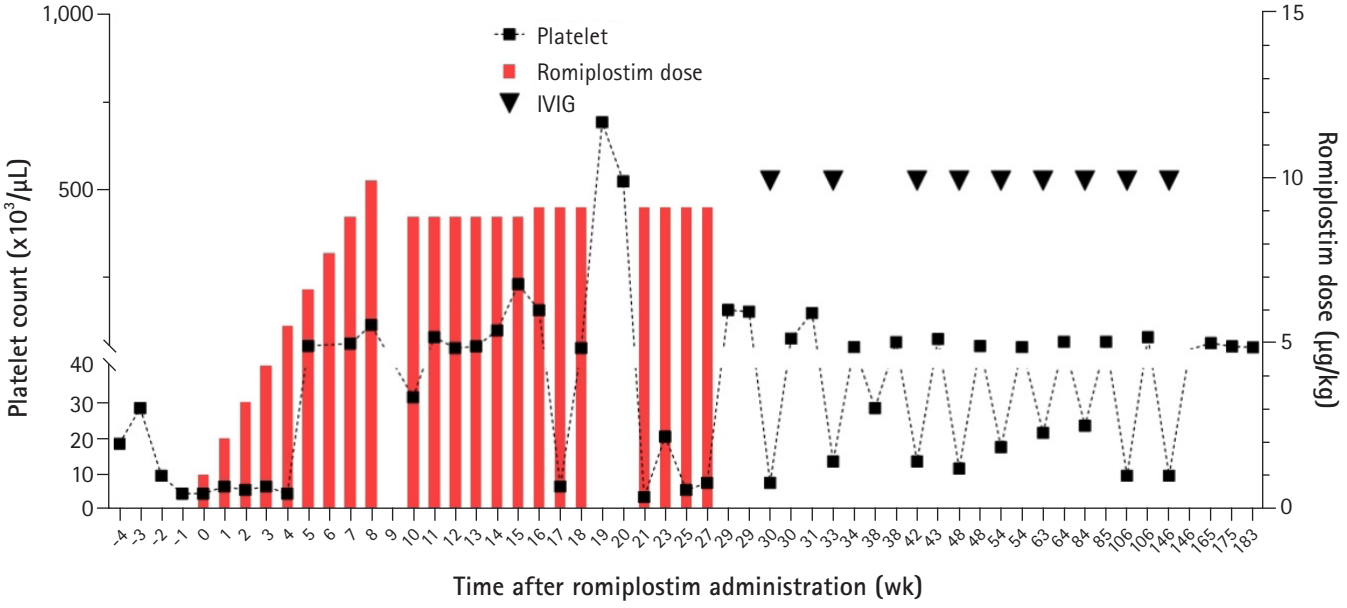

Fig. 1. Changes in the platelet count during romiplostim treatment. IVIG, intravenous immunoglobulin.

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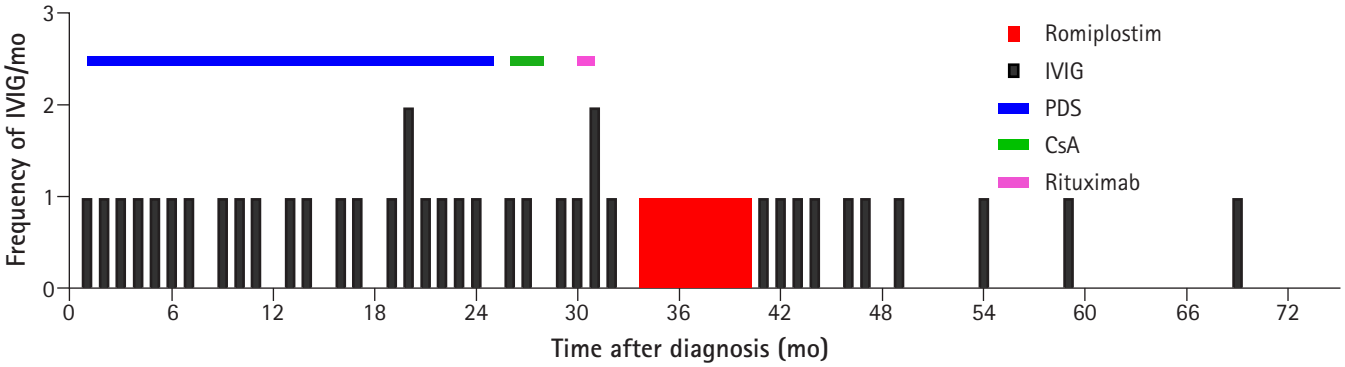

Fig. 2. Treatment course in a patient with chronic immune thrombocytopenia. The frequency of intravenous immunoglobulin (IVIG) administration was reduced after romiplostim treatment. Treatment included prednisone (PDS), IVIG, rituximab, oral cyclosporine (CsA), and romiplostim.

was previously considered to be due to increased platelet destruction by autoantibodies. However, it has recently been found that platelet count reduction in ITP occurs via more complicated mechanisms related to impaired platelet production and T cell-mediated effects [6,7]. ITP usually presents with bleeding, fatigue, thrombosis, and symptoms associated with disorders causing secondary ITP, such as systemic lupus, hepatitis C, infection, and lymphoid malignancy. Primary ITP is diagnosed by exclusion.

TPO is a 94-kDa protein primarily synthesized in the liver and secreted into circulation; it has no storage form. TPO and TPO mimetics reverse the apoptotic effects of antiplatelet/megakaryocyte antibodies (or local T cell inhibition) on late megakaryocyte progenitors, but not on the late megakaryocytes themselves because it takes 5 to 7 days before the platelet count increases in response to a TPO-RA [8].

The efficacy of romiplostim in 125 adult patients with ITP, including 63 splenectomized and 62 non-splenectomized patients, was assessed in a double-blind randomized controlled trial. The overall platelet response rate was 88% in non-splenectomized patients and 79% in splenectomized patients treated with romiplostim. In addition, 87% of patients who received romiplostim reduced or discontinued concurrent therapy. Thus, the study shows that stimulation of platelet production by romiplostim may provide a new therapeutic option for patients with ITP [8].

In a phase 3, randomized, double-blind, and placebo-controlled study of 62 children under 18 years treated for ITP, romiplostim increased platelet counts and improved health-related quality of life in children with primary ITP [4,9]. In a study of long-term treatment with romiplostim in children with chronic ITP, romiplostim increased and maintained platelet counts without significant toxicity for ≥ 6 months [10]. TFR was maintained in 23% of children for ≥ 6 months with no medication, including romiplostim. In that study, the factors predictive of spontaneous TFR in children with ITP included a higher platelet count at diagnosis (> 60,000/μL), younger age, recent onset (< 2 weeks) of bleeding symptoms, decreased bleeding in the first 6 months, and high-grade bleeding at diagnosis. In a multicenter Spanish adult study, receiving romiplostim as the first TPO-RA was positively associated with the likelihood of achieving TFR, while switching the TPO-RA negatively predicted TFR [11].

Our patient was diagnosed at a very young age and showed a good response to romiplostim; therefore, romiplostim was not switched to any other TPO-RA. Although his platelet levels decreased after romiplostim discontinuation, a delayed TFR was observed.

Although eltrombopag, another oral TPO, may be a better option when considering patient comfort, it was not recommended for use in children in Korea at the time. Romiplostim was supplied by the KOEDC; therefore, we used romiplostim first.

In conclusion, romiplostim is a potential treatment option for chronic ITP in children when considering the long-term complications of splenectomy, such as infection and thromboembolism after splenectomy. The possibility of TFR is high with romiplostim; therefore, romiplostim should be considered when choosing an alternative therapy in children with chronic ITP. Further studies with long-term follow-up are required to determine the efficacy of romiplostim and TPO-RA-associated TFR.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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High-grade mucoepidermoid carcinoma in the thyroid gland with poor prognosis

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Mucoepidermoid carcinoma (MEC) is the most common malignant neoplasm of the salivary gland, but primary thyroid MEC has rarely been reported and usually has a good prognosis. Herein, I report a case of thyroidal MEC with a poor prognosis in an 82-year-old woman with an anterior neck mass. Ultrasonography and computed tomography revealed a thyroid mass. The patient initially underwent fine-needle aspiration, was diagnosed with malignancy, and underwent a right lobectomy. On gross examination, a 4.0×3.6×2.6 cm-sized ill-defined, unencapsulated, and infiltrative tan to whitish mass with necrosis was identified. Microscopically, epidermoid tumor cell nests or solid sheets were identified. Mucous cells that were positive for periodic acid–Schiff and mucicarmine stains were also identified within epidermoid cell nests. Frequent mitosis and necrosis were observed. Immunohistochemical staining for p40 and p63 was positive, and that for thyroid transcription factor-1 and paired box gene 8 was focally positive. According to the Armed Forces Institute of Pathology grading system for salivary gland MEC, the current case was classified as high-grade MEC. After surgery, the patient suffered from dyspnea due to a remnant neck mass that compressed and obstructed the trachea; therefore, the patient refused further treatment. Thyroidal MECs are considered low-grade with a favorable prognosis, but there are several reported cases of thyroidal MEC with poor prognosis. The current case is a rare presentation of high-grade thyroidal MEC with a poor prognosis.

Keywords: Carcinoma; Mucoepidermoid carcinoma; Prognosis; Thyroid gland

Introduction

Mucoepidermoid carcinomas (MECs) are malignant neoplasms that mostly arise in the salivary gland [1], and also in the digestive tract, respiratory tract, pancreas, and breast [2]. In rare cases, MECs arise in the thyroid gland. MECs are classified as low-, intermediate-, or high-grade according to their histologic features [3], with most cases being classified as low-grade. However, only 49 MEC cases in the thyroid have been reported in the English literature, with nine cases having a poor prognosis [4].

Herein, I present the case of a high-grade MEC in the thyroid of an 82-year-old woman with a poor prognosis.

Case

This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No: DSMC 2021-01-041), and the need for informed consent was waived.

An 82-year-old woman visited our hospital because of a right anterior neck mass that persisted for a month. She had undergone a left lobectomy of the thyroid gland approximately 30 years ago at an outside hospital because of unknown causes. On ultrasonography, a 4.5 cm hypoechoic mass was identified in the right thyroid gland. On computed tomography, the mass showed as a hypodense lesion with peripheral enhancement (Fig. 1).

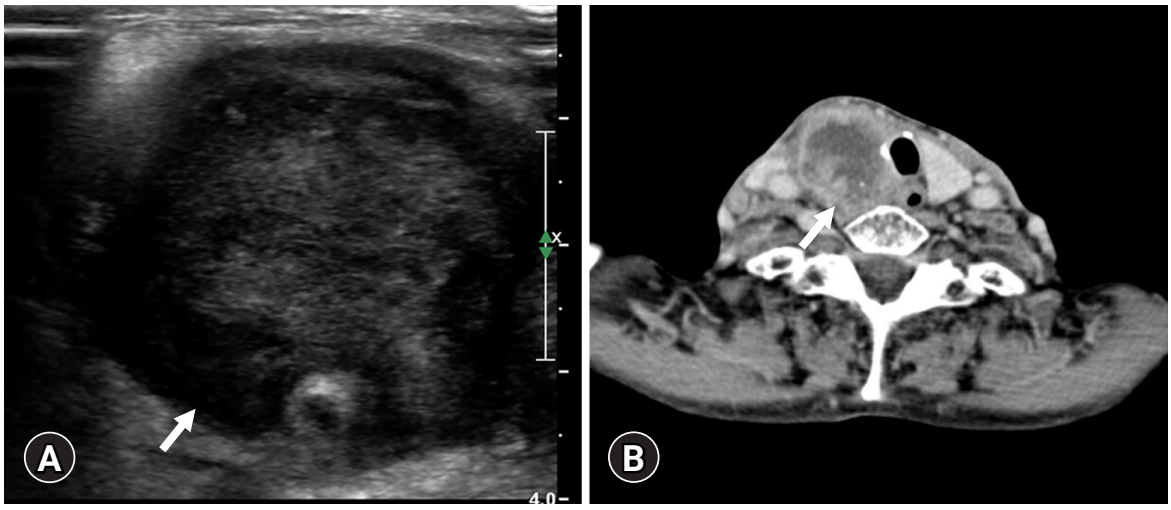

Fig. 1. Radiological findings. (A) A 4.5 cm-sized hypoechoic mass (arrow) on ultrasonography and (B) a hypoechoic mass (arrow) with peripheral enhancement on computed tomography.

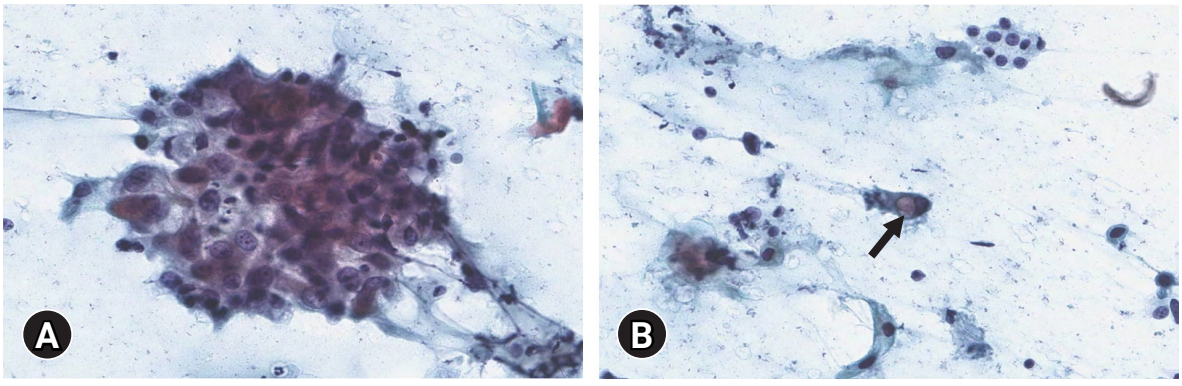

Fig. 2. Cytological findings. (A) Polygonal-shaped atypical cell clusters with high nuclear-cytoplasmic ratio and prominent nucleoli are seen (Papanicolaou stain, ×400). (B) Scattered single cells with intracytoplasmic vacuole (arrow) are identified (Papanicolaou stain, ×400).

The patient initially underwent fine-needle aspiration of the right thyroid mass. The smear showed atypical cell clusters and scattered single cells with a dirty inflammatory background. The atypical cells were polygonal-shaped. The nuclear-cytoplasmic ratio was high, and prominent nucleoli were observed. Some scattered single cells with intracytoplasmic vacuoles were identified as signet ring cells (Fig. 2). These cytologic features strongly implied malignancy.

Two weeks later, the patient underwent right lobectomy with selective neck dissection for right level IV lymph nodes. In the surgical field, the right thyroid mass was adhered to the surrounding tissue and invaded the trachea; hence, the mass could not be completely removed.

On gross examination, a 4.0×3.6×2.6 cm-sized ill-defined, unencapsulated, and infiltrative tan to whitish mass was identified.

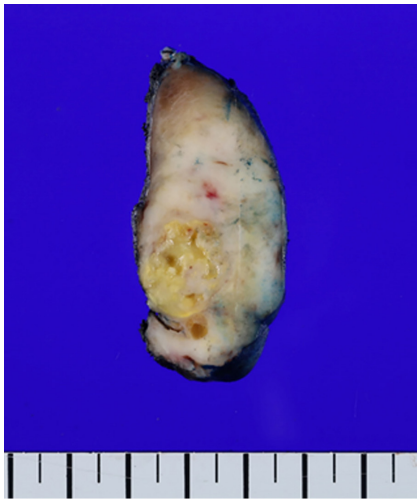

Fig. 3. Gross findings. A 4.0×3.6×2.6 cm-sized ill-defined infiltrative tan to whitish mass with necrosis is present.

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Necrosis was also observed in the mass (Fig. 3). The remaining thyroid gland parenchyma was unremarkable. All of the right thyroid mass was made into formalin-fixed, paraffin-embedded blocks.

Microscopically, the right thyroid mass was composed of large irregular nests or solid sheets of tumor cells surrounded by fibrotic stroma with necrosis. The tumor cell populations consisted predominantly of polygonal epidermoid cells with abundant amphophilic cytoplasm and large nuclei having prominent nucleoli. Keratin pearls were also identified in epidermoid cell nests. Mitoses were frequently observed as up to 25 per 10 high-power fields (HPFs). Individually vacuolated cells were present within epidermoid cell nests. Special stains, periodic acid–Schiff and mucicarmine, demonstrated mucin globules in vacuolated cells (Fig. 4). There was no evidence of well-differentiated thyroid carcinomas, such as papillary thyroid carcinoma, follicular thyroid carcinoma, or medullary thyroid carcinoma. In addition, there were no anaplastic features on any of the slides.

Immunohistochemical staining for p40, p63, thyroid transcription factor-1 (TTF-1), and paired box gene 8 (PAX8) was performed. The epidermoid cells were positive for p40 and p63 and were focally positive for TTF-1 and PAX8 (Fig. 5). These histologic findings and immunohistochemical staining results were consistent with the diagnosis of thyroidal MEC. Metastatic carcinoma with perinodal extension was also revealed in one out of seven right level IV lymph nodes.

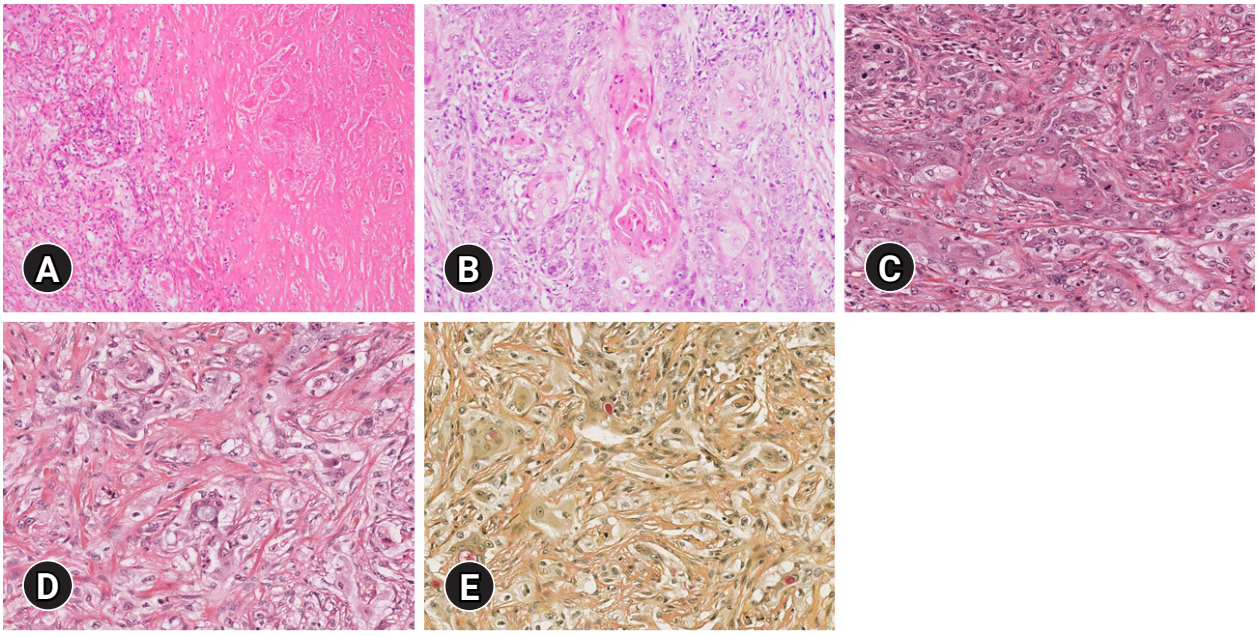

Fig. 4. Histological findings. (A) Large irregular nests or solid sheets of tumor cells surrounded by fibrotic stroma with necrosis are identified (hematoxylin and eosin [H&E] stain, ×100). (B) The epidermoid cells have prominent nucleoli and keratin pearl formation (H&E stain, ×200). (C) Mitoses are frequently identified (H&E stain, ×400). (D) Vacuolated cells are located within epidermoid cells (H&E stain, ×400). (E) Mucicarmine stain highlights intracytoplasmic mucin droplets (mucicarmine stain, ×400).

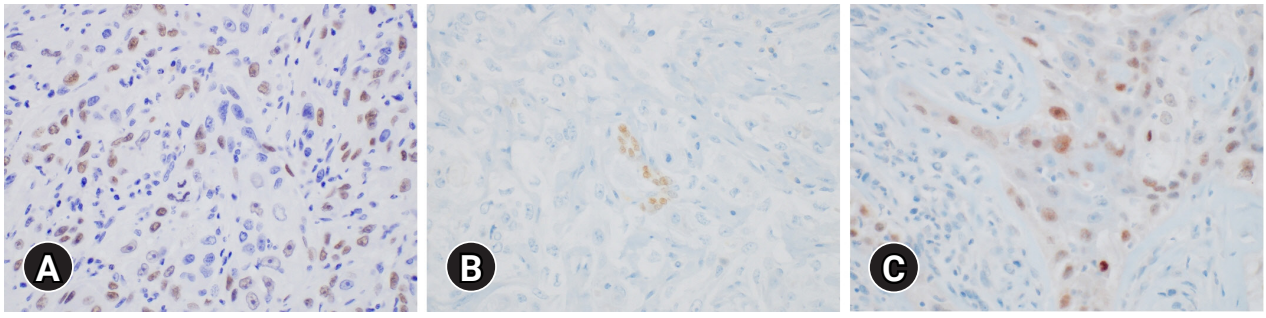

Fig. 5. Immunohistochemical results. The epidermoid cells are diffusely positive for (A) p63 and focally positive for (B) thyroid transcription factor-1 and (C) paired box gene 8 (immunohistochemical stain, x400).

Radiation therapy for residual tumors was planned as a further treatment for the patient. However, 1 month after surgery, the patient visited our emergency room for dyspnea due to a cystic right neck mass that compressed and obstructed the trachea. The patient refused further adjuvant therapy and was transferred to an outside hospital.

Discussion

MEC is a malignant epithelial neoplasm composed of epidermoid, mucous, intermediate, columnar, and clear cells that often demonstrate prominent cystic growth [5]. MECs are most commonly encountered as malignant neoplasms of salivary glands [6]. MECs also arise in the bronchus, breast, esophagus, and pancreas [7], and are thought to originate from intermediate cells that differentiate into epidermoid, mucous, and clear cells [5]. On immunohistochemical staining, epidermoid cells are positive for p63, p40, and cytokeratin 5/6. Therefore, these are useful markers for MECs [8].

MECs in salivary glands are graded as low-, intermediate-, and high-grade based on morphological and cytological features. Prominent cystic components are the hallmark of low-grade MEC, and mucous cells are more frequently identified in low-grade MECs than in intermediate- and high-grade MECs [5]. In the Armed Forces Institute of Pathology (AFIP) grading system, high-grade features include a low proportion (less than 20%) of intracystic components, neural invasion, necrosis, mitotic figures, and anaplasia. A quantitative AFIP grading system was used based on the scores for each of the five histopathological features. Tumors with a score of 0 to 4 were considered low-grade, a score of 5 or 6 was intermediate-grade, and a score of 7 to 14 was considered high-grade [3]. The prognosis of high-grade MECs is very poor compared to that of intermediate- and low-grade MECs. The overall survival and disease-free survival of high-grade MECs are approximately 50%, compared to approximately 90% of intermediate- and low-grade MECs [9].

In the thyroid, MECs are rare malignant neoplasms, accounting for 0.5% of thyroid malignancies, with approximately 49 cases reported in the English literature [4]. Patients are aged 10 to 91 years and predominantly female [1]. The origin of MECs in the thyroid gland is unclear; however, thyroid follicular epithelium [10] or solid cell nests [11] are regarded as suspicious candidates. Some authors have proposed that MECs can arise from metaplastic dedifferentiation of papillary thyroid carcinoma, follicular thyroid carcinoma, or oncocytic carcinoma [7]. The microscopic findings of MEC in the thyroid gland are similar to those in the salivary gland. Intermingled epidermoid and mucous cells are arranged in cords, nests, or solid sheets in the fibrotic stroma. Epidermoid cells have intercellular bridges and undergo keratinization. The mucous cells have abundant foamy to clear or vacuolated cytoplasm and exhibit a peripherally displaced nucleus. The foamy to clear cytoplasm is positive for periodic acid–Schiff and mucicarmine stains [12]. Mitosis and necrosis are rare. Unlike the salivary gland, a grading system for thyroidal MEC has not yet been established. MECs in the thyroid are generally considered low-grade malignancies and have a favorable prognosis. However, poor prognostic cases of MECs have also been reported [4].

In the current case, the tumor had large irregular nests or solid sheets of tumor cells surrounded by fibrotic stroma. The tumor was composed of epidermoid cells with prominent nucleoli, keratin pearls, and vacuolated mucous cells. Necrosis and frequent mitoses were also identified. Based on the AFIP grading system [3], the score of the current case was eight (Table 1) and was therefore classified as high-grade. The patient's hospital course matched the tumor grade. As previously described, MECs in the thyroid may be associated with well-differentiated thyroid tumors [7]; however, in the current case, there was no evidence of a well-differentiated thyroid tumor on any of the slides.

The differential diagnosis of high-grade MEC includes poorly differentiated thyroid carcinoma (PDTC), anaplastic thyroid carcinoma (ATC), sclerosing MEC with eosinophilia (SMECE), and squamous cell carcinoma (SCC). PDTC is a rare follicular cell-derived thyroid tumor with limited evidence of thyroid follicular differentiation. Histologically, PDTC is a solid, trabecular, and insular growth pattern with convoluted nuclei, increased mitotic activity (three or more mitoses per 10 HPFs), and coagulative tumor necrosis. No mucous cells are observed in PDTC. Immunohistochemically, PDTC is positive for TTF-1 and PAX8 but negative for p63 and p40 [13]. ATC is a highly aggressive thyroid malignancy that is composed of undifferentiated thyroid follicular cells. Histo-

Table 1. The point score and grade of present case according to Armed Forces Institute of Pathology (AFIP) grading system for mucoepidermoid carcinoma

AFIP grading system	Current case
Histologic parameter (point value)	
Intracystic component < 20% (2)	Yes
Neural invasion present (2)	No
Necrosis present (3)	Yes
Mitosis, 4 or more per 10 high-power fields (3)	Yes
Anaplasia present (4)	No
Total point score	8
Tumor grade (point score)	
Low (0–4)	
Intermediate (5–6)	
High (7–14)	Yes

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logically, ATC is composed of sarcomatoid spindle cells and giant cells that are morphologically indistinguishable from sarcomas. Immunohistochemically, ATC is positive for PAX8 but negative for TTF-1, p63, and p40 [14]. SMECE is a rare thyroid tumor derived from the metaplastic squamous epithelium or solid cell nests. The histologic findings of SMECE include squamous and mucus-secreting cells within a fibrohyaline stroma and eosinophilic infiltrates in the background of Hashimoto thyroiditis [15]. SCC of the thyroid gland is an extremely rare thyroid tumor composed entirely of tumor cells with squamous differentiation without mucous cells [16].

Initially, fine-needle aspiration cytology revealed polygonal-shaped malignant squamoid cells. The differential diagnosis of the current case included MEC, ATC, diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC), and carcinoma showing thymus-like differentiation (CASTLE). In ATC, the smear shows markedly anaplastic, spindle, or squamoid cells with marked nuclear pleomorphism. In DSVPTC, the smear shows cohesive epithelial cell clusters composed of squamoid cells with classic papillary thyroid carcinoma features [17]. In CASTLE, a single epithelial cell with three-dimensional fragments of cohesive epithelioid cells with squamoid and basaloid features is observed [18]. In the current case, vacuolated cells were observed. Also, classic papillary thyroid carcinoma features were not identified.

Thyroidal MEC is a rare malignant neoplasm, with only 49 reported cases to date [4]. Commonly, this rare malignant tumor is considered low-grade, but several cases with poor outcomes have also been reported [1,4]. Herein, a very rare case of primary thyroid high-grade MEC with a poor prognosis has been described.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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YUJM reviews all manuscripts received. A manuscript is previewed for its format and academic relevancy, and then rejected or sent to the 2 (or more) relevant investigators available for review of the contents. The editor selects peer referees by recommendation of the editorial board members or from the board's specialist database. The identities of the reviewers and authors will not be revealed (double blinded review). All the radiologic images and pathologic (microscopic) images are reviewed by radiologist or pathologist for appropriateness. A manuscript containing statistical analysis will be reviewed by a statistical editor.

Upon completion of the review, authors will receive notification of the Editor's decision by e-mail with comments offered by the reviewers. Revised manuscripts must be submitted within 3 months of the date on the decision letter.

Acceptance of manuscripts is based on many factors, including the importance, originality, and priority of the research. Acceptance of the manuscript is decided based on the critiques and recommended decision of the referees. A referee may recommend "accept", "minor revision", "major revision", or "reject." If there is a marked discrepancy in the decisions between two referees or between the opinions of the author and referee(s), the editor may send the manuscript to another referee for additional comments and a recommended decision. The reviewed manuscripts are returned back to the corresponding author with comments and recommended revisions. Names and decisions of the referees are masked. A final editor's decision on acceptance or rejection for publication is forwarded to the corresponding author from the editorial office.

The usual reasons for rejection are topics that are too specific and target audience that is too limited, insufficient originality, serious scientific flaws, poor quality of illustrations, or absence of a message that might be important to readers. Rarity of a disease condition is itself not an acceptable justification for a case report. The peer review process takes usually 2–4 weeks after the manuscript submission.

Revisions are usually requested to take account of criticisms and comments made by referees. The revised manuscript should be resubmitted via the web system. Failure to resubmit the revised manuscript within 2 months without any notice from the corresponding author is regarded as a withdrawal. The corresponding author must indicate clearly what alterations have been made in response to the referee's comments point by point. Acceptable reasons should be given for noncompliance with any recommendation of the referees.

If the author disagrees with the editorial board's decision, he or she can apply for an objection through individual contact (e-mail, etc.).

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Manuscript preparation

Review article

Review articles are usually solicited by the Editor-in-Chief. However, unsolicited Reviews will be also considered. Authors should contact the Editor-in-Chief in advance to determine the appropriateness of their review articles for publication. All Review articles will undergo peer review. An abstract is required whereas Materials and methods section and a Results section are not required (no more than 250 words). The length of review articles is limited to 5,000-8,000 words with a maximum of 100 references. Also, there should be no more than 3 authors.

Original article

Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Materials and methods, Results, Discussion, References (no more than 30), and tables and/or illustrations.

1) Title page

The tile page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list (first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

2) Abstract

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) Keywords

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) Text

The text of manuscripts must have the following sections: Introduction, Materials and methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

Introduction

This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

Materials and methods

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer's name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results

This should include a concise textual description of the data presented in tables and figures.

Discussion

This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References

References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading "References," and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed." (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles

List all authors when six or less; when seven or more, list the first six and add et al.

Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.

Book

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Luzikov VN. Mitochondrial biogenesis and breakdown. Galkin AV, translator; Roodyn DB, editor. New York: Consultants Bureau; 1985. p. 362

Book chapter

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Web resources

Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

5) Tables

Tables should fit within a single page. The Table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

6) Illustrations

Figures must be cited consecutively using Arabic numerals. Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient's photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the YUJM website (https://www.e-yujm.org/authors/ethics.php) including each patient's signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations

Typed legends that use double-spacing should start on a separate page with Arabic numerals corresponding to the Tables or Illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the Tables or Illustrations, they should be individually identified and explained clearly in the legend.

8) Abbreviations

Authors should limit the use of abbreviations to an absolute minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report

Case reports should consist of an Abstract, Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors. The abstract should be concisely written (no more than 250 words).

Communications

Although communication articles are not limited in the format, they should contain a self-standing abstract and references. The abstract should be concisely written and not exceed 250 words.

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ing author to ensure that all of the authors concerned are aware of and agree to the change in authorship. The YUJM has no responsibility for such changes.

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Research and publication ethics

Enactment May 22, 2012

Research ethics

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports, state whether informed consents were obtained from the study participants. The editor of YUJM may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The YUJM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

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Authorship

Each author is expected to have made substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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- Formal analysis
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- Project administration
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Registration of the clinical trial research

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered to the primary registry to be prior publication. YUJM accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall be published at the end of the abstract.

Data sharing statement

YUJM accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

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