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# Darwinian Selection in Prostate Cancer and Medical Treatment

Chunjiao Song

Medical Research Center, Shaoxing People's Hospital/Shaoxing Hospital of Zhejiang University, Shaoxing, China

Email: chunjiaosong@163.com

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## Abstract

Organisms evolved into different species to adapt to the environment according to the laws of Darwinian evolution. In a single life, prostate cancer cells can also evolve into tumor stem cells to adapt to the microenvironment, such as different chemotherapeutic drugs. These cancer cells become an unrestricted growth group relatively independent of the individual. The present review attempts to establish evidence that prostate cancer cells may survive by hormonotherapy and chemotherapy by gene amplification, mutation, and alternative splicing. Simultaneously, novel treatment strategies have been cited and evaluated, avoiding the resistance mechanisms.

## Keywords

Prostate Cancer, Androgen Receptor, Tumor Microenvironment, Darwinian Selection

## 1. Introduction

In Europe and the USA, prostate cancer (PCa) is one of the most common malignant tumors and the second leading cause of cancer-related deaths in men. PCa is primarily an androgen-dependent tumor that is treated using androgen deprivation therapy (ADT). The androgen receptor (AR) is a key driver molecule leading to the occurrence and progression of PCa, even in the stage of castration-resistant PCa (CRPC). The AR is a multi-domain, ligand-inducible nuclear transcription factor encoded at Xq11-Xq12. It is encoded by eight exons and has four structural domains: the N-terminal transcriptional activation domain (exon 1), the DNA-binding domain (DBD) (exons 2 - 3), a hinge region (exons 3 - 4), and the C-terminal ligand-binding domain (LBD) (exons 4 - 8). The AR may be activated by androgen through binding to LBD of the receptor, then the AR is internalized to the nucleus and interacts with target genes through its conserved DBD binding to androgen-responsive elements (ARE).

Moreover, AR complex regulates the transcription of its target genes with the help of coactivator and corepressor proteins.

The AR signaling axis (Figure 1, from WikiPathways) is the core of all stages of the PCa pathophysiology and serves as the primary target for endocrine-based therapy [1]. The current treatments for PCa involve inhibitors of androgen production and antiandrogens blocking the interaction between ligands with AR-LBD [2].

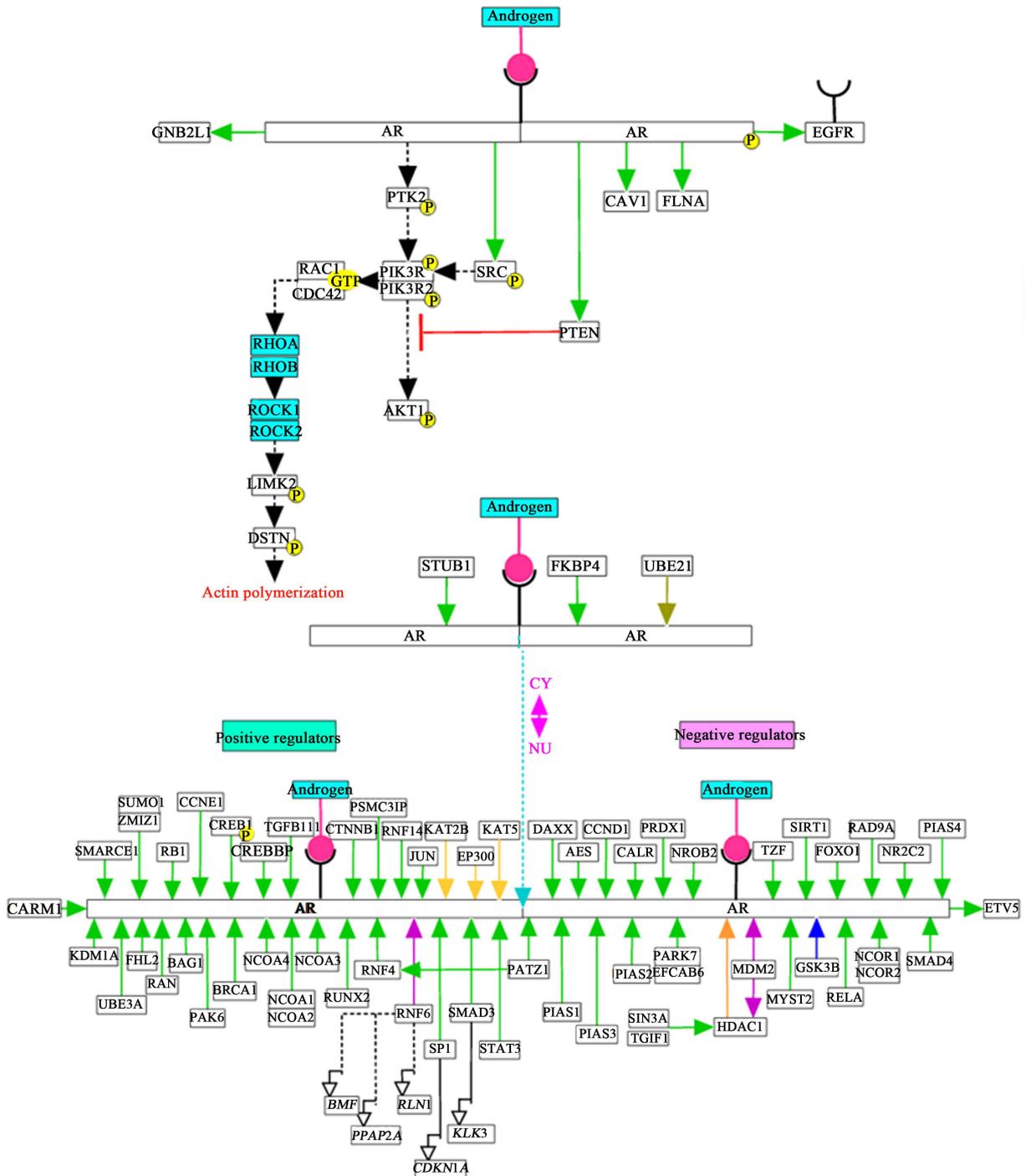


Figure 1. Androgen receptor signaling pathways (Homo sapiens) from WikiPathways.

## 2. Darwinian Selection in the Therapies for Prostate Cancer

“Natural selection, survival of the fittest” dogma states that species evolve and develop from junior to senior, from simple to complex, from less to more through heredity, mutation, and natural selection. The principal mechanism of evolution, natural selection, has been confirmed by several observations and experiments. Natural selection is an adaptive evolution, *i.e.*, if the variation of species is suitable for the changing environment, then the species will emerge victorious in the struggle for survival; however, if the variation of species is unsuitable for the survival conditions, then it tends to perish.

Darwin’s natural selection mainly refers to organisms in the natural world. Nevertheless, the survival mechanism also exists in an independent individual, and similar to Darwin’s theory, it constantly affects human health and life, for example, the disposition between PCa and clinical treatments. Although ADT is originally effective in the most PCa patients, the effectiveness is short-lived. Most PCas will progress to the lethal castration-resistant and metastatic phenotype. Genomic alteration, clonal selection, and evolution of the tumor microenvironment will contribute towards unique physiological characteristics under selection pressure. These pressures contain the chemotherapeutic drugs applied in the clinical setting, and the exposures of PCa cells to hormonal stimuli in the tumor microenvironment. AR is a key driver molecule to take part in PCa development and progression, response to initial ADT, and subsequent resistance to chemotherapeutics. These malignant cells undergo several adaptive changes to ensure persistent androgen signaling.

For a long time, docetaxel was the only drug to treat CRPC. Recently, new drugs for CRPC based on different mechanisms have become available, including CYP17A1 inhibitors reducing androgen production and antiandrogens targeting AR signaling. Scientists have found two types of antiandrogens, including the steroidal antiandrogens and the non-steroidal antiandrogens. Among them, the steroidal antiandrogens are limited in clinical use because of their severe side effects and low efficacy. While the non-steroidal antiandrogens include the first-generation antiandrogens: nilutamide, bicalutamide, flutamide, and the second-generation: enzalutamide and ARN509, etc. These non-steroidal antiandrogens have been widely used clinically due to avoiding the constraints of the steroidal antiandrogens. However, after an initial effective response, approximately 50% of the PCa patients recurred under the treatment of antiandrogens [3].

Several major resistance pathways focus on androgen signaling, including AR overexpression and amplification, expression of AR mutants inducing promiscuity, response to non-androgen ligands, and constitutively active AR splice variants (AR-Vs) with ligand-independent activity. Intratumoral de novo biosynthesis of androgen and conversion of weak adrenal androgen into strong dihydrotestosterone (DHT) may also contribute to ligand-dependent AR activation.

### 2.1. AR Amplification, Mutants, and Variants

One of the most common events observed in PCa progressing from hormone-

sensitive to castration-resistant form is AR gene amplification, occurring in 45% [4]. In addition, a correlation between elevated expression of full-length AR or AR copy number gains resistant to second-generation antiandrogens has been documented [5]. This could be explained by an adaptive pharmacokinetic change, in which, the androgen is unable to achieve sufficient concentrations within the tumor, and thus, the increased intratumoral steroidogenesis overcomes the inhibitory effects of antiandrogens [6].

The mutations of AR are rare in untreated PCa patients and take place in approximately 15% of CRPC patients. Notably, the mutations of AR in PCa under the therapeutic pressure are responsible for such phenomena that conversion of the antiandrogens into AR agonists and progress of the early PCa to its lethal state, CRPC. **Table 1** shows the confirmed AR mutants and the related drug resistance.

Over the last few years, along with AR mutations, constitutively active AR splice variants also promote the progression of PCa. As shown in **Figure 2**, Lu *et al.* decoded the AR splice variant transcripts [7]. Among them, two most common AR-Vs, AR-V7 and AR-v567es, were detected in 67.53% and 29.87% of CRPC samples, respectively [8]. AR-V7 lacking the AR LBD still retains the ability to activate transcriptions of its target genes. Antonarakis *et al.* found that AR-V7 conferred resistance to abiraterone and enzalutamide in metastatic CRPC, not to taxane [4] and cabazitaxel [9]. Constant expression of AR-v567es in the benign prostate tissues may induce epithelial hyperplasia and invasive adenocarcinoma [10].

## 2.2. Tumor Microenvironment

In hormone-sensitive, localized PCa, intraprostatic androgen has been found to categorize by ~75% after the initial treatment, with residual androgen sufficient to drive the transcriptions of AR target genes [11]. However, in castration-resistant tumors, the elevated tumor androgen is characterized by the capability to activate the expression of AR and its target genes, by steroid synthesis, enzyme alterations that may increase de novo androgen level, or by the absorption of circulating hormone substrates and adrenal androgens into the tumor microenvironment [4] [12].

## 3. New Drugs

AR is encoded by the most complex gene in the nuclear steroid receptors, consisting of 4 domains (NTD, DBD, a hinge region, and LBD). An unsophisticated model of AR signaling includes 6 steps: 1) interaction between androgen and AR LBD; 2) dissociation of heat shock proteins from AR; 3) dimerization of AR and nuclear transport; 4) combination of AR and ARE located in the promoters of its target genes; 5) recruitment of AR co-activators to form AR complex; and 6) transcription and expression of AR target genes. In addition, AR phosphorylation, degradation, and interaction with co-regulators also play crucial roles in modulating the AR signaling pathway. Given the above criteria,

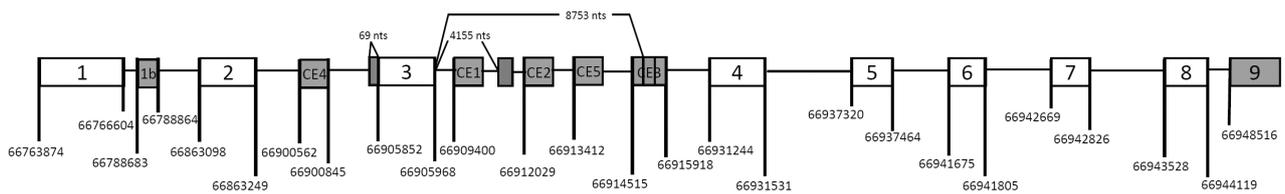
**Table 1.** AR mutants and drug-resistance.

AR mutations	Resistance to	Domain	Reference	Mechanisms
E463G	abiraterone/dutasteride	NTD	[42]	unknown
C595X	abiraterone	DBD	[42]	unknown
S613F	abiraterone/dutasteride	DBD	[42]	unknown
S646R	ketoconazole	Hinge region	[42]	unknown
Q670R	hydroxyflutamide	Hinge region	[43]	unknown
I672T	hydroxyflutamide	Hinge region	[43]	unknown
L701H	abiraterone, bisphenol A	LBD	[43] [45]	receptor promiscuity
E709Y	bicalutamide	LBD	[46]	unknown
V715M	bicalutamide, bisphenol A, flutamide, hydroxyflutamide	LBD	[10] [47]	receptor promiscuity
V731M	bicalutamide, flutamide	LBD	[48]	receptor promiscuity
W741C/L	abiraterone, bicalutamide, flutamide, hydroxyflutamide	LBD	[24] [40] [49]	antagonist-to-agonist switch
M749I	bicalutamide	LBD	[45]	unknown
V866M	abiraterone	LBD	[42]	unknown
G872Q	cyproterone acetate	LBD	[45]	unknown
E873Q	abiraterone, cyproterone acetate	LBD	[49]	receptor promiscuity
H874Y/Q	abiraterone, bisphenol A, flutamide, hydroxyflutamide, nilutamide	LBD	[40] [44]	receptor promiscuity, antagonist-to-agonist switch
F876L	ARN-509, bicalutamide, enzalutamide, hydroxyflutamide, MDV3100	LBD	[24] [51] [52] [53]	antagonist-to-agonist switch
T877A/S/C/G	abiraterone, bicalutamide, bisphenol A, cyproterone acetate, hydroxyflutamide, flutamide, nilutamide,	LBD	[10] [44] [48]	receptor promiscuity, antagonist-to-agonist switch
D879G	bicalutamide	LBD	[54]	antagonist-to-agonist switch (controversial)
D880E	enzalutamide	LBD	[2]	unknown

Continued

L882I	enzalutamide	LBD	[2]	unknown
S889G	bicalutamide, enzalutamide	LBD	[48]	antagonist-to-agonist switch
D891H	bicalutamide	LBD	[48]	antagonist-to-agonist switch
E894K	enzalutamide	LBD	[2]	unknown
M896T/V	bicalutamide, S-1	LBD	[1] [40] [48]	antagonist-to-agonist switch

AR: Xq11-12



(a)

AR-Vs	Alternative names	Transcriptional activity	Transcripts
AR-FL		Ligand-stimulated	1 2 3 4 5 6 7 8
AR-45		Conditional	1b 2 3 4 5 6 7 8
AR-23		Ligand-stimulated	1 2 3 4 5 6 7 8
AR-V1	AR4	Conditional	1 2 3 CE1
AR-V2		Unknown	1 2 3 3 CE1
AR-V3	AR1/2/2b	Constitutive	1 2 CE4 3 CE1
AR-V4	AR1/2/3/2b, AR5	Constitutive	1 2 3 CE4 3 CE1
AR-V5		Unknown	1 2 3 CE2
AR-V6		Unknown	1 2 3 CE2
AR-V7	AR3	Constitutive	1 2 3 CE3
AR-V8		Unknown	1 2 3
AR-V9		Conditional	1 2 3 CE5
AR-V10		Unknown	1 2 3
AR-V11		Unknown	1 2 3
AR-V12	AR <sup>v567es</sup>	Constitutive	1 2 3 4 8 9
AR-V13		Inactive	1 2 3 4 5 6 9
AR-V14		Unknown	1 2 3 4 5 6 7 9
AR-8		Inactive	1 3 CE3

(b)

**Figure 2.** Decoding the androgen receptor splice variant transcripts. (a) AR gene structure with canonical and cryptic exon splice junctions marked according to GRCh37/hg19 human genome sequences; (b) Nomenclature, functional annotation, exon compositions, and variant-specific mRNA (4).

investigators have been pursuing effective therapies for PCa, some already successful in the clinical application inducing drug resistance, which in turn necessitates the development of new drugs and clinical trials.

### 3.1. Specific Drugs Binding with Different AR Domains

The antiandrogens: enzalutamide, bicalutamide, and flutamide, primarily target the LBD of AR [13]. However, the LBD is non-conservative and susceptible to mutations; PCa cells might survive as AR signaling could be activated after mutation. The novel chemotherapeutic drugs targeting the conservative domains of AR, combat PCa cells that alter to integrate with the tumor microenvironment.

3-(2,3-dihydro-1H-indol-2-yl)-1H-indole, VPC-13566, is one of binding function 3 (BF3) inhibitors that directly disturbs recruitment of AR cofactors, efficiently inactivates the AR signaling [10] [14] [15]. Additionally, the small molecule inhibitor EPI-001 [16] and its analog Epi-506 [17] can identify activation function-1 (AF-1) of N-terminal of AR binding with tubulin. A phase I/II trial testing Epi-506, is planned to open in the near future [17]. Furthermore, niphatenones bind to the N-terminal of AR, inhibit the transactivation of AR splice variants, and block the N/C interactions of AR [18].

### 3.2. Inhibitors of AR Transcriptional Activity, Nuclear Translocation, and Degradation

PCa cells survive from various therapies through AR amplification, mutation, splice variants, and elevated androgen concentration in the microenvironment. Scientists continually strive to find advanced treatments for PCa; for example, blocking AR transcription, interfering with AR nuclear localization, and promoting AR degradation that blocks the initiation of AR signaling pathways.

miRNA binding sites are found within the AR 3'-untranslated region (UTR) or coding regions. The miR-30 family members are direct AR inhibitors [19]. miR-124, as a tumor suppressor, limits the growth of PCa by targeting the AR transcripts and directly downregulating AR-V4 and AR-V7 [20]. miR-212 downregulates hnRNPH1 expression which decreases the expression of AR and AR-V7 in PCa cells [21]. PCGEM1 is a long non-coding RNA (lncRNA) that is often upregulated in PCa. Rescue experiments demonstrate that the re-expression of PCGEM1 lead to the upregulation of AR-V3 that is responsible for castration resistance [22]. Lin28 enhances the expression of AR-V7 by upregulating splicing factor hnRNPA1, and promotes the development of drug resistance [23].

The taxanes, cabazitaxel, and docetaxel, function at 3 aspects : stabilizing the microtubules, inhibiting the cell mitosis, and inducing apoptosis. They inhibit AR activity by interfering with AR nuclear translocation [24]. Taxanes effectively lessen the transcriptional activity of wild-type AR, but not those of AR-Vs lacking the microtubule-binding domain. In addition, ICRF187 and ICRF193, DNA topoisomerase II (Topo II) inhibitors, decrease transcription of the wild-type AR, mutant ARs (W741C and F876L), and AR-V7, reduced the AR recruitment

to promoters of its target genes, and obstruct the nuclear localization [25]. CH5137291, an AR antagonist, inhibited the nuclear translocation of the wild-type AR, mutant ARs (W741C and T877A) [26]. Moreover, ODM-201, a non-steroidal oral AR inhibitor, potently inhibits the interaction between androgen and AR LBD, and nuclear localization of AR. Importantly, ODM-201 is an effective antagonist for AR F876L-resistant to enzalutamide and ARN-509, and AR mutants (W741L, F876L, and T877A) resistant to bicalutamide and hydroxyflutamide. ODM-201 is currently in a phase 3 trial in CRPC [27]. The Src-Abl dual kinase inhibitor, PD180970, decreases AR-V7 expression, nuclear translocation, and androgen-independent transcription of target genes [28]. A thiohydantoin derivative, BAY 1024767, exhibits strong repressive activity to the wild-type AR and nine AR mutants by promoting nuclear localization in the absence of R1881 [29].

Galeterone, an AR antagonist, may inhibit CYP17 lyase activity and ubiquitylate AR protein. Galeterone selectively enhances the degradation of AR T878A. At low micromolar concentrations, it enhances AR protein degradation, whereas, at high concentrations, it could induce an endoplasmic reticulum (ER) stress response and may decrease AR translation. Based on results of the phase I/II trial, a phase III study on galeterone in CRPC is planned [30]. Niclosamide, an anti-helminthic drug, potentially suppresses the AR-V7 expression by enhancing its degradation, a phase I trial testing enzalutamide plus niclosamide in CRPC is being pursued [4] [31]. In addition, C-4 heteroaryl 13-cis-retinamides inhibit the AR transcriptional activity through degradation of the wild-type AR and AR-V7 in PCa cells [32]. ASC-J9, an AR degradation enhancer, may degrade both the wild-type AR and AR-V3 [33].

### 3.3. AR Signaling Inhibitors

In addition to truncating the initiation of AR signaling pathways, the scientists also design the other drugs targeting multiple key sites upstream and downstream of AR signaling, in order to further to reduce the AR-dependent signaling pathways for the development of PCa.

#### 3.3.1. Co-Activator Inhibitors

Transcriptional machinery is complicated, at first, AR recruits RNA polymerase II and several co-activators, then AR complex binds to the trans-acting factors of its target genes to initiate transcriptional program [34]. Downregulation of histone deacetylase 1 or 3 (HDAC1 or HDAC3) may prevent the expression of AR target genes by interfering with the assembly of the AR complex. Unfortunately, a small phase II study about the HDAC inhibitor romidepsin failed to demonstrate sufficient activity in CRPC patients [35].

#### 3.3.2. AR Phosphorylation Inhibitors

AR protein may be phosphorylated at tyrosine and serine/threonine residues. Etk/BMX tyrosine kinase and Src kinase may phosphorylate AR at Tyr-534, inducing AR nuclear localization, AR recruitment to the promoters, and tumor

growth. AR Tyr-223 may be phosphorylated by Fer tyrosine kinase. Ack1 kinase phosphorylates AR at Tyr-267 and Tyr-363, promoting the recruitment of AR to trans-acting regions. Mutant ARs (Y267F and Y363F) inhibit Ack1-mediated AR transactivation and chromatin binding. In addition, cyclin-dependent kinase 1 or 9 (CDK1 or 9)-mediated phosphorylation of AR at Ser-81 associated with the AR-chromatin interaction [36]. JNK and p38 kinases phosphorylate AR at Ser-650, regulating the nuclear export of AR [37], whereas dephosphorylation by protein phosphatase 1 regulates the AR transcriptional activity and nuclear localization [38] [39].

### 3.3.3. Upstream Inhibitors of AR Signaling

The transcription factor GATA-binding protein 2 (GATA2) colocalizes with AR on chromatin to increase the recruitment of co-activators and formation of the AR complex. GATA2 directly promotes the expression of both the wild-type AR and AR-Vs; in turn, the expression of GATA2 is suppressed by AR and its ligands, suggesting a negative feedback regulatory loop [40].

Prostate cancer gene expression marker 1 (PCGEM1) interacts with splicing factors, hnRNP A1 and U2AF65, suggesting a role for PCGEM1 in alternative splicing. Androgen deprivation induces the expression of PCGEM1 and causes its accumulation in nuclear speckles. PCGEM1 regulates the competition between hnRNP A1 and U2AF65 for AR pre-mRNA. While the interaction of PCGEM1 with hnRNP A1 suppresses AR-V3 by exon skipping, its interaction with U2AF65 promotes AR-V3 by exonization [41].

### 3.3.4. Downstream Inhibitors of AR Signaling

The bromodomain and extra terminal (BET) inhibitor, ABBV-075, inhibited the androgen-stimulated transcription of AR target genes without significant effect on AR protein expression. ABBV-075 displayed a potent anti-proliferative activity in multiple models of resistance to second-generation antiandrogens and inhibited the activity of AR-V7 and AR F877L/L702H. This provides a promising therapeutic option for CRPC patients who have developed resistance to second-generation anti-androgens [42].

Transcriptomic profiling analysis of AR mutant (W741L) reveals 3 important genes, including *RASD1* (Ras dexamethasone-induced 1), *TIPARP* (TCDD-inducible poly (ADP-ribose) polymerase), and *SGK1* (serum- and glucocorticoid-regulated kinase 1). SGK1 is upregulated in the KUCaP cells and a CRPC patient tissue containing AR mutant resistant to bicalutamide. GSK650394, a SGK1 inhibitor, may reduce the tumor growth induced by AR W741L. These results indicate that SGK1 is a key downstream protein of AR W741L, and SGK1 may be a new and efficient therapy for CRPC patients [43] [44].

## 4. Perspective

Previously, when scientists developed a treatment for PCa, it was commonly expected to cure all the PCa patients. However, the accumulation of clinical experiences and advancement in medical knowledge led to the realization that a ma-

jority of PCa patients were successfully treated initially; however, recurrence to incurable CRPC with malignant phenotypes occurred after several years. We have to accept the phenomena mentioned above that PCa can evolve to drug-resistant variant cells under the selection pressure. In order to effectively treat PCa, it is essential to completely understand the mechanisms of PCa progression, and to develop novel drugs to counter resistance. This theory potentially explicates the smallest possibility of curing cancer, rendering an endless struggle with the disease.

Nowadays, investigators are attempting to develop new treatments effective against PCa in patients demonstrating resistance to clinical therapies. Additionally, a cocktail of various drugs and key enzyme treatments may increase the curative effect. The inhibitors targeting crucial enzymes or signaling pathway proteins may be more effective because the mutations of key enzymes or proteins induced by drug pressure are mortal to tumor or normal cells. Nevertheless, the side effects of these inhibitors are yet to be verified by several studies. These may be the developing direction of the PCa treatment in the near future. Moreover, all these therapies that have been successfully used in the clinic or ongoing trials do not consist of natural ingredients. The treatments cause an extra stimulus to the human body, which might not be an appropriate way to eliminate PCa. Thus, if a therapeutic method cannot bring extra stimulus, simultaneously remove the tumor, or make the body to eliminate the tumor actively, it will be the most yearned treatment. It will be the ultimate goal of developing PCa treatment.

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## Abbreviations

<b>PCa</b>	Prostate cancer
<b>ADT</b>	Androgen deprivation therapy
<b>AR</b>	Androgen receptor
<b>CRPC</b>	Castration-resistant PCa
<b>DBD</b>	DNA-binding domain
<b>LBD</b>	Ligand-binding domain
<b>ARE</b>	Androgen-responsive elements
<b>AR-Vs</b>	AR splice variants
<b>DHT</b>	Dihydrotestosterone
<b>BF3</b>	Binding function 3
<b>AF-1</b>	Activation function-1
<b>UTR</b>	Untranslated region
<b>lncRNA</b>	Long non-coding RNA
<b>Topo II</b>	Topoisomerase II
<b>ER</b>	Endoplasmic reticulum
<b>HDAC1 or HDAC3</b>	Histone deacetylase 1 or 3
<b>CDK1 or 9</b>	Cyclin-dependent kinase 1 or 9
<b>GATA2</b>	GATA-binding protein 2
<b>PCGEM1</b>	Prostate cancer gene expression marker 1
<b>BET</b>	Bromodomain and extra terminal
<b>RASD1</b>	Ras dexamethasone-induced 1
<b>TIPARP</b>	TCDD-inducible poly (ADP-ribose) polymerase
<b>SGK1</b>	Serum- and glucocorticoid-regulated kinase 1



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# Atrial Myxoma with a Dual Coronary Artery Supply

Massar Omar<sup>1</sup>, Jesper Eske Sindby<sup>2</sup>, Asta Blaskauskaite<sup>3</sup>, Tomas Zaremba<sup>1</sup>, Svend Eggert Jensen<sup>1,4</sup>

<sup>1</sup>Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

<sup>2</sup>Department of Thoracic Surgery, Aalborg University Hospital, Aalborg, Denmark

<sup>3</sup>Department of Cardiology, Hjørring Hospital, Hjørring, Denmark

<sup>4</sup>Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Email: Massar\_omar@hotmail.com, jeess@rn.dk, asbl@rn.dk, tz@rn.dk, svend.eggert.jensen@rn.dk

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## Abstract

Primary cardiac tumours are rare, with myxoma being the most common benign heart tumour. The prevalence of coronary disease or neovascular in patients with atrial myxomas is high, yet angiography is not routinely performed. Echocardiography is preferred for evaluation of myxoma, where coronary angiography clarifies the vascular supply of the tumour and may alter the surgical planning. We here report an interesting and rare case of a left atrial myxoma hyper vascularised by two anomalous arteries, from right coronary artery and circumflex artery demonstrated by preoperative coronary angiography. The mass was successfully excised and the diagnosis of cardiac myxoma was confirmed via histopathology. A review of the value of coronary angiography in detecting myxoma neovascularization is provided. Offering additional valuable information, coronary angiography can alter the surgical approach and may therefore be considered prior to myxoma resection.

## Keywords

Atrial Myxoma, Cardiac Tumour, Coronary Angiography, Stroke, Echocardiography, Embolism, Coronary Vascularisation, Case Report

## 1. Introduction

Atrial Myxoma tumours are rare, but are nonetheless the most common among primary heart tumours. Approximately 85% of the myxomas are located in the left atrium [1], where the tumour is typically pedunculated attached to the left atrial septum in the region of fossa ovalis. The mean age of the patients with myxoma is 56 years and 70% are female [2]. Symptoms are weak and nonspecific.

ic, which makes early diagnosis a challenge. Symptoms could be presented as dyspnea, palpitations and atrial embolism [3] [4] [5].

Over the past three decades, diagnosis of cardiac myxomas through echocardiography has been the favoured procedure and major diagnostic tool. Other imaging techniques such as magnetic resonance imaging (MRI), scintigraphy and computed tomography (CT) imaging have also proven their usefulness in diagnosis. As echocardiography is a routine procedure in the detection of myxomas, coronary angiography is only performed under special circumstances.

The main arguments against performing coronary angiography routinely in all myxoma cases include the procedure-related complications and risk of sudden death [6]. At the present time, the indications of coronary angiography to rule out coronary artery disease before myxoma excision are primarily based on the patient's age and gender or the presence of angina. In previous observational studies, coronary angiography was performed in 27% - 85% of cases before surgery, and the main reason was to rule out subclinical coronary artery disease [6] [7]. However, beyond coronary angiography's value in ruling out coronary artery disease before surgery, coronary angiography is essential in detecting the neovessels of the tumour. Coronary angiography visualises feeding vessels, which has several clinical and therapeutic implications. A nonvascularized myxoma with blood leak into the atria can create a steal phenomenon and subsequent myocardial ischemia. The steal phenomenon can be due to the spurting of blood from the myxoma surface. Umeda *et al.* reported a right atrial myxoma, where bleeding from the tumour surface was noted during surgery [8].

This report presents a 56-year-old female diagnosed by an atrial myxoma through echocardiography. The patient had a coronary angiography to exclude treatable coronary artery disease and evaluate tumour neovascular. This revealed a rare condition with a left atrial myxoma vascularised with two anomalous arteries arriving from right coronary artery (RCA) and circumflex coronary artery (CX). The findings lead us to believe that all patients with cardiac myxomas should have coronary angiography as routine workup.

## 2. Case Description

### This Case Report Is Created with the Patient's Consent

A 56-year-old female, previously without neurovascular disease, was admitted to the hospital with a cerebral ischemic stroke documented with MRI. The symptoms were blurred speech, dizziness and decreased force in the right hand, all with a duration of less than one minute. Subsequently, the patient showed a complete recovery and free of symptoms. The physical examination was normal, with normal auscultation of heart and lungs. Previously, the patient had undergone a full pulmonary examination due to coughing, and all tests had shown normal results.

More recently, cerebral MRI scanning demonstrated 2 - 3 cortical located diffusion weighted imaging (DWI)-positive lesions frontal on the left side.

Routinely, the patient underwent cardiac examination to determine the cause

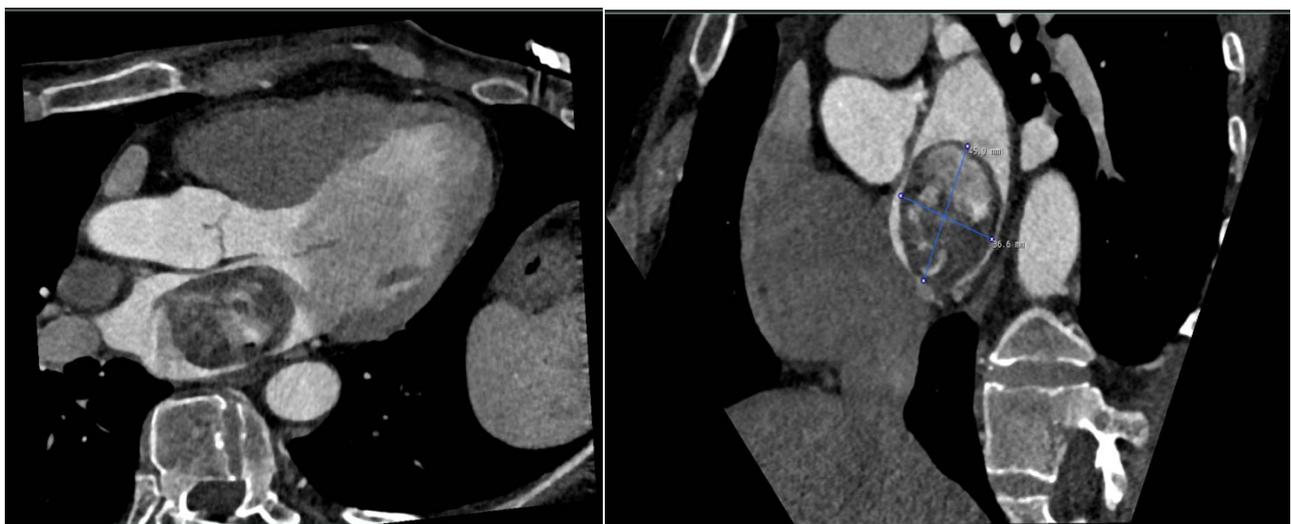
of the vascular event, ECG was found to be normal.

Transthoracic echocardiography revealed a tumour originating from the interatrial septum fossa ovalis in the left atrium (**Figure 1**). To determine the size and shape a CT-scan of the heart was conducted; the tumour measured  $51 \times 49 \times 37$  mm (**Figure 2**). Coronary angiography revealed abnormal arterial supply from RCA and CX to the tumour (**Figure 3**).

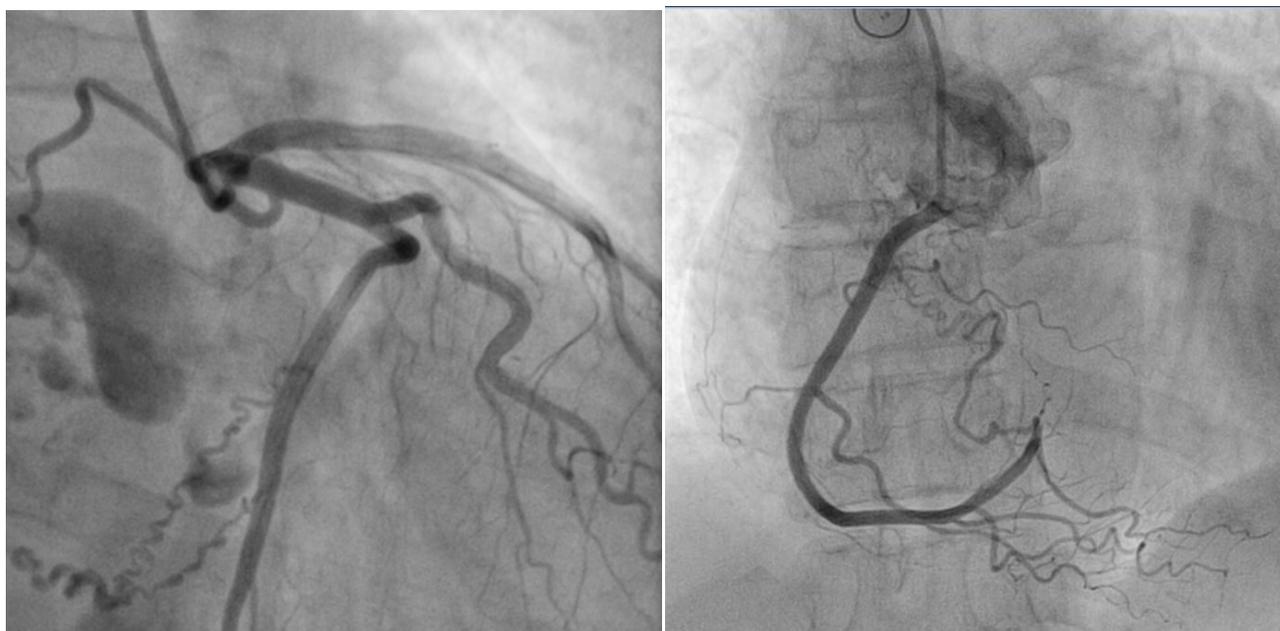
The patient underwent surgical treatment with a median sternotomy, and during surgery a tumour the size of a golf ball was removed (**Figure 4**). Histologically, it proved to be myxoma (**Figure 5**). The patient had an uneventful postoperative course and was discharged 5 days after the surgery in well-being. Echocardiography performed four months after the surgery showed no evidence of myxoma recurrence and the patient was asymptomatic, without adverse events.



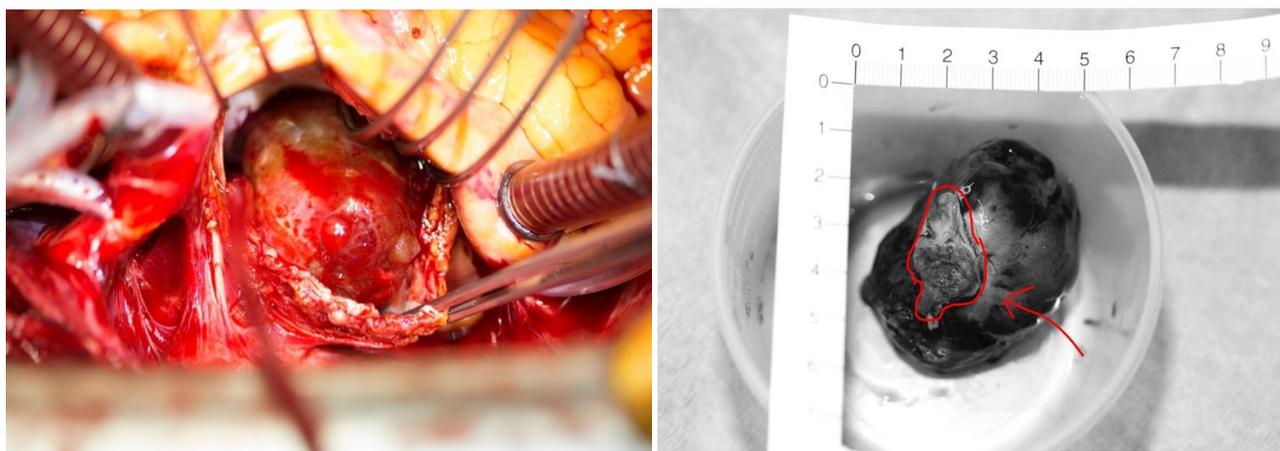
**Figure 1.** Transthoracic echocardiography showing a huge left atrial myxoma. Left: two chambers view with the myxoma in left atrium, attached to the upper area of interatrial septum. Right: transoesophageal echocardiography with myxoma located in left atrium.



**Figure 2.** Computed tomography of the heart with intravenous contrast demonstrating a large filling defect in the left atrium. The myxoma measured  $51 \times 49 \times 37$  mm.



**Figure 3.** Anomalous vessel supply to the myxoma. Angiogram of the circumflex (left) and right coronary (right), demonstrating supply to the mass.

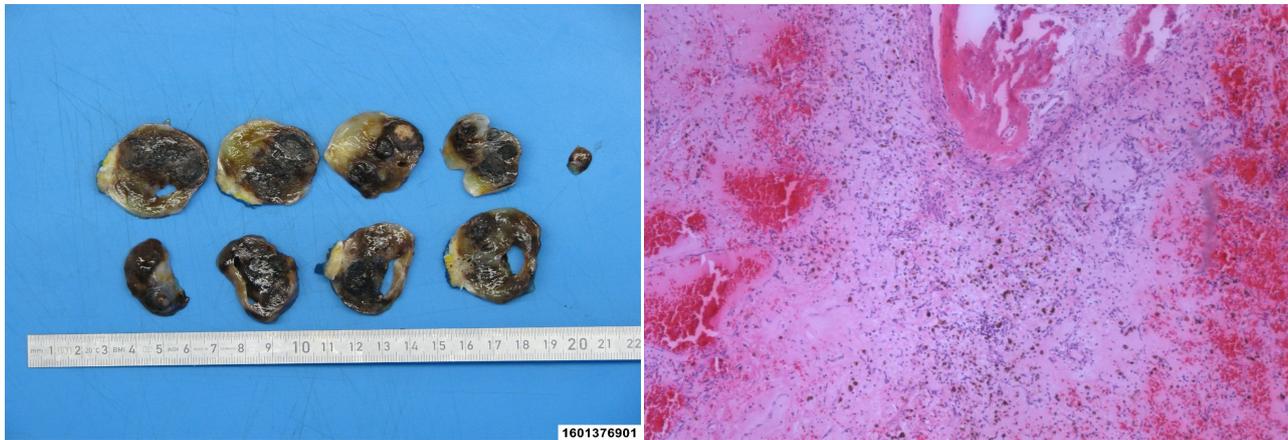


**Figure 4.** Photograph showing the resected left atrial mass. The red line on the right picture shows the attachment of the myxoma.

### 3. Discussion

Myxomas are the most frequent benign form of heart tumour. The majority of the myxomas (85%), are located in the left atrium [3] [9]. Although the myxomas are histologically benign, they may nonetheless be lethal because of their position. Mattle *et al.* [10] report that myxomas initially manifest with features of embolic stroke in approximately a third of patients, as in our patient. Other patients can develop cardiac failure due to obstructed filling causing dyspnea or syncope, as reported by Simsek *et al.* [11]. Some myxomas are asymptomatic and are discovered as an incidental finding.

Detecting myxoma through echocardiography is the first choice procedure; however, coronary angiography and computed tomography can be useful in diagnosing and evaluating the supply of atrial myxomas [9] [12]. The origin of the



**Figure 5.** Left: photograph shows the macroscopic resected left atrial mass, sliced before histology. Right: the classic structure of cardiac myxoma is shown. There are areas with larger vessels containing blood (left), fresh bleeding (right) and calcification with suggested osseous metaplasia (top centre). (H & E, orig.  $\times 10$ ).

vessels supplying the tumour is most commonly CX followed by the RCA [6], while a limited number of studies have demonstrated the rare condition with coexisting coronary artery supply as seen in our case [12] [13] [14] [15] [16].

There is considerable variation in the way the growth rate of myxomas is reported. In one review, an average rate of growth of 0.15 cm per month in one plan was described [17]. The current case, however, raises the idea of a more rapid growth rate due to dual supply. However, no studies have measured the growth rate on myxoma with dual supply.

Today, surgical resection of myxomas safe, with very low mortality or morbidity rate [8]. A previous case report describes a case of left atrial myxoma mimicking an atrial thrombus on echocardiography, thereby posing diagnostic difficulty [18]. Here, differentiating between these two masses through coronary angiography is of value. Both of which have different therapeutic approaches (surgery in the myxoma and anticoagulation in thrombi). The presence of neovascularisation favours the diagnosis of a cardiac myxoma rather than thrombus, which is most often non-vascularised.

Neovascularisation of atrial myxomas with blood leak into the atria can create a steal phenomenon and subsequent myocardial ischemia. The steal phenomenon is defined as a leak from the coronary artery into the atria, causing blood to spurt from the myxomas surface. A study has reported bleeding from a myxomas surface during surgery [8]. The visualisation of coronary supply to myxoma has changed the surgical approach where identifying the supplying arterial branches was preformed to prevent postoperative steal phenomenon and myocardial ischemia [5] [19]. Surgical excision is the definitive treatment and should not be delayed because of the incidence of embolization; however, as mentioned in our discussion, angiographic visualisation of the feeding vessels has several clinical and therapeutic implications.

#### 4. Conclusion

In conclusion, we advocate the use of preoperative coronary angiography in all

cases of atrial myxomas even in the absence of angina symptoms. Furthermore, the angiographic presence of tumour neovascular should be recognised as it may potentially pose a significant challenge to surgeons.

### Disclosure of Interest

The authors report no conflicts of interest.

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# Effect of Conjugated Estrogen in Stress Urinary Incontinence in Women with Menopause

Somayeh Khanjani<sup>1\*</sup>, Sareh Khanjani<sup>2</sup>

<sup>1</sup>Obstetrics and Gynecology, Isfahan, Iran

<sup>2</sup>School of Medicine, Shahr e Kord University of Medicine Science, Shahr e Kord, Iran

Email: \*somayeh.khanjani@yahoo.com, sareh.khanjani@yahoo.com

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## Abstract

Menopause is one of the natural stages of life of women that is associated with instability of vasomotor, flushing, sweating, anxiety and depression, urogenital atrophy and urinary problems. The age range of physiological event is between 48 - 55 years old. With regard to the role of genetics, nutrition and geographical conditions of the age of menopause in Iranian women is lower than and among 46 - 53 years. With the increase in life expectancy in recent decades, duration of menopause is increased and almost involved a third of the life of women so special issues of this era have had more attention. Since menopause is not the end of the life of a woman and keep her physical and mental health and problems resulting from the process of menopause such as urinary problems and incontinence will lead to improve the quality of life in this period. Many studies have tried to find a therapy for postmenopausal women with stress urinary incontinence using hormone. So this article seeks to examine the effect of conjugated estrogen in stress urinary incontinence of menopausal women with using the library method. The survey showed that by starting menopause, decreasing estrogen causes atrophy of mucosa of urogenital and the lining of the urethra and bladder, estrogen causes to maintain muscle tonicity. Also sacral nerves are also rich in estrogen receptors and by estrogen deficiency, elasticity of the urinary system decreases. Estrogen deficiency causes excitability of nerves and frequency of urine. So estrogen can increase the resistance of the urethra, bladder sensory threshold and sensitivity in Adorno in smooth muscles of the urethra and the rest of detrusor.

## Keywords

Menopause, Stress Urinary Incontinence, Steroid Hormones, Vaginal Atrophy, Bladder Prolapse, Conjugated Estrogen

## 1. Introduction

Urinary incontinence is common diseases of women in childbearing ages that by

increasing age, its incidence will be more [1]; the patients involved 15 to 50 percent of women in society that type of stress is more common [2]. Women because of the anatomy, social and cultural are more prone to this disease [3]. Urinary incontinence is the involuntary loss of urine which is objectively demonstrable and is a social and health problem [4]. The urinary incontinence that occurs in various forms, including the severe form of daily attacks a lot, an average of 1 to several times a week in the perspiration, the slight *i.e.* drop oozing weekly or monthly. Stress Urinary Incontinence is a common problem that in women its prevalence is 10% to 58.4% and most recently, with increasing survival, its incidence has increased [5].

Urinary incontinence is a major problem in menopause that affects almost 56% of menopausal women [6]. Menopause is one of the critical stages of women's lives and is inevitable [7]. This step is the mark of the transition from fertility to infertility [8]. Menopause is the most important event of middle-aged women that in terms of personal, cultural and social; it is important as a health problem in the whole reproductive health and women have a particular significance [9]. Now menopause happens between the ages of 40 - 60 years and an average of 51 years [10] and by increasing the lifespan, women spend about a third of their life for postmenopausal. Onset of menopause is gradual and usually begins with changes in the menstrual cycle; these changes begin at the end of the third decade of life [11]. Postmenopausal women involved with endocrine changes, physical and psychological, which have arisen due to prolonged deprivation of estrogen and cause considerable distress and disability in women [12].

The health problems caused during menopause have been considered. One of the physical changes during this period is urogenital changes, genital-urinary atrophy that leads to various symptoms and impact on the comfort and quality of life.

Vagina, external genitalia, urethra and bladder trigone have embryonic close together and all have large numbers of receptors of estrogen. The aging of the genitourinary system by high levels of circulating estrogen is adjusted. Urinary incontinence in women causing great financial pressure for them so that direct cost of which is estimated 10.5 million dollars per year. In addition to the Financial Times, these people are mentally loss of self-confidence, a sense of shame and a tendency to isolation and are suffering from bed sores [13].

Studies show that urinary incontinence has a strong influence on physical activities, social, emotional and mental of patients, especially women. This disease is considered a shameful position in person's mind which leads to drop out of society, loss of sense of self-efficiency and hence the drop in quality of life [14]. Quality of life of each person is considered a main indicator and involved various aspects like physiologic aspects, mental performance, so pay attention to it has a particular importance [15]. There is a reciprocal relationship between the disease and quality of life, so that the primary goal of treatment is to improve the quality of life by reducing the effects of disease on the lives of individuals [16].

Women constitute half of the population and women's health affects the health of future generations, so the question of quality of life for women, because of their position in family is important Jaygashan [17]. On the one hand, intervention for incontinence with physical, mental and social effects to improve quality of life requires comprehensive theories [18].

The role of estrogen and progesterone and p53, in creating prolapse of pelvic organ and stress urine incontinence is reported in numerous research studies [19]. That based on the subject of this article, a number is mentioned. Results of various studies show that vaginal atrophy, uterine prolapse, cystocele, Rectocele, Ectropion, cervix ulcer and irritation in women increases. Traumatic vaginal bleeding was observed in 15% of cases. The urethral syndrome, nocturnal enuresis, urinary tract infection is reported in 7% - 10% of postmenopausal women [20]. In the study by Bai *et al.* that P53 level and estrogen receptor, progesterone in perry urethral fascia of postmenopausal women with stress urinary incontinence and normal women was investigated, the incidence of P53 and estrogen receptor in stress urinary incontinence significantly was lower than the control group [21]. In a study by Zhu and his colleagues, the level of estrogen receptor in tissues of Pelvic floor of patients with stress incontinence was reported significantly lower than the control group [22]. [23] is titled the relationship between menopause and urinary incontinence that women with urinary incontinence than those who did not have, significantly had higher BMI [24]. In a large study of postmenopausal women with symptoms of urinary incontinence (URG or SU) with Estrogen treatment, a big improvement was observed in the number of incontinence, frequency and increasing bladder capacity and increasing the capacity of the first sensation to urinate [25]. In one study, use of vaginal cream in 1.3 outer of the vagina increase blood flow to the urinary but in depth of vagina with effect on the uterus, urinary incontinence has increased *i.e.* the location of estrogen in frequency of incontinence has been effective [26].

Today, due to increasing life expectancy and life expectancy in women and reduce the average age of menopause, understanding the problems of women in this age is very important. Therefore, this article seeks to examine the effect of conjugated estrogen in stress urinary incontinence of menopausal women.

## 2. The Definition of Concepts

**1) Definition of menopause:** according to the definition of World Health Organization, menopause means the cessation of menstruation for at least 12 months due to the loss of activity of ovarian follicles [27]. In terms of laboratory, cessation of menstruation, along with a decrease in estrogen and an increase in FSH (follicle stimulating growth hormone) to more than 40 mm units per liter represents menopause [28]. Now menopause between the ages of 40 - 60 years and average 51 years happens [29].

**2) Stress urinary incontinence:** the involuntary excretion of urine when coughing, sneezing, running, and jumping or any activity leading to increase pressure inside the abdomen [30].

## 2.1. Menopause and Steroid Hormones

Estrogen is female sex hormones which consist of three main types, Beta estradiol, estrone and estriol and is a major factor in the incidence of secondary sexual characteristics [31]. Menopause is associated with hormonal changes, clinical and biological. With the onset of the menopause, the ovaries stop producing considerable quantities of estrogen; hence the symptoms and problems associated with estrogen deficiency occur gradually. Among the changes is atrophy of urinary-genital tract that followed by it problems such as urinary urgency, urinary frequency, nocturia, urinary stress incontinence, urge incontinence, vaginal atrophy and dyspareunia occurs [32]. Studies have attributed the physiological cause of this association to estrogen receptors in genitourinary system. The existence of the first estrogen receptor alpha in the urinary-genital tract proved in 1958 [33]. Then in 1996, the second beta estrogen receptor was identified [34]. These receptors exist in cells of squamous epithelium of the initial and final part of the urethra, bladder triangle, urinary sphincter, the walls of the vagina, pelvic floor muscles and pelvic diaphragm and thus the role of estrogen in the performance of the device and also lack of this hormone in disorders of the urinary-genital tract is undeniable [35]. In addition to estrogen, other receptors in other tissues of the urinary-genital tract have been identified that have specific performance for hormones such as androgen and progesterone. It should be noted that the role of these receptors is less than estrogen receptors, but these receptors in the bladder triangle, the overall context of the bladder, urethra and the vaginal walls has been proved. New studies indicate the role of progesterone in the genitourinary system, but the functional role of androgens in this device is still not clearly determined.

Steroid hormones in addition to environmental effects in the urinary tract have a central role in the neural control of urination process. However, the exact mechanism of this action is unknown, but the presence of both types of estrogen receptors in the brain cortex, limbic system, the hippocampus and the cerebellum has been proved [36]. Due to the position and function of steroids in the urinary tract, the use of replaced hormone therapy in menopause has long attracted the attention of researchers and providers of health care in this area.

## 2.2. Natural Changes of Genitourinary Tract in Menopausal

Content of external genitalia, including vagina-urethra and bladder trigone have embryonic close together, and all have estrogen receptor unit. The aging of the urinary system is determined by the amount of circulating estrogen. Tissues of urogenital do not find atrophy with one speed. Atrophy in the period before menopause is started and will continue for many years. The external genitalia, although not derived from Mullerian structures but with estrogen deprivation quickly is with atrophy. By increasing age, hair becomes thinner in pubis, labia will be shrink and by the reduction of subcutaneous fat and elasticity, the great lip is wider and so vaginal epithelium becomes thinner and less resistance more and more pale and superficial cells replace intermediate cells also, vaginal dis-

charge and vaginal acid also subsequently reduced and pathogens can easily grow in it. Change in vaginal PH from 3.5 - 4 to 6 - 8 lead in alkaline of environment which results in colonizing a large number of bacteria prone. Vaginal or systemic administration of estrogen reverses the trend of thinning of the vaginal mucosa and reduce its PH. Treatment should continue for 1 - 3 months and to remain in effect, only its interrupted use is enough [37].

Urethral area is affected by lack of estrogen. The lower portion of the urethra may be hard and inelastic that this case predisposes diverticulum and Ureterocele. Urethral syndrome is the most common problem in postmenopausal women associated with changes in the urethra. This syndrome includes burning and frequent urination, difficulty in urination, nocturia and urinary urgency. When these symptoms are associated with negative urine culture, diagnosis of urethral syndrome arises. This condition is treatable with therapy of estrogen or wide the urethra. Bacteriuria is seen in 7 - 10 percent of menopausal women while this rate before menopause is 4 percent, higher incidence in postmenopausal women may be due to vaginal atrophy and increasing pollution through the vaginal by the natural disability the external urethral perforation into the anterior vaginal canal, estrogen therapy often leads to healing. The natural shorten of urethra that with postmenopausal atrophic changes will lead to incontinence should be considered [38].

Estrogen deficiency results in decreasing muscle tonicity in the pelvic floor and following the reduction of the circulation of blood of genitourinary muscle area causes to reduce muscle strength and so drooping of muscles. By doing Kegel Exercises, strength in the muscles of genitourinary increases thus recommended that the diet containing soy products, sunflower oil and nuts, which contain high levels of estrogen and are useful in improving muscle work to be used.

Also stop the flow of urine in midstream urine causes to strengthen the pelvic floor muscles. The most common symptoms and complaints in postmenopausal women is external genital itching. Usually replacement therapy with hormone or estrogen in removing itching is quite effective. However dystrophy of genital can cause itching. Differentiation of dystrophy from simple atrophy is important because 5 percent of dystrophies of external genitalia after 3 - 5 years become squamous cell carcinoma [39].

It does not seem that the first cause of dystrophy or carcinoma of external genitalia is estrogen deprivation. Estrogen deficiency causes ease of vulnerability of vaginal. Hit to vaginal may be responsible for about 15 percent of bleeding after menopause, and on the other hand, the incidence of Vaginitis over the years after menopause increases.

Three types of lesion of erosion, ectropion and cervical lesions in post-menopause is seen more. Endocervix glandular tissue activity during menopause and subsequently the amount of mucin decreases that this causes to vaginal dryness that arises as a main complaint in postmenopausal women. The junction of cylindrical cobblestone coverage and columnar and transformation zone

moves a lot to the endocervical canal that creates problems in Pap test and colposcopy.

The incidence of uterine prolapse, cystocele and Rectocele increases in menopause that only limited evidence consider the cause from estrogen deprivation. This increase probably is due to lack of estrogen with age-related decline in cell division and reducing elasticity of tissues of area [40].

### **2.3. Bladder Prolapse and Urinary Stress Incontinence**

The bladder is a sac like organ that is inside the pelvis and its duty is to hold urine that from kidneys and through ureter pipe is leaking into it. The hollow member by supporting muscles is placed in a right place and if for any reason the supporting muscles lose the ability, bladder displaced from its place and creates problems for the individual. The name of this disease is prolapse of bladder [41].

The first symptom of the disease is feeling of pressure that the individual feels in vaginal area and when touch it, it is like a round and small ball. Another very common signs is urinary incontinence that person with a sneeze, cough or laugh suddenly excreted urine. Prolapse of bladder disease is specific for ladies. Normally anterior vaginal wall in women protects the bladder in its place. When the wall is placed under pressure, muscles stretch and relaxes their supportive role of the bladder is destroyed. One of the cases that are in expose of this disorder is post-menopausal women. Common causes of bladder irritability during menopause include:

- 1) Weakening of the pelvic floor muscles: pelvic floor muscles during menopause naturally become weaker and may the control of bladder be less and may lead to that person to go to the bathroom constantly.

- 2) Prolapse: prolapse is prolapse of organs (such as Uterus, vagina and bladder) in the pelvic floor. Some women who have prolapse feel that have a mass in their vagina that can result from prolapse of Uterus, bladder or bowel into it and damage or strain to pelvic floor muscles.

- 3) Reduce elasticity and stretching of the bladder: bladder may lose its ability to stretch and in this case cannot have elongation and increasing the volume and hold more urine. As a result it is triggered as soon as the filling. It is leading to overactive of bladder and causes an urgent need to go to the bathroom and urinate constantly.

- 4) Estrogen reduction: with the beginning of menopause, estrogen level becomes lower. Reduce estrogen level is leading to severe urinary incontinence. Because the hormone estrogen in the body cause to muscles have strength in well. By cutting off estrogen, muscles all over the body, including the anterior vaginal relaxed and bladder prolapse is seen in postmenopausal women.

- 5) Overweight: many women during menopause because of changes that occur in their body are overweight. As a result, by increasing weight, pelvic floor muscles and bladder will be strained and leading to stress incontinence (stress incontinence) in them [42].

## 2.4. Diagnostic Measures of Stress Urinary Incontinence

By describing after suspect to stress incontinence, it can be proved its measures. Important diagnostic measures include:

- 1) Urodynamic test where pressures of bladder and urethra are measured.
- 2) Cystoscopy: The most important diagnostic test in which maneuvers of abdominal pressure and urine leakage can be seen [43].

## 2.5. Conjugated Estrogen

Estrogen in healthy women causes growth and development of sex organs and maintaining the normal function of genitourinary and increase stability of blood vessels (as a result avoid cramp). Hormone therapy (estrogen) in postmenopausal women alleviates urinary frequency and dysuria and blood flow of bladder tissue increases and leads to increase the strength of muscles around the urethra [44].

When estrogen is used as replacement therapy in postmenopausal women with natural menopause or after surgery become menopausal, the treatment prevents estrogen deficiency symptoms, such as hot flashes and vaginal dryness, osteoporosis and atherosclerosis (hardening of the wall of the arteries or atherosclerosis) [45].

Conjugated estrogen for women in continuously (every day) or period (in 21 to 25 days per calendar month) is indicated. Edible form drug can be taken with vaginal forms [46].

Warnings and side effects of conjugated estrogens has been long-term without use of progestin with the risk of endometrial cancer. In addition, women who are taking estrogen, if vaginal bleeding should refer doctor immediately. Patients using estrogen should report symptoms like, pain in the chest, groin, or legs, sudden and severe headache, sudden shortness of breath, slurred speech, sudden changes in vision, or weakness in hands and feet immediately to doctor. Also symptoms like, cramps, bloating, nausea, mild dizziness, mild diarrhea, change in sexual desire, or the inability to tolerate contact lenses may be created if causes problem they should be discussed with doctor [47].

In the case of catching thrombophlebitis, thrombosis (blood clots in the veins), or thromboembolic disorders, endometriosis, gallbladder diseases, uterine fibroids, breast cancer or suspected (except on those who use due to estrogen), abnormal and undiagnosed vaginal bleeding, or liver problems, patients should be caution in using estrogen drug [47].

## 3. Conclusions

Menopause is one of the natural phases of a woman's life that associated with changes in the ovaries and the hormones secreted from it. These changes occur before stopping menstrual cycle. Sometimes the changes are long and show themselves as increasing or decreasing hormone level. The time range of the change is between 1 - 10 years. The average age of natural menopause is 51 years old. Menopause sometimes occurs following the removal of both ovaries after

surgery, radiotherapy, chemotherapy, endocrine disorders or malnutrition. Menopause can be affected on different organs including the cardiovascular systems, nervous, urinary and reproductive that the genitourinary tract changes were discussed in this article.

Menopause is usually associated with urinary incontinence. Menopause is a period that creates changes in the lives of women. Urinary incontinence is common in postmenopausal women which can also affect their social life. When due to the menopause, estrogen level decreases, urogenital system, including urinary mucus layer begins to atrophy and reduce urethral mucosal vascular network and urinary muscle sensitivity to alpha-adrenergic stimulation decreases which causes urinary incontinence. The anterior vaginal wall in maintenance of urine by supporting the urethra and bladder when increasing abdominal pressure helps and ligament sacral prevents the uterus and vagina prolapse by fixing the upper part of vagina and cervix and uterus to the pelvic diaphragm. The effect of estrogen and progesterone on the connective tissue is connective to the reproductive system through receptors in the tissues. Estrogen is influenced through two types of estrogen receptor of alpha and beta and possibly due to reduce the level of these receptors and genetic background, connective tissue disorders occur.

Many studies have tried to find a therapy for postmenopausal women with stress urinary incontinence using hormone and in some studies the effect of hormone therapy (conjugated estrogens) in the treatment of these disorders has been reported. Hormone therapy (estrogen) in postmenopausal women alleviates urinary frequency which leads to increase in the strength of muscles around the bladder.

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# Doxorubicin Induces Apoptosis through down Regulation of miR-21 Expression and Increases miR-21 Target Gene Expression in MCF-7 Breast Cancer Cells

Roghayeh Tofigh<sup>1</sup>, Saeedeh Akhavan<sup>2</sup>, Nastaran Tarban<sup>3</sup>, Amin Ebrahimi Sadrabadi<sup>4</sup>, Arsalan Jalili<sup>5</sup>, Kaykhosro Moridi<sup>6</sup>, Sara Tutunchi<sup>7\*</sup>

<sup>1</sup>Department of Animal Biology, Tabriz University, Tabriz, Iran

<sup>2</sup>Department of Biology, School of Basic Sciences, Science and Research Branch, Islamic Azad University (IAU), Tehran, Iran

<sup>3</sup>Department of Biology, Kish International Campus, University of Tehran, Kish, Iran

<sup>4</sup>Department of Cell Engineering, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

<sup>5</sup>Department of Stem Cells and Developmental Biology at Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

<sup>6</sup>Department of Biology, Faculty of Advanced Sciences and Technology, Pharmaceutical Sciences Branch, Islamic Azad University (IAUPS), Tehran, Iran

<sup>7</sup>Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Email: \*Tutunchi.sara@yahoo.com

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## Abstract

miRNAs play an important regulatory role in variety of cellular functions and several diseases, including cancer. MicroRNA-21 (miR-21) is overexpressed in almost all types of human cancers. Studies revealed that the knockdown of miR-21 results in reduced tumor cell growth, cell cycle arrest and cell apoptosis. In this study, we evaluated the effect of doxorubicin on miR-21 expression in mcf-7 breast cancer cells. miRNA was extracted from mcf-7 cells treated with doxorubicin and untreated cells using miRNeasy Kit (Qiagen) according to the manufacturer's instructions. cDNA synthesis was performed using miScript II RT Kit (Qiagen) and Real Time-PCR was performed using Real Q Plus 2x Master Mix Green-(Ampliqon, Denmark). The relative expression of miR-16 and miR-21 was calculated using comparative Ct method. All tests were run in triplicate to minimize the experimental errors. Samples with a Ct > 37 were excluded from the analysis. Statistically, a significant decrease in cell proliferation of mcf-7 cells was found in doxorubicin group compared with control groups 24 hours after transfection, dose dependently (p value < 0.001). After 24 hours, Doxorubicin (100 µm) significantly decreased miR-21 expression in mcf-7 cells (p = 0.0001). Also, the expression of caspase 9 sig-

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nificantly increased after Doxorubicin (100  $\mu$ m) treatment ( $p = 0.0003$ ). Together, these findings indicate that miR-21 plays a key role in regulating cell apoptosis in mcf-7 cells and may serve as a target for effective therapies.

## Keywords

miR-21, mcf-7 Cells, Caspase 9, Cancer

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## 1. Introduction

Cancers are a group of disease with abnormal cell growth and potential to spread to different tissues of body [1]-[6]. Despite much progress in the management of cancer, cancer is still a major public health problem and one of the deadliest diseases worldwide, with approximately 14 million new cases and 8.2 million death each year [7] [8]. Breast cancer is a very common malignant tumor among female patients and it is estimated that 1 in 10 women worldwide is affected by breast cancer during their lifetime [9]. Many studies were interested to identify specific molecules involved in breast cancer and understand their characteristics [10]. The rapidly increasing technology development leads to the identification of many biomarkers which are easily detectable, measurable, dependable, and inexpensive with a high sensitivity and specificity which play a critical role in breast cancer [11] [12] [13]. MicroRNAs (miRNAs) are a class of small, non-coding, single-stranded RNAs with a 19 - 25 nucleotide length which are found in both animals and plants [14]. MiRNAs are a novel group of gene regulators, binding to complementary sequences in the 3' untranslated region (UTR) of their target mRNAs [15]. MiRNAs are negative regulators of gene expression which induce mRNA degradation or translational repression [16]. Over the past years, it was shown that many miRNAs are influential in the development of many human cancers [17]. miRNA dysregulation is shown to contribute to cancer development through a range of mechanisms [18]. Identified in many types of tumors, miRNAs can act as oncogenic or tumor suppressors [19]. Dysregulation of miRNA expression has been implicated in estrogen-related diseases including breast cancer and endometrial cancer [20]. MiR-21 is one of the most extensively investigated miRNAs which is tightly regulated by a variety of extracellular and intracellular signaling molecules. The important target genes of miR-21 are involved in cell proliferation, activation, and apoptosis [21]. MicroRNA-21 (miR-21) is overexpressed in almost all types of human cancers [22] [23]. Several studies using cell lines revealed that miR-21 knockdown results in reduced tumor cell growth, cell cycle arrest and cell apoptosis [24] [25]. In this study, we evaluated the effect of doxorubicin on miR-21 expression in mcf-7 breast cancer cells.

## 2. Methods & Materials

Doxorubicin was purchased from Sigma. All primers were produced by Pishgam

company (Iran). The media, FBS, trypsin and antibiotics were purchased from Gibco.

### **2.1. Cell Culture**

Mcf-7 cells were purchased from the Pasteur institute of Iran and were cultured in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum (FBS), penicillin (100 units/ml), and streptomycin (100 µg/ml), incubated at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> 95% air. All experiments were performed in a similar medium contain.

### **2.2. MTT Assay**

Cell survival was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay, as previously described [20]. Cells were cultivated at sub confluence before being washed twice with phosphate-buffered saline (PBS). Cells were then resuspended in culture medium with FBS, counted, and plated in 100 µL media at  $15 \times 10^3$  cells/well in 96-well microliter plates. After 24 hours, the cells were washed and treated with doxorubicin. The best concentrations of doxorubicin were calculated. MTT absorbance was measured at 492 nm.

### **2.3. miRNA and Total RNA Extraction and First Strand cDNA Synthesis**

miRNA was extracted from treated and control cells using the miRNeasy Kit (Qiagen) according to the manufacturer's instructions. First strand cDNA was synthesized from miRNA using high Specificity miRNA 1st-Strand cDNA Synthesis Kit (Agilent Technologies, USA). cDNA synthesis was performed in 2 steps. First, a polyadenylation reaction was performed at 37°C for 30 minutes and then the reverse transcription step was conducted.

### **2.4. Quantitative RT-PCR for miRNA Expression**

Quantitative Real-Time PCR reactions were performed in Rotogene Q (Qiagen, Hilden, Germany) in 20 µl of PCR master mix containing 10 µl of SYBR-Green QPCR Master Mix, 1 µl of primer of miR-21, 1 µl universal primer, 1 µl cDNA products and 8 µl of RNase free water. Quantitative Real Time-PCR was performed using SYBR® Premix EX Taq II (Takara, biotechnology, LTD, Dalian, Japan). miR-16 and miR-21 forward primers were CTCGCTTCGGCAGCACA and TAGCTTATCAGACTGATGTTGA, respectively. Forward and reverse primers of caspase-9 were CTCAGACCAGAGATTTCGAAAC and GCATTTCC-CCTCAAACCTCTCAA respectively and forward and reverse primers of b-actin were CATGTACGTTGCTATCCAGGC and CTCCTTAATGTACGCACGAT respectively. The relative expression of caspase-9, miR-16 and miR-21 was calculated using comparative Ct method. All tests were run in triplicate to minimize the experimental error. All assays were inspected for distinct melting curves and the T<sub>m</sub> was checked to be within known specifications for each particular

assay. Furthermore, the samples must be detected with a Ct < 37 to be included in the analysis.

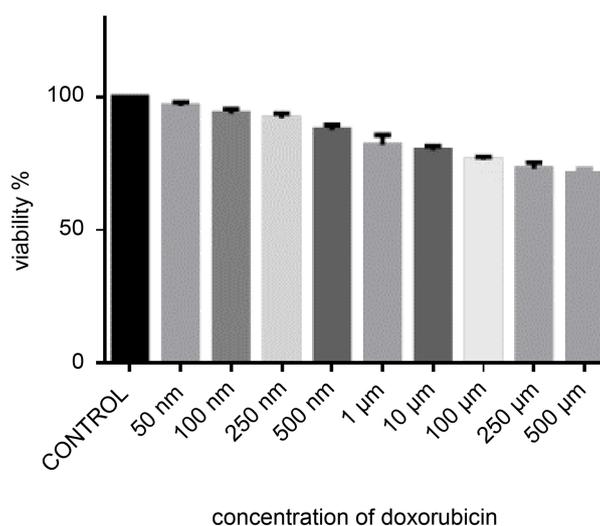
### 3. Statistical Analyses

All statistical analyses were carried out using the statistical program SPSS (version 22, SPSS, Chicago, IL, USA); p-values are two-sided throughout, and  $p < 0.05$  was considered significant. Baseline quantitative results are expressed as mean  $\pm$  SD; Comparison between groups was performed using unpaired student's t test.

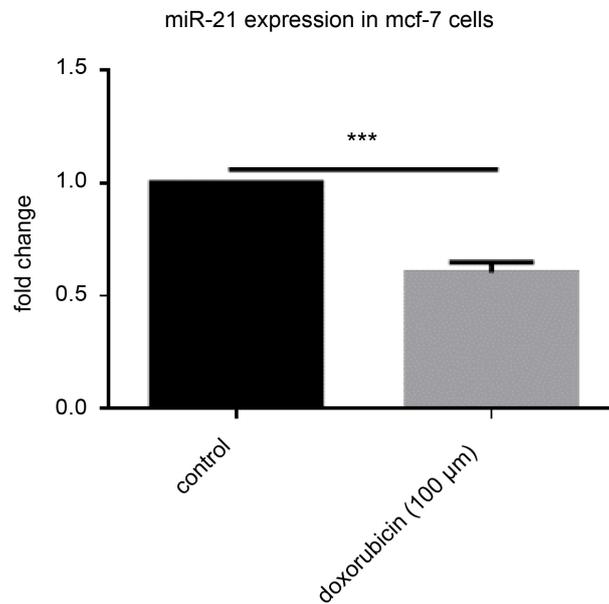
### 4. Discussion and Conclusions

Doxorubicin induced cell proliferation in mcf-7 cells. After 24 h of incubation with different doxorubicin concentrations (50 nm to 500  $\mu$ M), a decline of about 30% in cell numbers was observed (Figure 1). Among different concentrations, 100  $\mu$ M concentration was chosen for next experiments. A significant decline was observed in miRNA-21 expression in MCF cells which were treated with 100  $\mu$ M doxorubicin (Figure 2). Considering the role of mir-21 in breast cancer, the results show that doxorubicin can be effective in breast cancer. Next, we investigated the effect of doxorubicin in caspase-9 expression, because caspase-9 is an important upstream factor leading to apoptosis. Consistent with the result, we found that 100  $\mu$ M doxorubicin caused a significant increase in caspase-9 expression in mcf-7 cells (Figure 3).

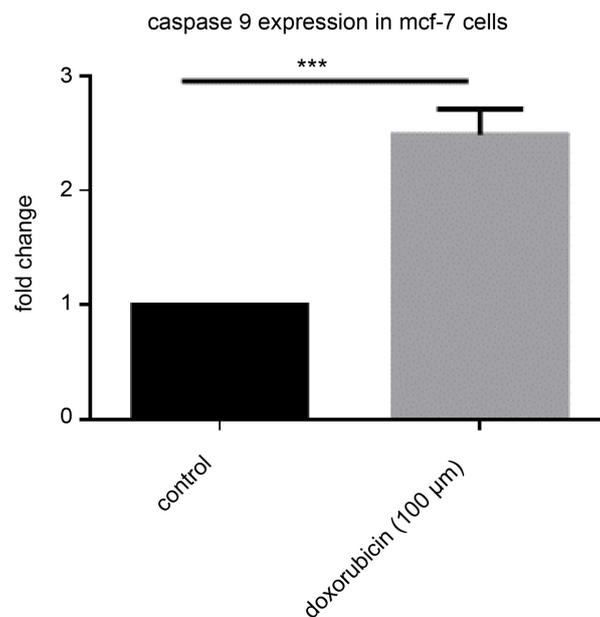
In this study, we demonstrate that doxorubicin decreases mir-21 expression and increases caspase-9 expression in mcf-7 cells. Breast cancer is one of the most commonly diagnosed types of cancer among women [26] [27] [28]. Chemotherapy is an important component in the treatment of breast cancers [29] [30]. Recent studies have focused on new approaches to treat breast cancer [31]. Thus, understanding the molecular mechanisms involved in the progression of



**Figure 1.** MTT assay for mcf-7 cells treated with different concentration of doxorubicin.



**Figure 2.** The expression of miR-21 in mcf-7 cells treated with doxorubicin 100  $\mu\text{m}$  and control cells. miR-21 expression was significantly reduced in mcf-7 cells treated with doxorubicin 100  $\mu\text{m}$ . \*\*\* p value < 0.001.



**Figure 3.** The expression of caspase9 in mcf-7 cells treated with doxorubicin 100  $\mu\text{m}$  and control cells. Caspase 9 expression was significantly increased in mcf-7 cells treated with doxorubicin 100  $\mu\text{m}$ . \*\*\*\* p value < 0.001.

breast cancer is crucial. In the recent years, micro-RNAs have attracted the attention of many researchers [32]. As a result, it has become clear that the dysregulation in the expression of microRNA (miRNA) genes contributes to the pathogenesis of most human cancers and these dysregulations can be caused by

different mechanisms [33]. According to the relationship between dysregulated expression of miRNA genes and the development of cancers, these miRNAs provide important opportunities for the development of future miRNA-based therapies [34] [35]. miR-21 has been found to be overexpressed in many cancers, including breast cancer [36] [37] [38]. In a study conducted by Yan L. X *et al.* in 2008, it was shown that miR-21 is highly up-regulated in breast cancer cell lines, which suggests that miR-21 overexpression is correlated with specific breast cancer bio pathologic features, such as advanced tumor stage, lymph node metastasis, and poor survival of the patients, indicating that miR-21 may serve as an oncogene [39]. Another study also confirmed that the down-regulation of miR-21 can lead to apoptosis caused by increased amounts of caspases-9 [40]. To our knowledge, this is the first report that doxorubicin down-regulates miR-21 and thus, it upregulates the protein expression of miR-21 target gene caspase-9 in MCF-7 human breast cancer cells. The results of our study demonstrated that suppressing miR-21 by doxorubicin increases caspas-9 expression and increases apoptosis. Li Xu Yan *et al.* showed that the knockdown of miR-21 in MCF-7 cells inhibits in vitro and in vivo growth as well as in vitro migration. Also, they suggest that inhibitory strategies against miR-21 using anti-miR-21 may provide potential therapeutic applications in breast cancer treatment [40]. Taken together, miR-21 is shown to affect several targets which are very effective in apoptosis process including caspase-9. The results of this study suggest that miR-21 is an oncogenic miRNA and plays a role in apoptotic pathways.

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# Comparison of the Effects of Kinesio Taping to Local Injection of Methyl Prednisolone in Treating Brachial Biceps Tendonitis

Ahmad Zeinali, Abolghasem Rahimdel, Arezoo Shahidzadeh, Azadeh Shahidzadeh, Ali Mellat\*

Neurology Department, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Email: \*Ali\_mellat@ssu.ac.ir

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## Abstract

**Objectives:** This study compared the effect of Kinesio Taping (KT) with local Methyl Prednisolone injection in patients with biceps tendonitis based on visual analog scale (VAS) and range of motion (ROM). **Methods:** Thirty-eight patients (15 females and 23 males; mean age:  $29.87 \pm 6.31$ , years) with biceps tendonitis were participated in this study during 2014-2015. The patients were randomly assigned into two groups: 19 patients in KT group and 19 patients in injection group. In the first group, KT was used three times for 24 hours sequentially with four-day intervals; in the second group, one dose of Methyl Prednisolone (40 mg) plus 1% lidocaine was injected in the bicipital fissure around the long head of the biceps muscle. The injections and KT therapy were performed by the same physician. The patients were investigated for VAS and ROM in the first, second, seventh and twelfth days. **Results:** VAS and ROM indices were significantly improved in the second and seventh days ( $p < 0.05$ ) in KT group compared to injection group while VAS and ROM had no significant difference in first and 12<sup>th</sup> days ( $p > 0.05$ ). **Conclusion:** Regarding the more immediate effect of KT on ROM and VAS and the fast restoring of the patient to normal life, it could be used as a noninvasive alternative to injection and as the first line of treatment specially in patients who need the immediate effect of treatment.

## Keywords

Brachial Biceps Tendonitis, Methyl Prednisolone Injection, Kinesio Taping

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## 1. Introduction

Shoulder pain is the most common and debilitating musculoskeletal problem affecting 36% - 37% of the population [1] [2]. The most common cause is suba-

cromial impingement syndrome (SIS) [3]. The subacromial space includes the long head of the brachial biceps muscle, the cuff rotator tendons, bursae, and the coracoacromial ligament. Any kind of disturbance in this complex may lead to SIS [4]. One of these impairments is the inflammation of the tendon of the long head of the brachial biceps caused by the repeated use of upper extremities in athletes or by the normal course of aging [5]. There are various therapeutic methods for treating biceps tendonitis including rest, cryotherapy and NSAIDs which form the first line of treatment. In the case of lacking response to treatment, physiotherapy will be used consisting of a range of athletic (motion) exercises, calisthenics (strengthening exercises), heat therapies, laser and electrotherapy methods [6]. Kinesio taping (KT) is a relatively new noninvasive treatment modality which has been popular in recent years. Also, no adverse effects like limited joint movements and limited functional activities have been associated with its use [7] [8] [9] [10] [11]. Although its exact mechanism is unknown yet, some scholars believe that the use of KT may have several good effects including improved muscular functioning, increased deep sensation, reduced pain with neural inhibition, helping the removal of edema by guiding the exudate fluid towards lymphatic duct, correction of malalignment of joints, lifting of the skin, and creation of greater space under the KT area [12]. Local injection is the most common treatment used by various physicians such as specialists in occupational medicine, orthopedists, and rheumatologists for several decades since 1980 [3] [4] [13]. Some authors reject the use of injection which believes that the effect of injection is only for a short time conferring no extra benefit beyond that of NSAIDs [14]. There are also some concerns about its complications including the damage to rotator cuff tendons and the long head of the biceps [15]. Few studies have reported the therapeutic effects of KT and its comparison with other treatment modalities for shoulder pain. The results are, furthermore, controversial [16] [17] [18]. This study compared the effect of Kinesio Taping with local injection of Methyl Prednisolone in patients with biceps tendonitis.

## 2. Methodology

This study was carried out in the Physical Medicine and Rehabilitation Ward of Shahid Sadoughi Hospital in Yazd, central Iran from 2014 to 2015. The study protocol was approved by the Committee of Ethics in Research at the university and informed written consent was obtained for each patient. Thirty-eight patients (15 females and 23 males; mean age:  $29.87 \pm 6.31$ , years) with biceps tendonitis participated in this study. The inclusion criteria were pain onset prior to 150 of active shouldewr elevation in abduction and flexion, pain on activities of daily living, positive Yergason's Test, and age between 18 to 50 years. The exclusion criteria were a history of rheumatic diseases, Shoulder injury, acromioclavicular sprain, concomitant cervical spine symptoms, shoulder fracture, glenohumeral dislocation/subluxation, a history of shoulder surgery within the previous 12 weeks, history of diabetes, osteoporosis, Local infection at the injection site.

Diagnoses of patients were based on pain on bicipital groove and positive test. The specific test for the diagnosis of biceps tendonitis was Yergason's test applied for all participants (19). This test is performed by supination of the forearm against resistance at 90° elbow flexion. If the patient's pain increases, the test is rendered as positive [18]. The patients were randomly assigned into two groups: 19 patients in KT group and 19 patients in local injection group. In the first group, KT was used for biceps tendonitis. The Y-form tape was used for the deltoid muscle with slight traction (15% - 25%) applying the "muscle origin and target technique". The first end of the tape was stuck on the frontal part of the deltoid muscle with the upper arm in the abduct horizontal plane with outward rotation. The other end of the tape was applied to the dorsal part of the deltoid with the upper arm in the adduct horizontal plane with inward rotation. The third part of the tape was stuck on the muscle from the coracoid process to dorsal deltoid with 50% - 75% traction to correct mechanically the glenohumeral in all patients by Physical Medicine and Rehabilitation specialist [19]. KT was used three times for 24 hours sequentially with four-day intervals; in the second group, one dose of prednisolone plus 1% lidocaine was injected in the bicipital fissure around the long head of the biceps muscle by the same physician. The injections and KT therapy were performed by the same physician. The patients were investigated for visual analog scale (VAS) and range of motion (ROM) in the baseline, second, seventh and twelfth days of intervention. The required sample volume was 18 patients in each group for statistical power of 80% and confidence level of 95%. The gleaned data were analyzed with spss version 16 using Chi-square ( $\chi^2$ ) test, ANOVA, repeated measured, and Least Significant Difference (LSD). The amount of  $p < 0.05$  was accepted as statistically significant.

### 3. Results

The mean age of the patients was  $29.87 \pm 6.31$  years with a range of 19 - 42 years. Twenty-three patients were males (60.6%) and 15 were females (39.4%). Demographic variables, disease duration, and history of exercises were investigated for the two groups indicating no statistically significant difference (Table 1).

The patients were studied for VAS and ROM. Our findings demonstrated that there was a significant difference between groups in the second and seventh days with respect to pain severity and ROM with no significant difference in days 1 and 12 (Table 2).

**Table 1.** The demographic characteristics outcome measures of the groups at baseline.

	Injection	KT	p-value
Sex F/M (15/23)	39.5%/60.5%	39.5%/60.5%	0.72
Age	$29.68 \pm 6.63$	$29.68 \pm 6.00$	0.93
Symptom duration	$18.05 \pm 8.90$	$15.47 \pm 9.54$	0.68
Sports history	$1.57 \pm 0.50$	$1.63 \pm 0.49$	0.93

**Table 2.** The comparison of VAS and ROM between groups.

	Injection	KT	p-value
VAS1	6.47 ± 1.07	6.68 ± 1.10	0/83
ROM1	109.00 ± 14.28	117.31 ± 16.35	0/19
VAS2	3.60 ± 2.40	3.07 ± 1.18	0/00
ROM2	142.15 ± 31.35	159.57 ± 25.24	0/00
VAS7	3.21 ± 2.25	3.05 ± 1.26	0/01
ROM7	143.26 ± 33.78	159.84 ± 24.09	0/00
VAS12	3.21 ± 2.25	3.09 ± 1.26	0/90
ROM12	146.57 ± 32.95	160.78 ± 25.72	0/12

VAS was not significantly different in the two groups. ROM was also studied between groups indicating that in day 2, the KT group had greater ROM compared to the injection group ( $p = 0.03$ ).

#### 4. Discussion

Various treatments are available for shoulder pain and biceps tendonitis. Kinesio Tape is one of the relatively innovative noninvasive therapies. Different studies have been carried out so far on KT all reporting the improved functioning and reduced pain in patients with shoulder problems. Nevertheless, this number of studies will not suffice as most of them are case reports or are conducted on healthy individuals [20] [21] [22]. Moreover, the comparative studies on KT are deficient in number compared to other methods with contradictory results [16] [20] [21]. So, the present study embarked on comparing the effects of KT to the effects of injection on biceps tendonitis regarding VAS and ROM. Our findings indicated that there was a significant correlation between groups in days 2 and 7 with regard to ROM and VAS with no significant difference in day 12. Moreover, our study suggested that the KT and injection groups were similar in pain, yet, regarding ROM in day 2, KT had greater ROM compared to injection. Kaya, *et al.* compared the effects of KT and physiotherapy in subacromial impingement syndrome (SIS) patients in the first and second weeks. Their findings demonstrated that the effect of KT on pain and disability is greater during the first week of treatment while its effect is similar to physiotherapy in the second week [20]. Hsu, *et al.* also surveyed the effect of KT on shoulder movements and found that KT increased ROM [22]. Frazier, *et al.* showed that KT and physiotherapy significantly improved pain and DASH score in patients with various shoulder impairments [21]. Subasi, *et al.* compared the effects of KT and physiotherapy in day 1 and months 1 and 3 in patients with SIS. They reported that both methods had a similar effect on VAS and SPADI scores at the completion of treatment [16]. The study by Dong, *et al.* conducted on various treatments of scapular pain indicated that in the initial stages of SIS, exercises along with other treatment modalities such as KT are preferable and should be taken as the first line of therapy with injection considered as the second line of treatment [23].

Another study carried out by Bargahi *et al.* in Iran, elucidated the effect of KT on the superior trapezius muscle with regard to VAS, neck ROM, and neuromuscular control in the upper one-fourth part of the body. The general outcome of these studies indicated that KT can exert short-term effects on pain and neck and shoulder ROM [24]. The exact mechanism of KT is still unknown, however, the physiological mechanisms put forth by various studies may suggest that this method induces the deep sensation by irritating the dermal mechanical receptors, reduces pain by neurological inhibition, decreases pressure of the irritated nervous tissue, and corrects the joint malalignment through correcting the involuntary muscular tension and lifting the skin [25]. A noticeable point in the studies conducted so far was that they used different protocols for the frequency of the use of KT in patients with scapular (shoulder) problems [26]. In fact, there was no harmony in these studies in the methods and frequency of the use of KT in patients with SIS culminating in different results of KT application [27]. Anyhow, our findings are relatively consistent with those of the previous reports indicating that KT and injection may exert a positive effect on VAS, ROM, and function.

Some limitations of our study were that there was no control group for each of our experimental groups for comparisons. Also, low sample volumes may reduce the power of our study to indicate the probable differences among the groups. The strong points of our study were random selection of the patients and similar statistical basis of the groups regarding age, gender, and clinical features. Finally, our best approach in this study was the simultaneous investigation of the two main treatment modalities and their inter-comparisons.

## 5. Conclusion

Generally speaking, all two methods improved the pain and ROM in patients. Regarding the more immediate effect of KT on ROM and the fast restoring of the patient to normal life, it could be used as a noninvasive alternative to injection and as the first line of treatment specially in patients who need the immediate effect of treatment.

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# Serum Vitamin D Levels and Severity of Liver Dysfunction in Cirrhotic Patients

Kambiz Yazdanpanah<sup>1</sup>, Farshad Sheykhesmeeili<sup>2</sup>, Baran Parhizkar<sup>3</sup>, Abbas Ghasemi<sup>4\*</sup>

<sup>1</sup>Associate Professor, Department of Hepatology and Gastroenterology, Towhid Hospital, University of Kurdistan, Head of Department of Internal, University of Kurdistan, Kurdistan, Iran

<sup>2</sup>Assistant Professor and Head of Department of Hepatology and Gastroenterology, Towhid Hospital, University of Kurdistan, Kurdistan, Iran

<sup>3</sup>Assistant Professor, Department of Hepatology and Gastroenterology, Towhid Hospital, University of Kurdistan, Kurdistan, Iran

<sup>4</sup>Chief Resident of Internal Medicine, Department of Hepatology and Gastroenterology, Towhid Hospital, University of Kurdistan, Kurdistan, Iran

Email: \*dr\_ab\_ghasemi@yahoo.com

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## Abstract

**Background and objective:** Cirrhosis affects hundreds of millions of patients all around the world. Vitamin D deficiency is frequently observed in chronic hepatic disease. Vitamin D level may be an important survival marker in advanced liver cirrhosis. **Material and Methods:** The study is a sectional one of the descriptive-analytical type, where 90 of the patients with hepatic cirrhoses were selected with census sampling method. In all the cirrhotic patients, for diagnosis in clinical findings, the serological marker, autoantibodies were stable; biochemical endoscopy and imaging were the histological evidence and examinations and were then analyzed by SPSS version 22 software. **Results:** Based on the study, from the aspect of Child-Pugh classification, the highest vitamin D levels had the highest value in Child-Pugh class A with a frequency of 13 (43%) in the form of insufficiency, and had the highest value in Child-Pugh class B and C in the form of slight deficiency. **Conclusion:** It was specified based on the results obtained from the research that different vitamin D levels and liver failure severity have a significant relationship with each other ( $p < 0.05$ ) in patients suffering from hepatic cirrhosis, such that the serum vitamin D level decreases as liver failure severity increases.

## Keywords

Cirrhosis, Vitamin D, Liver, Child-Pugh

## 1. Introduction

A chronic Hepatic disease, cirrhosis affects hundreds of millions of patients all around the world. Vitamin D deficiency is frequently observed in chronic he-

patic disease. Vitamin D level may be an important survival marker in advanced liver cirrhosis [1]. The main source of the vitamin in humans is contact with the skin exposed to sunlight, where vitamin D hydroxylation occurs in the liver in the form of 25(OH)VIT D3 using enzymes like cytochrome P450 present in mitochondria and microsomes, and hydroxylation is in the form of 1.25(OH)VIT D3 in the kidney. Different factors are involved in vitamin D deficiency, one of which is hepatic 25-hydroxylation disorder. Vitamin D supplement level can best be measured by measuring 25(OH)VIT D3 levels [2]. Besides its role in calcium and phosphorus homeostasis, it plays an important role in body immune system adjustment in the form of antimicrobial peptide induction, innate immune response suppression, cytokine induction, and T helper 2 [3].

In a series of studies conducted before, the relationship between the severity of some chronic hepatic diseases and vitamin D deficiency value has been specified. In Arteh J's study, vitamin D deficiency prevalence in 112 hepatic cirrhosis patients visiting a clinic was 92%, at least around one third of whom suffer from intense deficiency ( $p < 0.05$ ) [4]. Caroline S's study demonstrated a significant relationship between vitamin D low level and mortality in chronic hepatic patients based on the severity of cirrhosis hepatic disease based on Child-Pugh classification ( $p < 0.012$ ). Vitamin D serum level was specified as an important mortality factor in this cohort study ( $p = 0.012$ ) [5]. Therefore, in view of the high prevalence of hepatic cirrhosis and its mortality as well as the high prevalence of vitamin D deficiency in the public and its higher prevalence in patients with hepatic cirrhosis and the role vitamin D plays in osteoporosis, bone fracture and muscle strength decrease and inflammatory response disorder and malignity and even mortality as well as better response to treatment of some patients with hepatic cirrhosis, convinced us to consider the factors disturbing the above studies such as multifactorial causes of vitamin D deficiency and also consider as far as possible all causes of hepatic cirrhosis and specify the hepatic disease severity to obtain serum vitamin D level and hepatic cirrhosis severity so that vitamin D level range can be determined to some extent at any level of hepatic cirrhosis severity, and it can be determined through this study how much vitamin D deficiency there is at each hepatic disease severity if the disturbing factors are removed, so that the required supplements are prescribed with the recommended dosage based on hepatic disease severity, and with prescription of the dosages of vitamin D determined based on disease severity, effective steps are taken in increasing muscle strength and treating inflammatory response disorder and malignity and even mortality as well as better response to treatment of some patients with hepatic cirrhosis and preventing from complications.

### Objectives of the Study

- Specification of the relationship between serum vitamin D level and hepatic cirrhosis severity in cirrhotic patients based on Child-Pugh classification.
- Specification of the relationship between serum vitamin D level and hepatic cirrhosis severity in cirrhotic patients based on MELD score.

- Specification of the relationship between serum vitamin D and serum albumin levels in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D and hepatic enzyme levels in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D and Plt levels in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D and GFR levels in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D and serum PTH, calcium, and phosphorus levels in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D level and age, gender, and BMI in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D level and cirrhosis cause in hepatic cirrhotic patients.
- Specification of the relationship between serum vitamin D level and visiting season in hepatic cirrhotic patients.

## 2. Material and Methods

The study is a sectional one of the descriptive-analytical type and Information on ethics committee approval and informed consent. In this cirrhotic study, for diagnosis in clinical findings, the serological marker of Hepatitis B and C, Hepatitis B virus DNA, and Hepatitis C virus RNA measurement using polymerase chain reaction method, autoantibodies (anti-cell antibody, anti-smooth muscle antibody) were stable; biochemical (such as iron studies, ceruloplasmin, and copper urine), endoscopy, imaging (such as abdominal sonography) were the histological evidence and examinations (liver biopsy examination). Diagnosis of cirrhosis was based on liver biopsy or clinical evidence or deterministic biochemistry of liver failure and/or portal hypertension [6]. 90 of the hepatic cirrhotic patients visiting and hospitalized at Towhid Hospital, Sanandaj were selected using the sampling method, in 2015-2016. During data collection, the BMIs, ages, genders, and visiting seasons and whether their locations are urban or rural was specified for all of the patients. Diagnosis in clinical and laboratory findings and the serological marker of Hepatitis B and C, Hepatitis B virus DNA, and Hepatitis C virus RNA measurement using polymerase chain reaction method, autoantibodies (anti-cell antibody, anti-smooth muscle antibody) biochemical (such as iron studies, ceruloplasmin, and copper urine), endoscopy and imaging were the histological evidence and examinations (liver biopsy examination). Diagnosis of cirrhosis was based on liver biopsy or clinical evidence or deterministic biochemistry of liver failure and/or portal hypertension. Blood sample was taken after one night 10 - 12 hours fasting, and sent to the unit laboratory. CBC was performed by Cell Counter machine (K\*21 Sysx), and ALT, AST, ALK, Ph, Ca, Cr, P, PTT, T, INR, and Alb, Bil T were performed by autoanalyzer machine and Japanese Prestige model biochemistry. Serum Ca Level was corrected with Alb density. PTH was measured by ELISA kit from American company Biomedical and 25(OH)VIT D3 by chemiluminescent kit from German company

ROSH. The tests were performed using available commercial kits based on the instructions provided by the producing factory. Abdominal sonography (Hitachi EUB-405, machine equipped with 3.5 megahertz convex probe) was used for examination of the liver, spleen, ascites, and portal vein in all the patients by a radiology specialist. The patients were classified into three groups using Child-Pugh: Class A (disease compensated well, scores 5 - 6) Class B (significant functional compromise, scores 7 - 9) Class C (disease decompensated, scores 10 - 15). MELD was measured.

In this research, using Chi Square statistical analyses for the categorical variables and Independent T-test for the continuous variables, Logistic Regression Test was used for specification of the predictive variables in occurrence of hepatic cirrhosis, Kolmogorov Test for investigation of the quantitative variable distribution type, variance analysis (ANOVA) for comparison of the variables between the groups of vitamin D, for Pearson correlation coefficients between vitamin D and Child-Pugh and the other variables in SPSS software version 22. The study was approved by the Ege University Ethical Committee. Written informed consent was obtained from patients who participated in this study.

### 3. Results

#### Analytical Results

The results of Chi Square statistical test did not demonstrate a significant relationship between Alkp, Alb, Plt, and Ca ( $p > 0.05$ ); but statistically significant relationships were observed between Child-Pugh classification, ALT, INR, AST, Ph, PTH, Season, Causes of disease, Location, and Gender ( $p < 0.05$ ) **Table 1**. The results on that basis, the highest vitamin D levels based on Child-Pugh had the highest value in insufficient form in Child class A with a frequency of 13 (43%) and the highest value in mild deficiency form in Child class B and C **Table 2**. For ALT enzyme, it had the highest value in mild deficiency form with a frequency of 20 (62%) for normal patients and 26 (44%) for abnormal ones; for gender, it had the highest value in mild deficiency form with a frequency of 24 (43%) for the men and 22 (62%) for the women; for AST enzyme serum level, it had the highest value in mild deficiency form with a frequency of 28 (51%) for normal patients and 18 (50%) for abnormal ones; for PH value, it had the highest value in mild deficiency form with a frequency of 39 (51%) for normal patients and 7 (50%) for abnormal ones; for PTH hormone, it had the highest value in mild deficiency form with a frequency of 28 (45%) for normal patients and 18 (64%) for abnormal ones; for the patients' visiting seasons, it had the highest value in mild deficiency and insufficient value form with a frequency of 5 (35%) for Spring, in mild deficiency form with a frequency of 22 (57%) for Summer, in mild deficiency form with a frequency of 12 (66%) for Fall, and in moderate deficiency form with a frequency of 8 (40%) for Winter; for cause of the disease **Table 3**. The results shows that the highest values respectively concern Hepatitis B with a frequency of 21 (53%) in mild deficiency form, Hepatitis C with a frequency of 4 (44%) in moderate deficiency form, Autoimmune H with a frequency

**Table 1.** Relationship between the variables being studied and vitamin D levels.

Variable	Dimensions	Severe deficiency	Moderate deficiency	Mild deficiency	Insufficient	Sufficient	$\chi^2$	(p. value)
Child-Pugh	Child A	0	3 (10%)	13 (43%)	11 (36%)	3 (10%)	20	0.007
	Child B	1 (2%)	12 (27%)	24 (55%)	5 (11%)	1 (2%)		
	Child C	0	4 (47%)	9 (52%)	0	0		
Alkp	Normal (64-06)	1 (2%)	13 (28%)	19 (41%)	11 (23%)	2 (4%)	4	0.05
	306 < Abnormal < 64	0	10 (22%)	27 (61%)	5 (11%)	2 (4%)		
ALT	Normal $\geq$ 31	0	4 (12%)	20 (62%)	6 (18%)	2 (6%)	5	0.001
	Abnormal $\leq$ 31	1 (1%)	19 (32%)	26 (44%)	10 (17%)	2 (3%)		
Gender	Male	1 (1%)	14 (25%)	24 (43%)	13 (23%)	3 (5%)	5	0.001
	Female	0	9 (25%)	22 (62%)	3 (8%)	1 (2%)		
AST	Normal $\geq$ 31	0	14 (25%)	28 (51%)	10 (18%)	2 (3%)	1	0.001
	Abnormal $\leq$ 31	1 (2%)	9 (25%)	18 (50%)	6 (16%)	2 (5%)		
Alb	Normal (3.5 - 5.5)	0	6 (14%)	22 (52%)	12 (28%)	2 (4%)	9	0.041
	Abnormal < 3.5	1 (2.1%)	17 (35%)	24 (50%)	4 (8%)	2 (4%)		
Plt	Normal (150,000 - 450,000)	0	4 (40%)	4 (40%)	0	2 (20%)	9	0.051
	450,000 < Abnormal < 150,000	1 (1%)	19 (23%)	42 (52%)	16 (20%)	2 (2%)		
Ca	Hypocalcaemia	1 (2%)	16 (47%)	15 (44%)	2 (5%)	0	19	0.012
	Normocalcaemia	0	7 (13%)	29 (54%)	13 (24%)	4 (7%)		
	Hypercalcaemia	0	0	2 (66%)	1 (33%)	0		
Ph	Normal (2.6 - 4.5)	1 (1%)	20 (26%)	39 (51%)	14 (18%)	2 (2%)	4.25	0.001
	4.5 < Abnormal < 2.6	0	3 (21%)	7 (50%)	2 (14%)	2 (14%)		
PTH	Normal (1.3 - 6.8)	0	17 (27%)	28 (45%)	13 (20%)	4 (6%)	6	0.001
	6.8 < Abnormal < 1.3	1 (3%)	6 (21%)	18 (64%)	3 (10%)	0		
Season	Spring	0	3 (21%)	5 (35%)	5 (35%)	1 (7%)	15	0.001
	Summer	0	9 (23%)	22 (57%)	4 (10%)	3 (7%)		
	Fall	0	3 (16%)	12 (66%)	3 (16%)	0		
	Winter	1 (5%)	8 (40%)	7 (35%)	4 (20%)	0		
Cause	Hepatitis B	0	8 (20%)	21 (53%)	8 (20%)	2 (5%)	19	0.001
	Hepatitis C	0	4 (44%)	3 (33%)	2 (22%)	0		
	Autoimmune	0	2 (33%)	3 (50%)	0	1 (16%)		
	Cryptogenic	1 (5%)	3 (15%)	10 (52%)	4 (12.1%)	1 (5%)		
	Thrombosis	0	2 (33%)	2 (33%)	2 (33%)	0		
	Cardiac	0	3 (37%)	5 (62%)	0	0		
	PSC	0	1 (100%)	0	0	0		
Location	Urban	1 (1%)	18 (32%)	32 (57%)	3 (5%)	2 (3%)	17	0.002
	Rural	0	5 (14%)	14 (41%)	13 (38%)	2 (5%)		
	INR	Normal (1 - 1.4)	0	4 (14%)	11 (39%)	9 (32%)		
	1.4 < Abnormal < 1	1 (1%)	19 (30%)	35 (56%)	7 (11%)	0	17	0.002

**Table 2.** Relationship between hepatic cirrhosis severities based on Child-Pugh and vitamin D serum level.

Child-Pugh	Patient frequency	Vitamin D level mean
A	30	52.56
B	43	35.68
C	17	24.73
	90	39.4

**Table 3.** Relationship between patients' visiting seasons and vitamin D serum level mean.

Visiting season	Number of patients	Vitamin D level mean
Spring	13	48.46
Summer	38	40.32
Fall	19	38.62
Winter	20	31.79

of 3 (50%) in mild deficiency form, Cryptogenic with a frequency of 10 (52%) in mild deficiency form, Thrombosis with a frequency of 2 (33%) in insufficient, mild deficiency, and moderate deficiency equal forms, Cardiac with a frequency of 5 (62%) in mild deficiency form, and PSC and Wilson with frequencies of 1 (100%) in moderate deficiency form; for location, it was in mild deficiency form with a frequency of 32 (57%) for the patients from urban locations and in mild deficiency form with a frequency of 14 (41%) for those from rural locations; as for INR, it was in mild deficiency form with a frequency of 11 (39%) for normal patients and in mild deficiency form with a frequency of 35 (56%) for abnormal patients **Table 4** and **Table 5**.

Based on the results obtained from Anova test, since the observed significance level is less than 0.05 at 95 percent confidence level, there is statistically significant difference between age, BMI, and MELD, BilT, and GFR criteria and different vitamin D levels ( $p < 0.05$ ); on that basis, the highest vitamin D value has the lowest value for the patients' ages with 66 and 57 average years of age, the highest value for BMI with 23 kg/m<sup>2</sup> in average and the lowest with 17 kg/m<sup>2</sup>, the highest value for MELD score with an average of 17 and the lowest with 16, the highest value for BILT with 4 mg/dl in average and the lowest with 2 mg/dl, and the highest value for GFR with an average of 59 ml/min and the lowest value with 40 ml/min.

Based on the results obtained from logistic regression, it was observed that the Wald test statistic is 2 for Alb, and with  $p\text{-value} = 0.86 > 0.05$ , the factor is not effective on the patients' hepatic cirrhosis severity in this study, and the variable is not considered as a prognostic factor, which can be caused by albumin reception during paracentesis of abdominal ascites liquid. But the other variables being studied (Gender, Alkp, ALT, AST, Plt, Ph, PTH, and INR) are effective on the patients' hepatic cirrhosis severity, and are considered as prognostic factors in the patients' hepatic cirrhosis severity. Lack of in Patients with testing, the limitations and shortcomings of the study.

**Table 4.** Vitamin D serum level mean based on the patients' genders.

Gender	Vitamin D serum level mean
Male	55
Female	35

**Table 5.** Relationship between cause of cirrhosis and vitamin D serum level mean.

Cause of cirrhosis	Number of patients	Vitamin D serum level mean
Hepatitis B	39	40.1
Hepatitis C	9	33.43
Autoimmune H	6	51.20
Cryptogenic	19	41.37
Thrombosis	6	38.75
Cardiac	8	30.42
PSC	1	22.90
Alcoholic	1	42.90
Wilson	1	35.60
	90	39.24

#### 4. Discussion

The results showed that a significant relationship was observed between Child-Pugh classification and different vitamin D levels ( $p < 0.05$ ); on that basis, there was a trend of lower vitamin D level with cirrhosis increase severity. The results of the research are in accordance with some studies [5] [6] [7] and are in contradiction to some other studies [8] [9]. A significant relationship was observed between MELD score and different vitamin D levels ( $p < 0.05$ ). Actually, it can be stated that with hepatic functioning disorder in chronic hepatic disease and in view of the role the liver plays in producing active vitamin D (25-hydroxylation), there is serum vitamin D deficiency. The results show that a significant relationship was observed between gender and different vitamin D levels ( $p < 0.05$ ) **Table 4.** The cross-sectional study demonstrated that there was an interaction between vitamin D density and gender in relationship [10]. A significant relationship was observed between different vitamin D levels and serum calcium value, on which basis most of the patients with vitamin D deficiency had normal calcium and phosphate serum levels which are in line with Arash Miroliaee's results [6]; this can be explained by reabsorption of minerals from bones. A significant relationship was observed between Ph and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D levels had a frequency of 39 (51%) for normal patients and 7 (50%) for abnormal ones in mild deficiency form. There was also a significant relationship between PTH and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D levels had a frequency of 28 (45%) for normal patients and 18 (64%) for abnormal ones in mild deficiency form. The results show that a significant relationship was observed between visiting season and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D level averages con-

cerned Spring, Summer, Fall, and Winter, respectively, with a frequency of 5 (35%) in mild deficiency and insufficient value form in Spring, a frequency of 22 (57%) in mild deficiency form in Summer, a frequency of 12 (66%) in mild deficiency form in Fall, and a frequency of 8 (40%) in moderate deficiency form in Winter **Table 3**. A significant relationship was observed between cause of disease and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D level averages were in Autoimmune Hepatitis, Alcoholic, and Cryptogenic, respectively, and the lowest level was in PSC. This can explain by cholestasis effect in VIT D level for PSC but low number of PSC and Wilson patients was interference in results. A significant relationship was observed between location and different vitamin D levels ( $p < 0.05$ ;  $r: 74\%$ ), where the highest vitamin D levels were in mild deficiency form with a frequency of 32 (57%) for the patients from urban locations and in mild deficiency form with a frequency of 14 (41%) for those from rural locations, which can be explained in terms of the fact that an important vitamin D production resource is exposure to sunlight. A significant relationship was observed between ALT enzyme and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D levels had a frequency of 20 (62%) for normal patients and 26 (44%) for abnormal ones in mild deficiency form. There was also a significant relationship between AST enzyme and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D levels had a frequency of 28 (51%) for normal patients and 18 (50%) for abnormal ones in mild deficiency form. A significant relationship was observed between BilT and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D value was with an average of 4 mg/dl, and the lowest was with 2 mg/dl. There was a significant relationship between INR and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D levels were in mild deficiency form with a frequency of 11 (39%) for normal patients and in mild deficiency form with a frequency of 35 (56%) for abnormal ones. It can be stated that with hepatic functioning disorder in chronic hepatic disease and in view of the role the liver plays in producing active vitamin D (25-hydroxilation). A significant relationship was observed between age and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D value was for an average age of 66 years, and the lowest value was for 57 years that was unlike expectation. This can explain by not equal number of male and female patients in our study. This A significant relationship was observed between GFR and different vitamin D levels ( $p < 0.05$ ), where the highest vitamin D value was for an average of 59, and 40 had the lowest value. ESRD was excluded in our study. Furthermore, the results obtained from logistic regression demonstrated that Alb is not effective on the patients' hepatic cirrhosis severity, and the variable is not considered as a prognostic factor. But the other variables being studied (Gender, ALKP, ALT, AST, Plt, Ph, PTH, and INR) are effective on the patients' hepatic cirrhosis severity, and are considered as prognostic factors in the patients' hepatic cirrhosis severity.

Based on the results obtained from the research, it became clear that there is a significant relationship between different vitamin D levels and hepatic failure

severity in patients suffering from hepatic cirrhosis. On that basis, as hepatic failure severity increases, serum vitamin D level decrease. In addition to its role in calcium metabolism, vitamin D derivatives may be involved in cell proliferation, differentiation, and immunomodulation. Vitamin D inhibits certain types of matrix metalloproteinases (MMP) [11]. Consequently, vitamin D deficiency has been associated with increased circulating MMP2.9, a situation that can be corrected with vitamin D supplementation [12]. Other effects of vitamin D include suppression of proliferation of fibroblasts and increased collagen production [13]. Vitamin D supplementation may have antifibrotic effects in patients [14]. Then, vitamin D levels should be monitoring and deficient patients should be treated with vitamin D supplementation [15]. Some studies demonstrated an association between vitamin D status and mortality amongst which liver diseases as a cause of death were included [16] [17].

## 5. Limitations and Suggestions for Future Studies

The limitation of this study concerned with the people who were examined as statistical population. It is suggested that the research be comparatively conducted in other hospitals on patients suffering from hepatic cirrhosis and determination required supplements are prescribed with the recommended dosage based on hepatic disease severity.

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# Challenges in the Management of Sepsis in a Resource-Poor Setting

Paul Ni\*, Yaguo-Ide Le

University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

Email: \*nspaul@yahoo.co.uk

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## Abstract

**Background:** Sepsis is a deleterious host reaction to microorganism and can lead to high mortality rate. Early recognition and prompt treatment increases the chances of survival. **Objective:** To outline the challenges in the management of sepsis in a resource limited setting and make appropriate recommendations. **Methodology:** The data was collected through an online literature search for cases of sepsis managed in resource limited settings from 1990 to 2015. Search terms used included: “sepsis”, “septicaemia”, “incidence”, “prevalence”, “morbidity”, “mortality” and “management challenges” using the English and American spellings. Studies from peer reviewed journals or those presented in professional conferences were selected. Finally, studies with proper definition of sepsis and positive blood cultures were selected. **Result:** Twenty one studies from eleven resource limited settings were found. A total of 14,862 cases of sepsis were studied with 9260 (62.3%) of neonatal sepsis and 5602 (37.7%) of post neonatal sepsis. Challenges in the management of sepsis that were identified at the community level included: false cultural beliefs and practices, ignorance and poverty, poor health seeking behavior, late presentation, lack of access to skilled care and patronage of unskilled medical practitioners. While challenges identified at the hospital level include: poor knowledge skills of the health workers, delay in making a diagnosis and initiating treatment, poorly equipped laboratory materials and personnel, no protocol for management of sepsis, limited supply of bedside monitoring equipment, poor staffing, repeated industrial actions, use of fake drugs and high cost of care and drugs. **Conclusion and recommendation:** Management of sepsis in resource limited settings is an uphill task and requires health education and re-orientation of the people. To significantly reduce the mortality associated with sepsis, there is a need to bring health care services to the communities where the people are, improve the management skills of health professionals and translate major components of sepsis management to resource limited settings.

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## Keywords

Sepsis, Management Challenges, Resource-Limited Setting

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### 1. Introduction

Sepsis, a term hard to define, is said to be the systemic inflammatory response syndrome (SIRS) resulting from a suspected or proven infection [1]. The systemic inflammatory response syndrome (SIRS) is an inflammatory cascade that is initiated by the host in response to infection with bacteria, viruses, fungi, rickettsiae and protozoa [1]. Its clinical presentation has three stages depending on the severity, ranging from its early stage termed sepsis to a more severe stage termed severe sepsis and then to its most severe stage known as septic shock [1] [2].

Sepsis is usually caused by a pathogenic bacteria and the clinical diagnosis requires a high index of suspicion [3], as its clinical features in children are often non-specific and may progress rapidly to become a paediatric emergency requiring immediate attention [4] [5]. The definitive diagnosis of sepsis is mainly by isolation of causative bacteria or organism from a blood culture [6]. International guidelines recommend that appropriate blood cultures should be obtained before starting antibiotics and the latter should be started as soon as possible especially within the first hour of recognizing severe sepsis [7] [8]. The type of bacteria causing sepsis and its anti-bacterial sensitivity varies depending on the geographical location and the age group being studied [9]. In addition, particularly in neonates, one organism or a group of organisms may over time replace another as the leading cause of sepsis in a particular region [1] [10] [11].

Sepsis is a significant cause of morbidity and mortality especially in new born where it contributes up to 13% - 15% of deaths and 30% - 50% deaths in developed and developing countries respectively [12] [13]. In developed countries, population sepsis incidence ranged from 22 to 240/100,000, of severe sepsis from 13 to 300/100,000 and of septic shock 11/100,000 [14]-[19], with a case fatality rate up to 30% for sepsis, 50% for severe sepsis and 80% for septic shock, depending on the setting and severity of the disease [14]-[19]. In developing countries, national population incidences are unknown, but various hospital based studies among neonates from different countries show a prevalence ranging from 6 - 9/1000 live births in Ethiopia to 20.3 - 29.3/1000 live births in India [7] [20] [21]. It is also important to note that 20% - 30% of survivors of neonatal sepsis come down with neurological sequelae [22].

Despite this high morbidity and mortality rates, sepsis related mortality is however largely preventable with a high index of suspicion, early recognition, rational antimicrobial therapy and aggressive supportive care [23] [24]. The aim of this study is to highlight the challenges in the management of sepsis in resource poor environment and to make appropriate recommendations.

## 2. Methodology

Online Literature search using PubMed and Google database of citations and abstracts of biomedical articles of all cases of neonatal and post neonatal sepsis managed in different resource limited settings from 1990 to 2015 was done. Resource-limited settings or countries are low income or lower middle income countries whose gross national income (GNI) per capita is US\$1.025 or less in 2015 or between US\$1026 and US\$4035 respectively as classified by the World Bank [25].

Search terms used included: “sepsis”, “septicaemia”, “incidence”, “prevalence”, “morbidity”, “mortality” and “management challenges” using the English and American spellings to ensure a thorough search. The terms septicaemia and sepsis are used interchangeably in the academic literature [26], so both were used in the search and by shortening the word sepsis, studies that reviewed severe sepsis and septic shock were included. See flow chart below.

In the next stage of screening, only studies from peer reviewed journals or those presented in professional conferences that outlined the management challenges and had specific figures on prevalence, incidence, morbidity and mortality were selected. Finally, studies with proper definition of sepsis with positive cultures of blood were selected—See flow chart below. The obtained data were retrieved and categorized into individual and community level challenges and facility (hospital) level challenges and presented as prose and Table.

## 3. Flow Chart

**No of papers retrieved after searching PubMed and Google database (14,862)**

↓↓ Criteria 1-incidence/prevalence/morbidity/mortality/case fatality studies/management challenges: Titles only

**No of studies retained after applying criteria 1 (142)**

↓↓ Criteria 2-criteria 1 plus studies in children only/peer reviewed journal/professional conferences: abstracts only

**No of studies retained after applying criteria 2 (39)**

↓↓ Criteria 3-criteria 2 plus set definition of sepsis/positive blood cultures: full article

**No of studies retained after applying criteria 3 (21)**

↓↓

**No of studies included in results (21)**

## 4. Result

Twenty one studies from eleven resource limited settings were found. A total of 14,862 cases of sepsis were studied with 9260 (62.3%) of neonatal sepsis and 5602 (37.7%) of post neonatal sepsis (Table 1).

Challenges in the management of sepsis that were identified are grouped into two levels; individual and community level and facility (hospital) level.

The challenges at the individual and community level include: false cultural beliefs and practices, ignorance and poverty, poor health seeking behavior, late presentation, lack of access to skilled care and patronage of unskilled medical practitioners (**Table 2**).

While hospital level challenges include: poor knowledge skills of the health workers, delay in making a diagnosis and initiating treatment, poorly equipped laboratories materials and personnel, no protocol for management of sepsis, unpredictable supply of bedside monitoring equipment, poor staffing, repeated industrial actions use of fake drugs and high cost of care and drugs (**Table 2**).

**Table 1.** Distribution of sepsis and no of studies in the different study region.

Study Location	No of Studies	Neonatal Sepsis No (%)	Post Neonatal Sepsis No (%)	Total No (%)
West Africa	5	2504 (55.5)	2005 (44.5)	4509
East Africa	4	1307 (51.9)	1212 (48.1)	2519
North Africa	2	1236 (81.3)	285 (18.7)	1521
Southern Africa	2	1126 (74.5)	386 (25.5)	1512
Asian	3	1422 (56.8)	1081 (43.2)	2503
South American	2	656 (81.3)	151 (18.7)	807
Others**	3	1009 (67.7)	482 (32.3)	1491
Total	21	9260 (62.3)	5602 (37.7)	14,862 (100.0)

\*\* : Brazil, Norway, and Finland.

**Table 2.** Challenges identified in the management of sepsis by the studies.

Individual/ community challenge	No of studies reporting the challenge	Hospital challenge	No of studies reporting the challenge
False cultural beliefs and practices	17	Poor health worker skill	14
Ignorance and poverty	16	Delay in diagnosis and Treatment	8
Poor health seeking behavior	11	Poorly equipped laboratories	19
Late presentation	10	No management protocol	18
Lack of access to skilled care	17	Unpredictable supply of monitoring equipment	8
Patronage of quacks	16	Poor staffing	14
-	-	Repeated industrial actions	13
-	-	Use of fake drug	10
-	-	High cost of care and drugs	16

N/B: There was an overlap in the identified challenges in the different studies.

## 5. Discussion

Sepsis especially severe sepsis and septic shock is a complex medical condition that has multiple interactions with other diseases, because of which, it can be a difficult condition to identify even in the hands of specialist. There are other medical terms that are associated with sepsis, which complicates the diagnosis and identification of the condition further [26]. The treatment of sepsis also requires good knowledge base by the medical team and good monitoring equipments so it is associated with poor outcome when diagnosis and onset of treatment is delayed.

As common with several other medical conditions in resource-limited area especially patients who are rural dwellers, late presentation of patient with sepsis is rife due to often intertwined multifactorial reasons. The reasons range from false cultural beliefs and practices to ignorance and poverty and poor health seeking behaviour. Beliefs such as; the practice of inscription of multiple scarification marks and herbal medications on them as health remedies, smearing of cow dung on umbilical cord stump to enhance its early fall off and that sickness are punishment from the gods still pervade [27]. The basic explanation is that in serious illness there is an underpinning of the supernatural, the most frequently evoked agency is ancestral spirit anger [27]. Ancestral spirit constitutes part of the ordered structure of many rural dwellers. People believe that upsetting the ancestors produces a disturbance of this order and hence disharmony and illness occur [27]. These beliefs are further reinforced by poverty which prevails in the area and so it's no wonder that there is poor health seeking behaviour and late presentation. With late presentation, the stage for poor prognosis is already set.

When eventually these are overcome, access to skilled medical practitioners becomes the next hurdle, and because they are scarce and far-fetched within the communities, patronage of readily available quacks that have limited or no clue about sepsis is not surprising. Eventually, only the few who are able to surmount these obstacles and remain alive find themselves in a proper health facility. So facility level health indices that we have are merely a tip of an ice berg, because the bulk of the mortality takes place at the community level and is never reported [28].

At the facility level, poverty trails many of these patients. Many times the medical practitioner is confronted with a desperate mother or caregiver with a very sick child with little or no funds who is expecting to receive medical care. This is because these patients have expended the little they have patronizing quacks and so come in terminally ill or near so, looking very desperate and helpless expecting free health care from government funding which usually is a mirage. Out of pocket expenditures still dominate most of the medical expenses in resource poor settings as insurance schemes are limited and poorly funded.

For patients who present early to health facilities, recognition of signs of early sepsis is key to good outcome. However, even in the hands of the available limited specialist, this requires experience as there are no specific clinical features much less with the general medical officers which are usually the first point of

call. This delayed recognition means delayed referral which further delays the onset of care and worsens prognosis.

Laboratory support is essential in diagnosis and monitoring of patients with sepsis. Apart from the challenge of the costs of these laboratory tests, there is limited laboratory support, so many are unable to culture the offending bacteria, viruses and fungi with prolonged turnaround time.

Many Health institutions in resource limited setting depend solely on Government funding for the running and maintenance of the centres. However, with limited health budgetary allocation, it is becoming increasingly difficult to run these centres. The effects are multiple including epileptic power supply and frequent breakdown of many crucial equipments, inability to maintain staff welfare, poor staffing and recurrent industrial strikes. All of these adversely affect many patients and especially those with severe sepsis and septic shock who require close staff monitoring and monitoring equipments.

Despite recent advances in the understanding and treatment of sepsis, no data or recommendations exist that detail effective approaches to sepsis care in resource limited low-income and middle-income countries (LMICs) [7]. In many tertiary centres in resource limited settings, the internationally recommended “Surviving Sepsis Campaign” guideline [29] [30] for the management of sepsis has many drawbacks. This is because the evidence for the recommendations has been mainly gathered from studies in high-income countries and often this evidence cannot be directly translated to the resource-poor setting. Again, the guidelines rely on protocols and complex invasive technologies not widely available in most LMICs [7]. For example, therapeutic plan, informed by such guidelines, considers emergency care for the early stage of sepsis—0 to 6 hours (which some of our patients will not qualify for due to late presentation) and treatment for patients in later stages who require critical care [31]—many of these take place in Intensive Care Units (ICUs) which are limited in LMICs and expensive. Though improving in some countries, the few ICUs in resource limited settings have to function with important limitations in material and human resources [32] [33]. Laboratory support is limited, supplies of consumables and medication can be unpredictable, the cost of providing this care is enormous and often not affordable and proper maintenance of crucial equipment for monitoring and treatment is often a challenge [32] [33]. However, the “Surviving Sepsis Campaign” guidelines for severe sepsis and septic shock management have been implemented widely in ICUs in high-income countries and have, together with timely administration of essential therapies, contributed to improved survival [29].

Pivotal to a good outcome in children with sepsis is the timely initiation of appropriate antibiotics in the right dose, route and duration. In resource limited areas, where antibiotics are often available without prescription, its abuse and administration of suboptimal doses before hospital presentation is common. This causes low culture yield of the organisms, reduced antibiotic sensitivity and increases the incidence of antibiotic resistance [34] [35] [36]. Also, where the

right antibiotics are prescribed the high cost of the medications encourages the search for alternative unbranded and often fake drugs. All of these adversely affect the outcome of patients and worsens mortality.

The foregoing suggests that sepsis management in a resource limited setting is an uphill task and so we conclude that; false cultural beliefs and practices, Ignorance and poverty, poor health care funding and limited skilled health professionals at the communities and facilities are major challenges in the management of sepsis in resource poor setting.

We hereby recommend as follows: health education and re-orientation of the people especially women and the rural dwellers. Many people carry out certain practices because they are unaware of better way of doing things. A multi-disciplinary approach at national and international level of advocacy and re-conscientization should be employed to expose the dangers of these cultural (negative) practices and the need to adopt orthodox practices.

Improved distribution of skilled health care professional to rural communities. The National health system should endeavour to bring health care services to where the people are. This is because the majority of the people live in areas where general health care is inaccessible and the people give interpretations to the problems they cannot solve and make use of what they have. Incentives like higher remuneration to health professional in rural communities can be used to attract them to the rural communities.

Government should increase its funding of health institutions with improvement on staff remuneration. Regulation on over the counter purchase of medications and proliferation of fake drugs should be ensured by government and its agencies. Also, managers of health institutions should seek for public private partnership to improve funding and sustenance of Public Health Institutions.

Research and quality improvement initiatives at different levels targeted towards critical care in resource-limited settings are warranted.

Key concepts and components of sepsis management should be made translatable to resource-limited settings with collaborations made between countries with well-established ICUs and those with ICUs in their formative age.

Health care professional should acquaint and update themselves on knowledge and skills in the management of sepsis. This will enhance early and rapid recognition of sepsis and goal directed treatment thereby averting or reducing the high mortality associated with severe sepsis and septic shock.

Limitations of this study include:

The literature review for this study was limited to studies identified in PubMed and Google database, but could have been extended to other databases, like UN and WHO data bases, Global Health Search and the French search engine LILACS, Web of science, non-journal based data. Inclusion of non-English language articles may have increased the completeness of the review. Several non-English papers were excluded and others were not considered due to a lack of an English abstract.

Lack of funding was also a limitation as some of the excluded search engines

required finances to access their abstracts and articles.

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# Case Report of Prosthetic Treatment of a Young Patient Suffering Papiilon-Lefever Syndrome

Masoumeh Rostamzadeh<sup>1\*</sup>, Ghasem Omati Shabestari<sup>2</sup>, Mohammad Rastegar Khosravi<sup>3</sup>

<sup>1</sup>Department of Prosthodontics, Faculty of Dentistry, Kurdistan University of Medical Science, Sanandaj, Iran

<sup>2</sup>Department of Prosthodontics, Faculty of Dentistry, Tehran University of Medical Science, Tehran, Iran

<sup>3</sup>Department of Endodontics, Faculty of Dentistry, Kurdistan University of Medical Science, Sanandaj, Ira

Email: \*masomehroostamzadeh460@gmail.com

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## Abstract

Papillon-Lefevre syndrome (PLS) is a rare recessive autosomal disease which occurs with palms and soles hyperkeratosis as well as primary and permanent teeth periodontal loss. Recently, it has been proved that a mutation at Cathepsin gene C is the genetic cause of PLS. All primary and permanent teeth of the patients are lost at ages 2 or 3 because of serious alveolar bone destruction. This paper presents a complete case of prosthetic treatment of an 8-year old girl with PLS.

## Keywords

Prosthetic Treatment, Young Patient, Papiilon-Lefever Syndrome

## 1. Introduction

Lefevre and Papillon first explained this syndrome which is called by their name in 1924. Inheritance pattern of this disease is Mendelian recessive autosome. This disease has some oral and skin demonstrations. Its outbreak is 1 - 4 million and carrier genes are 2 - 4 in every 1000 people. The skin symptoms are obvious in 3 first year of life as palm and sole keratosis in most patients. Diffused follicular hyperkeratosis and elbows and knees keratosis are rarely reported [1].

Oral symptoms include aggressive periodontitis in primary and permanent teeth. Severe periodontal damage causes loss of primary before age 4 [2]. After loss of the teeth, gum inflammation disappears and gums form normally. Periodontal damage begins after permanent teeth growth and gum inflammation that advances rapidly. Alveolar bone damage happens in two or three years and patients lose their whole teeth before age 15 - 16.

Patients with this illness have a high potential for infections including Middle ear infection, pneumonia, diphtheria liver abscess. Ectopic calcification in the

area of dura mater is seen in some patients but it is not considered as one of the clinical characteristics of the illness [3].

Clinical diagnosis was determined based on palmar and plantar hyperkeratosis associated with aggressive periodontitis in primary and permanent teeth.

It is inevitable to use dental prosthesis at this low age and the prosthesis must be made with regards to maintain the dental free ridge. Using narrow posterior teeth, reduction of vertical height of occlusion, reduction of posterior teeth number and less use of the prosthesis will lead to less loss of the ridge in long terms [4].

Dental implants were installed successfully for this patient.

## 2. Case Explanation

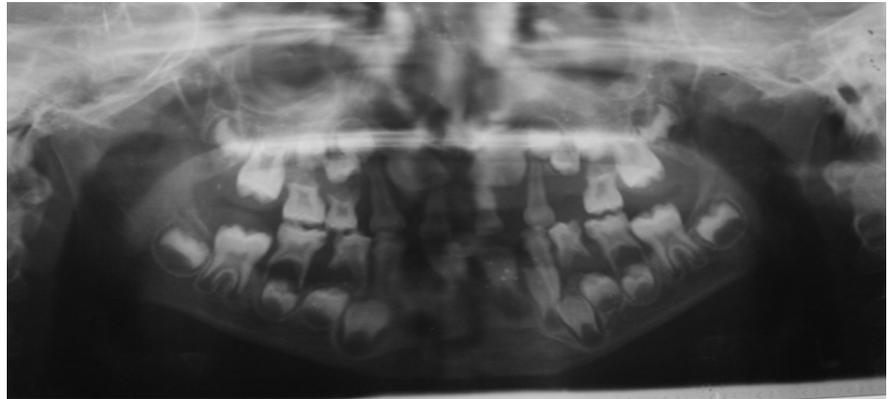
A little 8-year old girl (**Figure 1**) with early complaints of looseness of permanent teeth soon after their eruption with full Edentulous referred to Dentistry department of Tehran University. Panoramic radiography of ages 4, 5, 6, 7 of the patient was available (**Figures 2-5**). The patient underwent follow-up process and teeth with acute periodontal problems were removed from her mouth.



**Figure 1.** A little 8-year old girl.



**Figure 2.** Panoramic radiography at age 4.



**Figure 3.** Panoramic radiography at age 5.



**Figure 4.** Panoramic radiography at age 6.



**Figure 5.** Maxillary occlusal view.

At the time of referring to the hospital, patient's remaining teeth included mandibular left first and second premolars and first premolar both at maxilla side (**Figure 5** and **Figure 6**).

In clinical history, growth of the primary teeth was normal but at age of 3, signs of dental clearance were observed and at age 4, all primary teeth were removed from her mouth. Patient referred to pediatrician department of Tehran



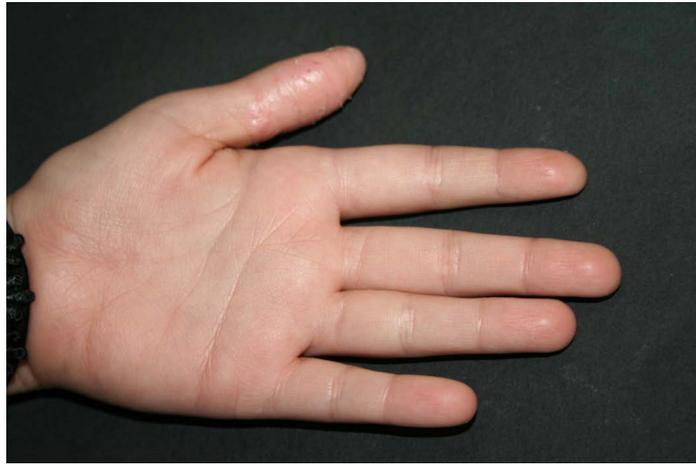
**Figure 6.** Mandibular occlusal view.

dentistry hospital with complaints about her early permanent teeth growth and problems about looseness and bleeding during brushing and eating. All her teeth were removed at age 7. Internal oral examination showed loss of the remaining ridge and imbalance of maxilla and mandible ridges that this loss was clear even for unerupted teeth in alveolar generalized loss radiography inspections. In order to determine the maintainable teeth, a pre-epical radiography was performed on this patient. In medical inspections, there was found no sign of systemic problem. Parents of the patient didn't have any clear historical problem but they had a familial marriage. Mother was physically and psychologically, normal only had problems of gum destruction at mandibular anterior region with calculus signs in the region. There were no sign of skin infection, ear infection, liver or pneumonia in the history of the family. Laboratory tests including complete blood count, alkaline phosphatase, and abnormal liver enzymes in which no abnormal sign was observed. In external oral inspections, there were evidences of hyperkeratosis of palms and soles clearly (**Figure 7** and **Figure 8**).

### 3. Method

Mandibular and maxilla over denture were performed because of lack of teeth eruption. A complete process of prosthesis was done with the exception that this patient had a small jaw and there wasn't available space for initial formation, we used compact Silicone putty and light body (**Figure 9** and **Figure 10**).

After preparation of the cast and inspection of dental undercut in semi-erupted teeth, a special tray was made on which border molding process was performed by green compound and the template (form) was built by forming material of compact silicone. After making the final cast, base record plus occlusion rim were built and jaw links were adjusted with lip support and oral, and external measurements were recorded in CR. According to the young age of the patient, and the limited space in the arc, we used primary teeth mould. Teeth were arranged with spaces available in order to reach a normal appearance of the teeth (**Figure 11**). Teeth were evaluated after being set in the mouth and denture curing process was completed and installed to the patient (**Figure 12**). Regarding the growing age of the patient, follow-up process was done every three



**Figure 7.** Palm hyperkeratosis.



**Figure 8.** Hyperkeratosis of soles.



**Figure 9.** Primary maxilla template.



**Figure 10.** Primary mandibular template.



**Figure 11.** Arranged teeth.



**Figure 12.** Installation of the teeth.

months with the recommendation of changing the denture every two or three years, in order to prevent loss of jaw growth because of the denture.

#### 4. Discussion

Papillon-Lefevre syndrome is a rare recessive autosomal syndrome determined by soles and palms hyperkeratosis and periodontal disease. Its etiological role hasn't been yet clearly defined and we don't know exactly which immunological, genetic or microbiological factors are effective in this disease [4] [5] [6].

Usually, dentists are among the first groups that determine Papillon-Lefevre syndrome at early ages and help dermatologists in this case.

In this disease, gum is inflamed after primary teeth growth which is followed by a Rapid destruction of periodontal. Diagnosis and treatment of periodontal part are very difficult. Hiam-Munk syndrome and hypophosphatemia are used for differential diagnosis [7] [8].

Psychological and social situation of the patients with Pappillon Lefevre-syndrome can be affected by losing teeth in childhood. As a result, dental inspections are essential at this age. In this disease, taking care of primary teeth include early treatments of acute periodontitis, otherwise, it is likely to have problems of alveolar loss or periodontal complaints [9] [10].

Also, prosthesis treatment is harder in patients with bone loss. Early removing of teeth instead of long-term treatment of periodontal can keep more alveolar bone and facilitate the restoration.

Over dentures are denture treatments made on the teeth or dental structures in the mouth. Using Over denture is not a new theory in dentistry and is becoming more common nowadays. The purpose of over denture treatment include: 1) The remaining teeth are as part of the residual ridge; 2) Reduce the loss of alveolar ridge; 3) Increase the proprioceptive sense.

Lefever syndrome is a hereditary disease that results in the loss of alveolar bone supporting the teeth and can be treated easily by over denture. Supporting prosthesis or implant is another more expensive method that was not accessible in this case because she was too young for this treatment for she has lost her vertical support of her teeth too.

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# Comparison between the Effects of Alfentanil, Lidocaine and Their Composition in Controlling the Hemodynamic Responses at the Time of Awake Extubation of Patients

Ali Alizadeh<sup>1</sup>, Mahmoud Aghaziarati<sup>2\*</sup>, Nasim Zarin<sup>3</sup>

<sup>1</sup>Assistant Professor of Medical Science University, Qazvin, Iran

<sup>2</sup>Anesthesiologist of Medical Science University, Tehran, Iran

<sup>3</sup>Assistant Professor of Anesthesiology, Medical Science University, Qazvin, Iran

Email: \*mziarati1970@gmail.com

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## Abstract

**Background and aim:** Instability in the hemodynamic symptoms has been common at the time of extubation in patients and the cause to create the side effects. The aim of this research was to study the effect of injection of Alfentanil, Lidocaine and their composition in reduction of side effects arising from extubation. **Materials and methods:** 172 patients (20 - 40 years old) that referred to Shahid Rajaei Hospital in 2014 and had been under the orthopedic surgery, were divided randomly and by using colored cards into four equal groups (43 patients in each group). Alfentanil (5 microgram/kilogram) was injected to the first group. The second group received Lidocaine (1 milligram/kilogram). The composition of these two drugs was injected to the third group and the normal equal volume of Saline was injected to the fourth group which was the control group. The means of systolic and diastolic blood pressure, average arterial pressure and the number of heartbeat at the time of extubation were measured and registered 1, 5, 10, 15 and 20 minutes after extubation. Also, the amount of situation of bucking after extubation was registered in the groups. **Results:** The demographic results were similar in all groups. The mean of systolic blood pressure and number of heartbeats in the group of Alfentanil and composition of Alfentanil-Lidocaine had significant reduction ( $p < 0.05$ ) in comparison with the control and Lidocaine group. The mean of diastolic blood pressure and average arterial pressure hadn't significant difference between the control group and other groups ( $p > 0.05$ ). The situation of bucking in three treatment groups had significant reduction in comparison with control group. **Conclusion:** Alfentanil and composition of it with Lidocaine both had caused reducing the systolic blood pressure and heartbeats.

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## Keywords

Alfentanil, Lidocaine, Hemodynamic Responses

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### 1. Introduction

Waking up from general anesthesia (emergence) and extubation are two important stages of anesthesia; because, numerous problems can occur at this time. Although, intubation has attracted much attention to itself especially when the airway has been affected by problem, extubation of patients hasn't been considered so much [1] [2] [3]. The anesthesia specialists know that a short time after extubation causes many incidents and the incidents like larynx spasm, aspiration, lack of complete openness of airway, insufficient pulmonary ventilation and severe coughs can occur that all cause emerging hypoxemia that this problem can cause emerging myocardial ischemia especially in the patients that are affected by the coronary arteries disease [4] [5].

Many techniques can cause reducing these harmful effects [6]. Narcotics, beta-adrenergic drugs and the blocker drugs of calcium canal have been studied vastly [7].

Lidocaine by competition with calcium in sitting on the neural membrane receptors causes controlling the passage of sodium from beyond the cellular membrane and the depolarization stage reduces the potential of the act [8]. These effects are started by revocable stabilization of neural cells membrane as the result of reduction of permeability of this membrane to the sodium ion and the conduction of the neural waves is stopped. In the event of absorption of many amounts of Lidocaine, it can have stimulator effect and then weakening effect on the central neural system [9] and [10].

The side effects of this drug include hands tremor, restlessness, ear buzz, sight darkness or diplopia that with much consumption, it also can cause reducing the heartbeat, spasm, cardiac arrest, asthma, respiratory arrest. Also, Lidocaine has caused reducing the activity of efferent C fibers of larynx and it causes suppressing the cough reflex and somehow it has succeeded in reducing the hemodynamic responses [11].

The narcotic drugs are usually used to reduce the side effects arising from extubation and among them, two drugs of Alfentanil and Remifentanil due to the start of quicker effect have been more common than other narcotic drugs in the recent years [12].

Therefore, the executors of plan intended to use of a method that has the least hemodynamic responses within and after extubation and also has a comparison between the effects of Lidocaine and Alfentanil in controlling the hemodynamic responses at the time of extubation.

### 2. Materials and Methods

This study was a randomized double-blind clinical trial which was done on 172

candidate patients for orthopedic surgery of upper organs in Shahid Rajaei hospital dependent on Medical Sciences University in 2014. This study was approved with ethics code of 29.281 and meantime acquiring the written testimonial from the patients eligible for entering to the study, they were ensured that had right to be dispensed with continuing the work with researchers group and the research units were also ensured that all information remains confidential. Determination of the number of needed sample for doing the current study was calculated according to the researches accomplished in this field and by considering the power of 80% and the first kind error of  $\alpha = 0.05$ .

The criteria for entering the patients to the study have included the age of 20 - 40 years old, weight of 60 - 80 kg and from two genders, the criteria for exiting from the study included existence of cardiovascular diseases, mental disease, spasm, glaucoma, numerous allergies, receipt of blood, blood products and addiction to the drugs. At first, the patients were monitored and then they received 0.03 mg/kg of Midazolam and 1 mcg/kg of Fentanyl, then they were inducted by 2 mg/kg of Propofol and 0.5 mg/kg of Atracurium and anesthesia was continued by receiving 100 mcg/kg Propofol, 50% of O<sub>2</sub> and 50% of N<sub>2</sub>O. Then, the patients were divided into 4 groups (43 patients in each group) randomly and by using of colored cards that the Alfentanil (5 mcg/kg), Lidocaine (1 mcg/kg), simultaneous amount of Alfentanil-Lidocaine and normal saline (with equal volume of 6 ml) were injected in order to the patients of groups A, B, C and D. The vital symptoms of patients including systolic and diastolic blood pressure and the number of heartbeats, existence or lack of existence of bucking were controlled and registered in 1, 5, 10 and 15 minutes after prescription of these drugs till extubation of patient. Extubation was done when the patient followed the orders (opening the eyes) and after extubation, the vital symptoms of patient were controlled and registered with interval of 5 minutes (till 15 minutes). According to the provided checklist, the data have been collected; according to the SPSS software, they have been entered to the computer and the data analysis was done by using of t-test, ANOVA, repeated measure ANOVA.

### 3. Results

172 patients (20 - 40 years old) were divided into four groups randomly (43 patients in each group). The patients of four groups didn't have significant difference with each other in terms of the demographic information.

The patients of all four groups were compared with each other in terms of the mean of systolic and diastolic blood pressure and number of heartbeats that as it is observed in the **Figure 1**, the systolic blood pressure was compared at the times of before injection of drug and 1, 5, 10, 15 and 20 minutes after injection of drug in four groups. The mean of systolic blood pressure in Alfentanil group has less amount than other groups and it has higher amount in the witness group; and statistically, Manova test indicated significant difference between the groups ( $p = 0.01$ ). The mean of systolic blood pressure and number of heartbeats in the group of Alfentanil and composition of Alfentanil-Lidocaine had significant reduction ( $p < 0.05$ ) in comparison with the control and Lidocaine group.

Also, the mean of average arterial blood pressure was compared at the times of before injection of drug and 1, 5, 10, 15 and 20 minutes after injection of drug in four groups. MANOVA test indicated that there is no significant statistical difference between the groups and the mean of the average arterial blood pressure is similar in the samples of all four groups ( $p = 0.21$ ) (Figure 2).

The diastolic blood pressure was compared at the times of before injection of drug and 1, 5, 10, 15 and 20 minutes after injection of drug in four groups. MANOVA test indicated that there is no significant statistical difference between the groups and the mean of diastolic blood pressure is similar in the samples of all four groups ( $p = 0.09$ ) (Figure 3).

As it is observed in the Figure 4, the mean of the number of heartbeats was

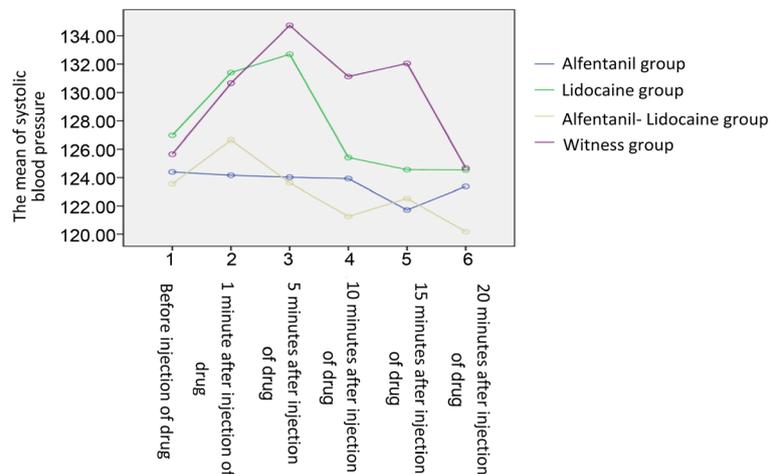


Figure 1. Comparison of the mean of systolic blood pressure in the specified times in four groups under study.

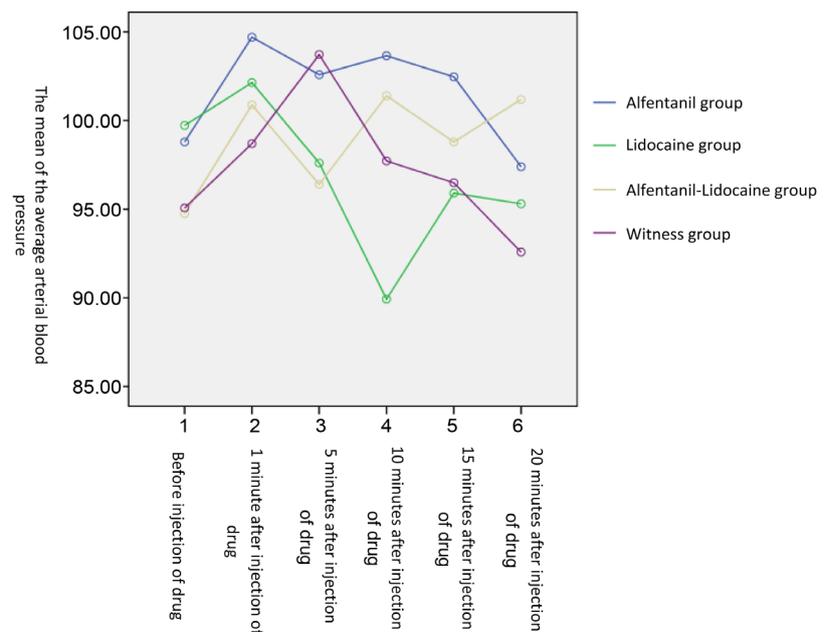
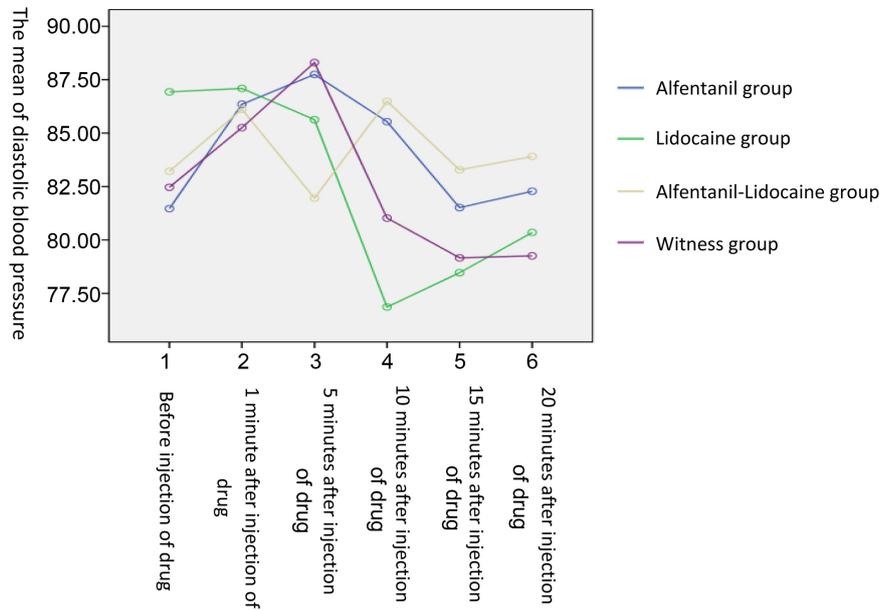
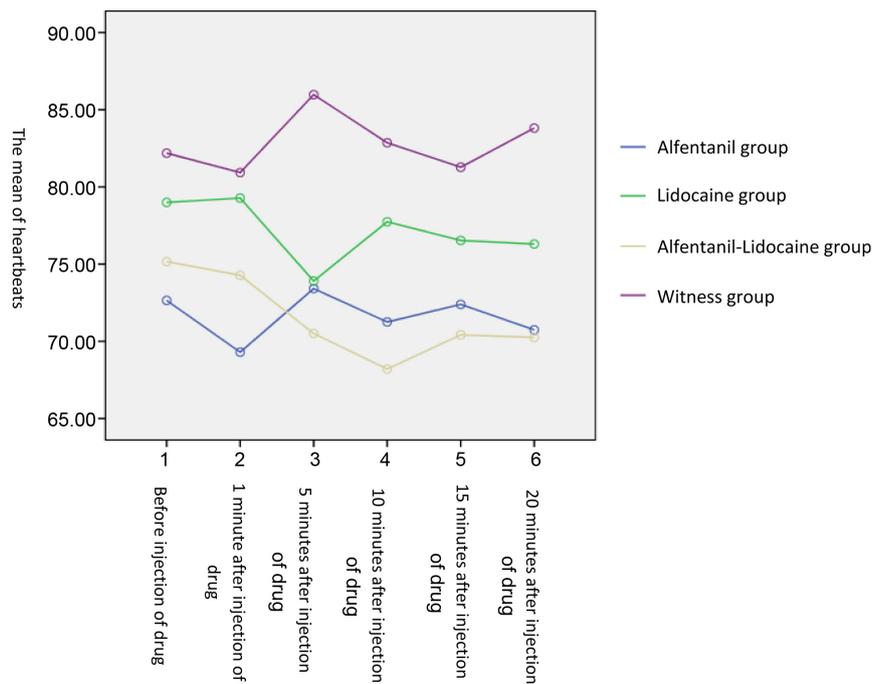


Figure 2. Comparison of the mean of average arterial blood pressure in the specified times in four groups under study.



**Figure 3.** Comparison of the mean of diastolic blood pressure in the specified times in four groups under study.



**Figure 4.** Comparison of the mean of the number of heartbeats in the specified times in four groups under study.

compared at the times of before injection of drug and 1, 5, 10, 15 and 20 minutes after injection of drug in four groups. As it has been indicated in this diagram, the mean of the number of heartbeats in two groups of Alfentanil and composition is in better range than two other groups and MANOVA test indicated that there is significant statistical difference between the groups.

The patients were controlled in terms of the tremor severity at the beginning

of entering to the recovery. All three treatment groups had significant reduction in emergence of tremor after surgery in comparison with other group in a manner that the most frequency was related to the witness group and the least frequency was related to the Lidocaine group; and Alfentanil and composition groups had equal frequency. The statistical test of Chi-square indicated that there is significant difference between the groups in terms of bucking frequency ( $p = 0.001$ ) (**Table 1**).

#### 4. Discussion

Generally, the results of study indicated that injection of Alfentanil and composition of two drugs of Alfentanil and Lidocaine caused good effect on systolic blood pressure and number of heartbeats; but, they hadn't any effect on diastolic blood pressure and average arterial pressure. Also, all three drugs caused to reduce the number of bucking cases after extubation. But, the mean of the time of drug injection till the time of extubation had become longer in injection of all three drugs.

Doing the extubation at the end of anesthesia can cause to create a series of hemodynamic changes such as increase of blood pressure and heartbeats that in many patients causes to emerge irreparable effects. Therefore, prevention from the intended changes is very vital for mentioned patients [13] and [14]. Although, the mechanism of increase of blood pressure and heartbeat within the intubation depends on the severe and short-term sympathetic stimulation arising from laryngoscopy in patient under general anesthesia; but, at the time of extubation, different factors such as the pain arising from wound, waking up from anesthesia and stimulation of chip have role in creating these hemodynamic changes [15]. Therefore, controlling these cardiovascular changes has been necessary and different drugs have been already suggested for this purpose such as Fentanyl, Esmolol Lidocaine, [16].

The effects of Lidocaine on blood pressure and heartbeat in responding to the extubation were studied by Bidowsky and his group, they poured 1.5 cc of Lidocaine 4% into the chip tube for 3 - 5 minutes before extubation and within extubation, and they poured one cc of the second dose of Lidocaine 4% into the chip tube. No kind of increase of blood pressure and heartbeat was seen during 1 to 5 minutes after extubation [17]. Also, the studies had indicated that injection of Lidocaine into the chip tube causes to block the airway receptors and consequently constrain the cough that the study of Tavakkol *et al.*, also indicated it;

**Table 1.** Comparison of the frequency of bucking amount in four groups under study.

	With bucking	Without bucking	P value
Alfentanil	18 (42%)	25 (58%)	0.001
Lidocaine	11 (25.5%)	32 (74.5%)	
Alfentanil-Lidocaine	18 (18%)	25 (58%)	
Witness	31 (72%)	12 (28%)	

but, in the continuation, Bidrowsky had reported that the changes of cardiovascular indexes are minimized in this method, a result that the study of Tavakkol didn't indicate it [18]. Also in a study, composition of Lidocaine with Captopril caused significant reduction in hemodynamic changes that in the Lidocaine group, these changes weren't lonely seen. Also in our study, Lidocaine lonely had good effect on reduction of bucking after extubation; but, it had no effect on reduction of hemodynamic symptoms.

Also in studying the time of extubation, Lidocaine like Alfentanil caused to increase the time of extubation; but, this difference wasn't significant in comparison with witness group that these results are similar with the study of Anderson and *et al.*, in a manner that in their study, injection of Lidocaine doesn't cause to increase the time of sedation and anesthesia for extubation [19].

Prescription of narcotic drugs intravenously before waking up from anesthesia is useful for prevention from cough, agitation and hemodynamic responses. Delay of recovery time, nausea and vomit arising from narcotic drugs are from the defects of prescription of narcotic drugs. Prescription of a short-effect narcotic drug is a trustable and safe method for prevention from cough during waking up from anesthesia.

Alfentanil has been a short-effect opioid which has a short half-life too. In the study of Mar'ashi, it was indicated that 10 µg/kg of Alfentanil caused to reduce and stabilize the systolic blood pressure after extubation. Also in his study, it was indicated that injection of Remifentanil in comparison with Alfentanil causes to reduce the average arterial blood pressure and diastolic blood pressure [20]. Also in our study, Alfentanil caused to reduce the systolic blood pressure; but, it didn't have any effect on average arterial blood pressure and diastolic blood pressure in comparison with other groups that these results are aligned with above study.

Also in the study of Fuhrman, comparison of Smolol and Alfentanil in reduction of hemodynamic side effects after extubation indicated that Alfentanil like Smolol caused to reduce the hemodynamic effects after extubation; but, it caused to increase the time of extubation [21] that in our study, Alfentanil group in comparison with the group of Alfentanil and Lidocaine composition and witness group caused to increase the time of extubation that this difference was significant. But, in the study of Mendel, prescription of Alfentanil caused to reduce bucking, coughing and hemodynamic effects after extubation without elongation of extubation time [22].

Also, in relation with the amount of creation of airway reflexes after extubation like coughing and bucking, in the study of Sadeghi and *et al.*, it was indicated that Alfentanil in comparison with Lidocaine had caused to reduce the amount of these side effects after extubation without elongation of extubation time [23], while in our study, it was indicated that the frequency of bucking amount in the Lidocaine group was less than two other treatment groups; but, generally all three groups had less amount than witness group that this difference was also significant statistically.

## 5. Conclusion

With regard to the results of this study that we witnessed the reduction of the mean of SBP and heartbeat in the Alfentanil and Alfentanil-Lidocaine groups and also reduction of bucking amount in both groups but in less amount in Lidocaine group, we didn't have significant reduction in the Lidocaine group in terms of the amount of heartbeat and SBP. It can be concluded that the composition of Lidocaine and Alfentanil can cause good effect on reduction of side effects arising from extubation, but adding Lidocaine doesn't cause better effect and it is the important point in increase of the time of extubation in comparison with witness group that this 3-minute difference can not reduce the importance of this issue so much.

## Limitation

This study had a limitation and it was about patients' consent. Many patients did not want to enter the study.

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# The Effects of Vestibular Rehabilitation after Bilateral Superior Semicircular Canal Dehiscence: A Case Report

Connor L. Naccarato<sup>1,2,3</sup>, Kristen M. Johnson<sup>1</sup>

<sup>1</sup>University of St. Augustine for Health Sciences, San Marcos, CA, USA

<sup>2</sup>Physio Strength LLC, Tacoma, WA, USA

<sup>3</sup>Bench Mark Rehab Partners, Ooltewah, TN, USA

Email: [cnaccarato25@gmail.com](mailto:cnaccarato25@gmail.com), [kjohnson@usa.edu](mailto:kjohnson@usa.edu)

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## Abstract

**Background and Purpose:** Despite the strong body of evidence for vestibular rehabilitation, research is lacking for effective clinical management of patients with superior semicircular canal dehiscence (SSCD) and endolymphatic hydrops (EH). The purpose of this case report is to describe the effects of physical therapy in the treatment of a patient diagnosed with bilateral SSCD. **Case Description:** The patient was a 56-year-old woman with a long-standing otologic history involving bilateral SSCD and EH. The patient's body structure and function impairments include constant headaches, dizziness with head rotation and eye movements, sensitivity to sounds and lights, and instability during gait. Her activity limitations include lower extremity dressing, driving, and playing her flute. Her participation restrictions include taking part in social gatherings, going to church, driving longer than 30 minutes, playing with her dogs, and teaching flute lessons. **Interventions:** Specific interventions included vestibular habituation and adaptation exercises, balance and gait training, and patient education. Physical therapy services were provided for approximately 11 weeks with a frequency of two times per week. **Outcomes:** After eleven weeks of physical therapy, the patient made improvements on the Lower Extremity Functional Scale (43/80 to 52/80), the Dynamic Gait Index (19/24 to 24/24), the Dizziness Handicap Inventory (86/100 to 68/100), and the Sharpened Romberg (2 seconds to >30 seconds). The patient improved in all her activity limitations and participation restrictions. She was able to play her flute for 20-minute intervals, play with her dogs, partake in social gatherings, and drive for 5 hours without symptoms. The patient had plans to pursue surgical intervention within the next year. **Discussion:** For a patient with a complex otologic history and a current diagnosis of bilateral SSCD, vestibular rehabilitation was an effective management option. The information from this case can be used to guide the effective treatment of similar patients diag-

nosed with vestibular dysfunction.

## Keywords

Physical Therapy, Superior Semicircular Canal Dehiscence, Vestibular Rehabilitation, Gaze Stabilization

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## 1. Introduction

### 1.1. Pathophysiology

Pathology or dysfunction of the vestibular system can lead to impairments of balance and overall postural control. There are numerous vestibular conditions, many of which are treatable with vestibular rehabilitation. This case report will provide insight on the conservative management of a particular vestibular pathology known as superior semicircular canal dehiscence (SSCD). SSCD is a relatively new condition, first described in 1998 by Minor *et al.* [1]. To understand the pathophysiology of SSCD, it is important to first review the anatomy of the inner ear and vestibular system. The semicircular canals are filled with a fluid called endolymph which has hair cells embedded within. In normal vestibular sensation, head rotation causes the hair cells in the cupula to bend. Mechanical motion of the cupula is detected by the sensory organ of the canals called the crista ampullaris and transmitted through the vestibular nerve (CNXIII) to the vestibular nuclei located in the brainstem [2]. The central pathways of the vestibular nuclei will not be discussed in detail in this case report. SSCD occurs when there is an opening at the apical turn of the superior SSC, which is thought to alter internal fluid mechanics and disrupt the normal firing rate of the vestibular nerve [2]. This opening in the superior canal creates what was described by Minor *et al.* as a “mobile third window,” in addition to the oval and round windows [1]. In normal inner ear systems, sound waves elicit movement of the stapes, which causes pressure to move through the basilar membrane of the scala tympani and out through the round window to be transmitted through the vestibular nerve and interpreted as sound [2]. In the presence of SSCE, the mobile third window allows for a shunt of acoustic energy. The energy can escape through the third window, causing movement of the cupula, which is then interpreted as a false sense of rotation leading to dizziness or feelings of unsteadiness in the patient [2].

### 1.2. Symptoms

Symptoms of SSCD are not always consistent between patients, and some patients experience bizarre symptoms that are not yet understood or explained pathoanatomically [3]. The most commonly noted symptoms in patients with SSCD are vertigo, oscillopsia, imbalance, hearing loss, and disequilibrium [1] [2]. Smaller dehiscence's (<2.5 mm) often present with either cochlear or vestibular symptoms, whereas larger dehiscence's (>2.5 mm) often present with a

combination of both cochlear and vestibular symptoms but this is not always the case [4]. The most common symptoms of SSCD are Tullio's phenomenon (nystagmus induced by loud noises) and Hennebert's sign (nystagmus induced by excessive pressure in the auditory canal) [2]. It is the disruption of perilymph and endolymph dynamics that makes the vestibular apparatus increasingly sensitive to auditory and pressure stimuli [2]. It is therefore imperative for the clinician to inquire about symptoms being brought on by noises [1]. Often the clinician will notice vertical-torsional eye movements induced by pressure to the inner ear or sound waves. However, without the use of Frenzel lenses, this sign of SSCD could be missed. Often, but not always, patients with SSCD will exhibit vertical-torsional eye movements the plane of the SSC when exposed to sound and pressure stimuli such as Valsalva maneuver [3]. These evoked eye movements are considered to be highly specific for SSCD. Patients with SSCD will often report strange perceptions such as getting dizzy from loud noises, being able to hear their footsteps, and even being able to hear their eyes blink [2]. These symptoms arise from a decrease in sensitivity of air conducted sounds and an increase in sensitivity to bone conducted sounds (especially at low frequencies), resulting in an air-bone gap. The air-bone gap creates a hypersensitivity to acoustics and explains why patients often report hearing their footsteps or heartbeats. The air-bone gap is also the explanation for why many patients with SSCD experience hearing loss at certain sound frequencies. The presence of these bizarre symptoms often causes patients to be mistaken for having a psychiatric condition and may lead to extensive psychiatric interventions and even unwarranted surgeries [2]. Despite the variability in symptoms, most patients end up seeking treatment due to chronic disequilibrium and unsteadiness.

### 1.3. A Review of the Literature on Etiology and Prevalence of SSCD

Due to a relatively new understanding of SSCD, there is not a well-established prevalence of the disorder. One dissection study proposed that the prevalence in the general population is around 0.5% with most cases occurring on the left side and a higher prevalence in males over females [2]. Another study analyzed 1000 adult temporal bone specimens to determine the incidence of SSCD and found dehiscence in only 0.5% of the specimens [5]. These researchers also noted that when dehiscence was present, it was often bilateral. It has been suggested that SSCD is due to failure of proper ossification in post-natal bone development, but etiology is poorly understood at this time [5]. It is estimated that in 2.5% of the population, the bones in the skull only develop to 60% - 70% of what is considered full thickness, which could explain a congenital predisposition to SSCD [6]. However, in normal human development, the superior canal is the first canal to ossify, which does not support the theory that SSCD is due to poor ossification in development [2]. In the absence of a congenital deformity, there is no known cause for the erosion of the superior semicircular canal bone, but physical trauma to the skull can play a role [6]. The exact mechanism of SSCD etiolo-

gy and predisposing factors are unclear as to whether or not it is a congenital or developed condition.

#### **1.4. Diagnosis**

Due to the high variability in patient reported symptoms, SSCD is often a difficult diagnosis to reach. Many patients are misdiagnosed with other vestibular conditions such as Meniere's disease, perilymph fistula, migraine, otosclerosis and patulous Eustachian tube [1] [3] [7] [8]. The accurate diagnosis of SSCD is dependent on a skilled interpretation of the patient's history, physical examination, and imaging results. Currently, the most reliable way to differentially diagnose SSCD from other inner ear conditions is through a high definition coronal plane computed tomography (CT) scan of the temporal bone [6]. CT scanning is the gold standard to detect the dehiscence of the superior canal and has been shown to have a specificity of 99% and a positive predictive value of 93% in the detection of symptomatic SSCD [2]. However, SSCD is detected in about 10% of all temporal bone CT scans which does not correlate to the 0.5% prevalence of SSCD in the population and may result in false positives. This discrepancy is explained by the technical issues associated with certain cuts of imaging. It is important to use clinical data in addition to CT scan when diagnosing SSCD in order to reduce the number of false positives [2]. MRI can also be used as a diagnostic tool but is rather expensive and not always deemed necessary in the diagnosis of SSCD. It has been shown to have 96% sensitivity and 98% specificity in detecting SSCD but is not always warranted [2]. Other vestibular testing such as vestibular evoked myogenic potential, electrocochleography, and the rotational chair test can also provide valuable information in the differential diagnosis process [6].

#### **1.5. Surgical Management**

Surgical plugging of the area of dehiscence is a valid option for patients with debilitating symptoms. The bone can be plugged with a bone graft from the temporal bone or cortical bone from the mastoid [2]. Surgical repair of SSCD via a middle fossa approach has been shown to resolve symptoms in 90% of patients but the bone used to repair the dehiscence can get reabsorbed [6]. There are also complications associated with the middle fossa approach including facial paralysis, cerebrospinal fluid leak, seizures, epidural hematoma, and intracranial bleeding [4]. Using cortical bone from the mastoid is the preferred surgical method because it is less likely to get reabsorbed [2]. Transcanal round window obliteration is another (less invasive) surgical intervention for SSCD that has been highly successful in short-term reduction of symptoms, but there is lacking research regarding the long-term effectiveness of this technique [4]. Given the fact that these surgeries are performed near sensitive, life-sustaining structures, it is crucial to differentially diagnose SSCD and be sure of the diagnosis before surgical intervention [8]. With that said, patients with severe, symptomatic SSCD can benefit from surgical intervention. There is limited research of patients with

SSCD who choose to decline surgery. However, one study concluded that most patients diagnosed with SSCD who declined surgery did not experience symptoms of hyperacusis, oscillopsia, or autophony. Based on that finding, the presence of autophony in persons with SSCD may warrant the decision to pursue surgery because of its effect on quality of life. Other symptoms that were apparent in almost all patients who chose surgical intervention include pressure induced vertigo, and hyperacusis in response to a tuning fork applied to the extremities [4]. Regardless of the patient's desire to pursue surgical intervention, all patients must be made aware of before electing for surgical intervention.

## 1.6. Conservative Management

Conservative management for SSCD is not well reported in the available vestibular rehabilitation literature to date. However, there is strong evidence supporting the use of vestibular rehabilitation therapy in the presence of vestibular hypofunction. When implemented appropriately, vestibular therapy can help the central nervous system adapt to a dysfunctional vestibular system and correct overdependence on the other two sensory systems (vision and proprioception) [9]. Correcting this imbalance can improve gait stability, reduce anxiety due to spatial disorientation, and address patients' activity limitations and participation restrictions [9]. The following case description will describe a patient with SSCD who attended an outpatient physical therapy clinic and was treated conservatively using vestibular rehabilitation therapy. All interventions used in this case are supported by previous literature to positively influence the vestibular system and will be discussed in further detail in the plan of care. Specific interventions used in this case include patient education, gaze stabilization exercises, environmental modification, sensory re-weighting exercises, perturbations, and core muscle activation [10] [11] [12] [13] [14]. The patient's progress in physical therapy was measured using valid and reliable outcome measures that accurately captured her impairments, activity limitations, and participation restrictions. These outcome measures will be thoroughly explained in the case description [15]-[25].

## 1.7. Purpose

The purpose of this case report is to describe the effects of physical therapy involving vestibular rehabilitation exercises such as gaze stabilization, sensory re-weighting, adaptation, and proprioceptive training in the treatment of a patient diagnosed with bilateral SSCD.

## 2. Case Description

### 2.1. Subjective

Informed consent was obtained from the patient to report her case. The patient is a 56-year-old woman with a complex otologic history and bilateral superior semicircular canal dehiscence. Her symptoms first appeared in 1990 with an insidious onset. After no successful diagnosis with over 30 different physician con-

sults, she finally met with a specialist in otology in 2010 and underwent a middle fossa approach to resurface her right superior semicircular canal. Initially, the patient experienced success from this procedure with a decrease in subjective report of symptoms. However, within the next three years, she subsequently developed reoccurrence of her symptoms due to the bone being resorbed. In 2014 she underwent a trans-mastoid plugging of her right superior semicircular canal which eliminated her symptom of hearing her heartbeat in that ear. After that surgery, she developed an onset of migraine headaches that she describes as present during all waking hours of each day. Despite her surgeries, she continues to experience an increase in her dizziness and headaches with exposure to bright lighting and loud noises, particularly low-frequency sounds. Driving, eye movements, and bending down to tie her shoes or play with her dogs also trigger her dizziness. She experiences autophony in her right ear and perceives an echo of her voice when she speaks as well as a sensation of hearing each footstep inside her right ear. Additionally, she is able to hear her eyes blink and the movement of her temporomandibular joints. When a 256 Hz tuning fork is applied to her extremities, she reports the vibration deep within her right ear. She experiences constant dizziness and gravitational receptor dysfunction vertigo, which explains her report of often feeling as if she is on a boat. She also experiences sound-induced dizziness (Tullio phenomenon) and spatial disorientation, especially while in social situations with multiple sensory stimuli. When lying supine, she experiences a feeling of increased pressure in her right ear. She has constant tinnitus in her right ear. The patient's stated goals are to return to her job as a professional flute player and flute lesson instructor, be able to drive up to 6 hours, be able to bend down to put shoes on, and be able to go out into social situations all without symptoms.

Other past medical history includes mitral valve prolapse, pulmonary embolism, systemic sclerosis, and tachycardia. Additional past surgical history includes in implanted Greenfield vena cava filter. The patient's current list of medication includes Acetaminophen, Bisoprolol, Celebrex, Cyclobenzaprine, Gabapentin, Hydroxychloroquine, Loratadine, Nifedical, Nortriptyline, Omeprazole, Sertraline, Topiramate, and Tramadol.

## **2.2. Medical Testing**

The patient has been referred to physical therapy for vestibular rehabilitation with a medical diagnosis of bilateral superior semicircular canal dehiscence and endolymphatic hydrops. Although her symptoms are primarily on the right side, a bilateral diagnosis was made due to evidence of bilateral dehiscence on imaging. Prior to her physical therapy evaluation she has undergone extensive vestibular testing for the following differential diagnoses: Meniere's disease, benign paroxysmal positional vertigo, vestibular neuritis, vestibular migraine, perilymph fistula, labyrinthine fistula, multiple sclerosis, multisensory dizziness, psychophysiological dizziness, Mal de Debarquement syndrome, labyrinthitis, ototoxicity, cervical vertigo, endolymphatic hydrops, delayed endolymphatic hydrops, laby-

rinthine concussion, vertebral basilar insufficiency, otosyphilis, presbystasis, mitochondrial myopathy, cardiac arrhythmia, and Arnold-Chiari malformation. Her high-resolution temporal bone CT scan showed superior canal dehiscence on the right, and her MRI showed superior semicircular canal dehiscence on the left as well. Her electrocochleography was positive for endolymphatic hydrops. Her moving Platform Pressure Test was positive in her left ear, which is consistent with SSCD. Her computerized dynamic posturography testing showed evidence of a vestibular deficit type of impaired postural control and increased sway, which is the reason for her referral to physical therapy.

### 2.3. Systems Review

Following the subjective portion of the examination, a thorough physical therapy systems review and screening process was completed as follows:

- Integumentary: WNL—Skin appeared grossly normal, no abnormalities noted.
- Cardiovascular: WNL—HR, BP, radial pulse.
- Musculoskeletal:
  - Cervical range of motion (ROM) and shoulder ROM both WNL.
  - Standing/seated posture appeared grossly normal, no significant deviations noted.
  - The patient demonstrated a dysfunctional gait pattern with non-rhythmic cadence, variable step length, with a tendency to favor her left side and drift toward the left during gait.
- Respiratory: WNL—visible recruitment of accessory breathing muscles.
- Neurological:
  - All cranial nerves intact.
  - Positive for blurred vision.
  - Balance screen indicated possible dysfunction of somatosensory system as patient was unable to perform single leg stance without support. Patient appeared to be heavily reliant on vision and demonstrated moderate sway in normal stance with eyes closed, requiring external support.

Following systems review and screen, the patient was deemed appropriate for further physical therapy testing.

### 2.4. Bedside Clinical Ocular Exam

All vestibular testing was performed with the naked eye as the physical therapist did not have access to Frenzel lenses. Head thrust test was negative indicating intact VOR. Gaze-evoked nystagmus testing was negative. Dix Hallpike test and supine roll test were both negative bilaterally, ruling out BPPV. Interestingly, none of the patient's symptoms were reproduced on the initial evaluation day with any of the vestibular testing. Despite an inability to reproduce symptoms with vestibular testing, further investigation was performed using specific outcome measures to gather objective data.

### 2.5. Outcome Measures

Specific outcome measures were chosen by the physical therapist to best capture

the patient's impairments, activity limitations, and participation restrictions (Table 1). These outcome measures were also used throughout the course of treatment to monitor the patient's response to treatment objectively.

- **Dizziness Handicap Inventory (DHI):** This test is a set of questioned specifically aimed at gathering data regarding how the patient's dizziness affects their overall quality of life and difficulty with certain activities. With regards to construct validity of DHI in vestibular dysfunction, there was an adequate relationship between the number of dizzy spells per year and the DHI score [15]. These researchers also found that those patients who reported more frequent attacks of dizziness and unsteadiness scored significantly poorer on DHI, demonstrating content validity [15]. Criterion validity of the DHI was found to have an excellent correlation with the Activities Balance Scale (ABC) ( $r = -0.64$ ) and the SF-36 ( $r = 0.53$  to  $0.72$ ,  $p = 0.001$ ) [16] [17]. The test-retest reliability of DHI total score for vestibular dysfunction was found to be excellent ( $r = 0.97$ ,  $p < 0.0001$ ) [15]. The minimal clinically important difference (MCID) of the DHI specifically for vestibular patients is a decrease of at least 18 points from pre-test to post-test [15].
- **Dynamic Gait Index (DGI):** This test assesses the patient's ability to change speed and direction, and navigate obstacles during gait. It also stresses the vestibular system by asking the patient to perform various head motions during gait. The DGI has a moderate correlation with the Berg Balance Scale (BERG) for patients with vestibular disorders ( $r = 0.71$ ;  $p < 01$ ) which establishes its criterion/concurrent validity [18]. The DGI is more sensitive than the BERG in identifying vestibular patients who are at risk of falling [18]. Test-retest reliability of the DGI total score for vestibular patients has been shown to be excellent (ICC = 0.86) [19]. Interrater reliability of individual DGI items varied from poor to excellent based on kappa values (kappa range, 0.35 - 1.00) [20]. Composite kappa values showed good overall interrater reliability (kappa = 0.64) of total DGI scores. The Spearman rho demonstrated excellent correlation ( $r = 0.95$ ) between total DGI scores given concurrently by two different raters [20]. To the author's knowledge, there have not been any studies determining the construct validity of the DGI with vestibular disorders. However, the DGI has been validated for its ability to determine

**Table 1.** Initial functional status.

Outcome Measure	Status at Initial Evaluation
Lower Extremity Functional Scale	43/80
Dynamic Gait Index	19/24
Dizziness Handicap Inventory	86/100
Sharpened Romberg	2 Seconds
Patient Reported Functional Limitations	Status at Initial Evaluation
Playing Flute	Unable to Perform
Lower Extremity (LE) Dressing	Severe Limitation, Falls
Driving	<30 Minutes
Stairs	Needs Railing, Head down

fallers versus non-fallers in patients with Parkinson's disease and multiple sclerosis [21]. When using the DGI for vestibular patients, the minimal detectable change (MDC) is calculated to be a change of 3.2 points [19] [22].

- **Sharpened Romberg:** This test involves having the patient stand in tandem stance first with eyes open and then with eyes closed, for a total of 30 seconds each. The Sharpened Romberg has been suggested as a simple test to assess postural control in patients with vestibular hypofunction [9]. The test-retest reliability of the Sharpened Romberg was found to be good at 0.90 - 0.91 eyes open and 0.76 - 0.77 eyes closed in healthy women [23]. However, with regards to construct validity, no correlation was found between the Sharpened Romberg and the ABC [24]. The MDC and MCID of the Sharpened Romberg have yet to be established.
- **Lower Extremity Functional Scale (LEFS):** This test is a questionnaire assessing the patient's difficulty with various activities of daily living. It is not often used for vestibular patients but was used in this case to capture how the patient's condition affected her ability to perform different activities. The construct validity of the LEFS has been shown to be excellent when compared to the physical function portion of the SF-36 ( $r = 0.80$ ; 95%) [25]. The test-retest reliability of the LEFS has also been shown to be excellent ( $r = 0.86$ ; 95%) [25]. The MDC and MCID of the LEFS are changes of at least 9 points [25].

### 3. Patient Evaluation

The patient's primary impairments associated with her vestibular condition are dizziness, autophony, acoustic hypersensitivity, Tullio phenomenon, pressure induced vertigo, and postural disequilibrium. The only secondary impairment determined at initial evaluation was the patient's decreased coordination, noted by visual observation of the patient performing outcome measures. The impairments mentioned above interfere with sensory systems that are critical for daily function and can lead to activity avoidance, loneliness, and depression [9] [22]. For the patient in this case, her impairments have led to limitations in certain activities and restricted her from participating in things she was previously able to participate in. All of the patient's specific impairments, activity limitations, and participation restrictions have been outlined in the context of the International Classification of Functioning, Disability, and Health (ICF) (Table 2).

### Diagnosis

The patient's physical therapy diagnoses have been established within the ICD-10 classification system as follows:

- R26.2 Difficulty walking, not elsewhere classified.
- R27.8 Other lack of coordination.

## 4. Plan of Care

### 4.1. Goals

The patient's stated goals are to eliminate her symptoms and return to her job as

**Table 2.** ICF impairments.

ICF Domain	Patient Status
Body structure function impairments	Constant headaches, dizziness with head rotation and lateral eye movements, sensitivity to sounds and lights and instability while walking.
Activity limitations	Lower extremity dressing (difficulty bending down with flexed head), driving, and playing her flute.
Participation restrictions	Participating in social gatherings with friends, going to church, driving to destinations that are greater than 30 minutes away, playing with her dogs, and teaching flute lessons.

a professional flute player and flute lesson instructor. Physical therapy goals were set using outcome measure data as well as patient-reported functional limitations (**Table 3**). All goals were initially set for 6 weeks considering expected prognosis of the patient in conjunction with her insurance coverage of physical therapy visits.

#### 4.2. Prognosis

Due to the patient's complicated otologic history and complex diagnosis, the physical therapy prognosis for this patient was determined to be fair. Her symptoms were not reproducible with vestibular testing and did not have a consistent pattern. Her medical diagnosis was structural in nature and therefore she was not expected to be completely symptom free upon discharge, but she was expected to make functional gains in the aforementioned functional goals. The patient was motivated to participate in physical therapy in hopes to improve her condition and overall quality of life. The frequency and duration of physical therapy sessions were set at two times per week for six weeks, totaling 12 visits, with plans to re-evaluate progress every 30 days. This frequency of twice per week allowed the therapist to monitor progress, review the home exercise program (HEP), and alter interventions accordingly. A successful vestibular rehabilitation program involves weekly visits to the therapist, in conjunction with daily repetition of exercises by the patient at home [26]. As a patient begins to show a decreased rate of progression, it is common to decrease the frequency of office visits to bi-weekly and emphasize a home maintenance program [26]. In this particular case, the patient was on vacation during week three of treatment and was forced to decrease frequency after week eight to once per week due to financial reasons.

#### 4.3. Treatment Plan

The proposed plan of care for this patient addressed the aforementioned body structure/function impairments, activity limitations, and participation restrictions. The treatment consisted heavily of vestibular adaptation exercises, habituation exercises, static and dynamic balance activities, gait training, and patient

**Table 3.** Patient goals.

<b>Outcome Measure</b>	<b>Initial</b>	<b>Goal</b>
Lower Extremity Functional Scale	43/80	55/80
Dynamic Gait Index	19/24	24/24
Dizziness Handicap Inventory	86/100	66/100
Sharpened Romberg	2 seconds	30 seconds
<b>Patient Reported Functional Limitations</b>	<b>Initial</b>	<b>Goal</b>
Flute	Unable to perform	2x/week for 30 minutes
LE Dressing	Severe limitation, falls	Easy, symptom free
Driving	<30 minutes	6 hours
Stairs	Needs railing, head down	No railing, looking ahead

education.

Educating the patient about her condition was the priority of the first treatment session. Compliance with physical therapy programs and HEP can be increased by addressing barriers that patients perceive, increasing positive feedback, and reducing perceived helplessness [10]. Helping the patient understand her condition and her role in the physical therapy management process is important to ensure compliance [10].

A conflict between sensory information from the vestibular and visual systems can lead to a disrupted perception of spatial orientation and cause a feeling of disequilibrium [11]. Repetition of vestibular and visual exercises has been shown to cause adaptation of these systems and eliminate symptoms in these patients [11]. One study using X1 and X2 gaze stabilization exercises showed significant improvements in recovery of gaze stability during head movements in patients with bilateral vestibular hypofunction [22]. The patients involved in this study were told to perform the exercises 4 - 5 times daily and demonstrated improvements in about five weeks, indicating that repetition is likely an important consideration in a vestibular adaptation exercise program [22].

Hearing can have an impact on balance as well. Impaired hearing has been shown to increase postural sway suggesting that auditory input is critical for maintaining balance [12]. With that evidence in mind, many of the adaptation exercises used in this case report were first performed in a quiet room and progressively carried out in the busy gym environment of the clinic to maximize external stimuli. Having the patient perform exercises in a therapy gym with different auditory stimuli including music and various voices was a strategy used to mimic other environments the patient will be exposed to throughout her everyday life.

Patients with vestibular system dysfunction tend to rely more heavily on proprioception and vision for maintaining balance and making postural adjustments. This tendency leads to abnormal patterns of dependence on other sensory stimuli and can result in further inhibition of the vestibular system [9]. Sensory reweighting interventions such as balance training are beneficial for

these patients because they can help restore a more normalized relationship between the three sensory systems involved with balance. One review of the literature concluded that balance training under single-task conditions does not transfer to multiple task situations [13]. This idea further supports the notion of training specificity and implies that successfully improving a person's balance in everyday life situations requires dual task balance training [13]. The balance training used in this case report started with single-task conditions and progressed to dual task balance training as the patient improved.

Perturbation training is effective in training the proprioceptive system to be able to recover balance in response to non-anticipatory stimuli [13]. This type of training utilizes the specificity principle of training and is most similar to real life balance recovery situations because the patient does not have anticipatory control over the situation. Perturbation training has been shown to be superior to traditional balance exercises in improving reactive postural control [13]. Based on the evidence, perturbation training was also utilized in this case report.

Activation of the core musculature is necessary for a person to make postural adjustments. Although there is a debate in the literature as to which exact muscles are considered "the core", it is widely accepted that the core consists of the muscles around the trunk and lumbopelvic region [14]. Performing exercises on a stability ball leads to greater recruitment of core musculature, which can therefore enhance one's ability to make postural adjustments and react to external demands [14]. Based on the balance screen portion of the neurological systems review and the DGI testing, the patient demonstrates difficulty with dynamic postural control. Stability ball training was used in conjunction with perturbation training to maximize the patient's ability to use core musculature in response to external stimuli.

Treatments were progressed based on patient response and it is important to note that there are no specific guidelines with regards to appropriate progression. The patient was advanced to more challenging vestibular adaptation and balance exercises once she was able to successfully complete an exercise for two 30 second intervals, in two consecutive sessions, without symptoms. Intervention progression of vestibular adaptation exercises consisted of increasing speeds and altering the external environment. The initial exercises given have been outlined and described (Table 4). Interventions were performed in the clinic twice per week and also taught to the patient to complete as her home exercise program (HEP). She also received a printout of her HEP with instructions and visual aids. The initial exercises were progressed as the patient tolerance to these activities improved, and new exercises were added as the patient's symptoms decreased (Table 5).

## 5. Implementation of Interventions

An overview of each week of treatment is provided with information about the patient's response to interventions. Symptoms were monitored clinically via subjective report of the patient using a modified version of the Borg category

**Table 4.** Initial exercises (weeks 1 - 4).

Specific Interventions	Description/Progressions	Rationale
Patient education	Education regarding relationship between visual, vestibular, and somatosensory systems.	Increase patient confidence in physical therapy and compliance with HEP.
VOR oculomotor exercises	Therapist holds pen out in front of patient and moves pen horizontally within 60-degree arc from patient's visual field while patient tracks pen with only eye movement. Progressed to vertical and diagonal patterns and different speeds.	Enhance vestibular adaptation.
VOR X1 gaze stabilization exercises	Therapist holds pen out in front of patient while patient fixes eyes on pen and slowly but continuously rotates head horizontally 60-degrees to either side. Progressed to vertical and diagonal patterns and different speeds.	Encourage dissociation of eye/head movement.
VOR X2 exercises (eyes/head opposite)	Therapist holds pen out in front of patient and moves pen horizontally within 60-degree arc from patient's visual field while patient tracks pen with eyes and slowly but continuously rotates head in opposite direction of pen. Progressed to vertical and diagonal patterns and different speeds.	Enhance vestibular adaptation by improving optokinetics and inducing retinal slip.
Walking with horizontal head turns, eyes fixed ahead on target	Patient ambulates straight ahead linearly while slowly and continuously turning head 30-degrees to either side. Progressed with various speeds of gait and head turning.	Enhance vestibular adaptation during dynamic activity.
Walking with vertical head nods, eyes fixed ahead on target	Patient ambulates straight ahead linearly while slowly and continuously nodding head 30-degrees up and down. Progressed with various speeds of gait and head movements.	Enhance vestibular adaptation during dynamic activity.
Walking with eyes looking left/right	Patient ambulates straight ahead linearly while moving eyes horizontally. Progressed with various speeds of gait.	Utilize all sensory inputs to improve dynamic postural control.
Walking with eyes looking up/down	Patient ambulates straight ahead linearly while moving eyes vertically. Progressed with various speeds of gait.	Utilize all sensory inputs to improve dynamic postural control.
Standing balance (dynamic surface)	Dynamic surface used was Airex pad. Progressed to unilateral stance, eyes closed, perturbations.	Promote increased utilization of somatosensory system in postural control.
Tandem balance (eyes open)	Standing with feet in tandem stance. Progressed to Airex pad, eyes closed, perturbations.	Promote increased utilization of somatosensory system in postural control by altering base of support.

**Table 5.** Additional interventions (added weeks 4 - 8).

Specific Interventions	Description/Progressions	Rationale
VOR X1/X2 exercises with walking	Same X1/X2 exercises described previously but now performed during forward ambulation with the patient holding the pen. Progressed with duration, speed of gait and head turns.	Mimic functional everyday tasks and promote safe vestibular adaptation.
VOR X1/X2 exercises with side-stepping	Same X1/X2 exercises described previously but now performed while side-stepping in frontal plane with patient holding the pen. Progressed with duration, speed of gait and head turns.	Challenge vestibular system and promote vestibular adaptation through functional movement.
Stool push	With patient seated on stool, therapist pushes patient (forward translation) while patient performed head turns in various directions. Progressed with speed of head turns and speed of linear translation.	Mimic functional driving scenario and enhance vestibular adaptation.
Stability ball arm reaches	Patient seated on stability ball and reaches arms in various directions with trunk excursion. Progressed to eyes closed and perturbations.	Challenge dynamic stability and encourage cephalocaudal functional activity.
Stability ball marching	Patient seated on stability ball alternating lifting legs from floor. Progressed to opposite arm/leg, eyes closed, and perturbations.	Narrow base of support in order to increase somatosensory demands.
Ladder drills	Various stepping drills with agility ladder. Progressed to head turns, different visual fixation, increased speeds.	Reinforce normalized movement patterns and ability for vestibular system to adapt to transition in direction and speed.
Cone reaches	Hip hinge on single leg (golfer's lift) reaching for cones placed near patient's feet.	Mimic functional reaching task and promote vestibular adaptation.
Patient education on playing flute	Patient brought flute into clinic so therapist could understand demands of the activity and offer suggestions to minimize symptoms.	Functional activity of high importance to patient.

scale [27]. The Borg category scale is often used to assess patients' rating of perceived exertion or perceived dyspnea [27]. It has been shown to have high concurrent validity when compared to the modified Medical Research Council scale ( $r_s = 0.79$ ), the Oxygen-Cost Diagram ( $r_s = -0.83$ ), and the Baseline Dyspnea Index ( $r_s = -0.71$ ) [27]. In the context of this case report, a modified Borg rating scale for dizziness was used, which asks the patient to rate their perceived dizziness from 0 (nothing at all) to 10 (maximal) [28]. When performing exercises in the clinic and during the HEP, the patient was instructed to keep her symptoms less than a 4/10 and discontinue the activity if her symptoms reached a 5/10 on

the modified Borg rating scale for dizziness.

**Week 1:** The first week of treatment consisted of VOR X1 and X2 exercises to challenge the vestibular system. The patient first performed all of these activities in the seated position. All X1 and X2 patterns were performed for 30 seconds or until her symptom of headache or dizziness exceeded 4/10 on the modified Borg rating scale for dizziness. Between each exercise she rested for 10 - 30 seconds or until her symptoms decreased to her baseline (which she reported as 2/10). The same 60-degree total arc of motion was used for each pattern. The patient had particular difficulty with the head and eyes moving in opposite directions, especially in the horizontal plane and diagonal planes. Her symptoms came on sooner, and she required increased rest time with these exercises. After her first treatment session, the X1 and X2 exercises were progressed to being performed in standing with a narrow base of support (BOS). All exercises during the first week of treatment were performed in private treatment room to minimize sensory stimuli.

**Week 2:** The second week of treatment involved increasing the speed of all VOR X1 and X2 exercises and further increasing difficulty by altering BOS on a foam pad. New interventions added in week 2 included walking 50 ft while continuously moving the head in all directions (side to side, up and down, and diagonal patterns). She presented with decreased ability to walk in a straight path (often drifting left) and demonstrated variable stride length and occasional stumbles. Her symptoms of dizziness occurred after each exercise and she was given a rest in between for her symptoms to calm down. After completing each direction of head/eye movement once, the patient was instructed to repeat each head motion while focusing eyes on target across the room. She completed these exercises with an increase in dizziness after each, especially the horizontal head movement.

Another intervention added in the second week of treatment was standing on the foam pad with wide BOS and eyes closed. The patient required hand-held assist (HHA) to complete this exercise for 1 minute and demonstrated increased ankle strategies to maintain balance. All interventions during week two and beyond were performed in therapy gym to allow for an increase in sensory stimuli to help mimic real world environment. The treatment gym has auditory stimuli (music and voices) and variable visual stimuli including natural lighting from windows, overhead lighting, and other patients moving about the therapy gym.

**Week 3:** Patient was absent from physical therapy due to personal vacation. Before leaving, she was instructed to continue with HEP and monitor symptoms. She was also instructed to perform her VOR exercises while on the train with a moving background. After vacation, she reported no symptoms while on the train but she did forget to perform her HEP on the train.

**Week 4:** During the fourth week of treatment the patient was able to tolerate a further increase in speed and duration of X1 and X2 exercise up to 2 minutes while standing on a foam pad. Her gait pattern with the walking exercise was

becoming more normalized with symmetrical step length and only occasional drift to her left side. She was able to increase gait speed as well. She was able to tolerate 30 seconds of standing on the foam pad with eyes closed, standby assist (SBA) and only minimal ankle strategies to maintain an upright posture. New interventions added in the fourth week of treatment included side-stepping while performing pen exercises in the horizontal plane. This intervention was added based on the patient's responses to interventions over the past couple weeks. She experienced increased symptoms when pairing a linear movement with head and eye movements in opposite directions.

**Week 5:** Interventions added during week five treatments included the stool push exercises was used specifically to reproduce the linear translation associated with driving. The therapist instructed the patient to turn head at various points in time while pushing the patient forward on the stool. Initially, the patient had difficulty with turning head due to fear of falling off stool and minor reports of dizziness. She progressed well through this exercise demonstrating improved ability to tolerate horizontal head and eye movements during forward linear translation. Other exercises were progressed appropriately.

**Week 6:** New interventions added in week six included stair training and seated exercises on a stability ball. The stair training began with allowing the patient to navigate the stairs using a handrail on her preferred side and visual fixation of her choosing. When asked to keep eyes fixed 3 - 4 steps ahead of her rather than straight down at her feet, she demonstrated decreased speed and occasional scuffing of feet on stairs. The Patient was able to navigate stairs without handrail only when compensating with visual fixation on her feet. She eventually progressed to safely navigating stairs without using a handrail. The patient initially demonstrated decreased postural control while performing upper extremity reaching and lower extremity marching exercises on the stability ball. However, by the end of the sixth week, she improved significantly with these activities. She was able to maintain upright posture with minimal trunk sway in response to perturbations. Other exercises were progressed appropriately.

**Week 7:** During week seven, single leg cone reaches and various drills using the agility ladder were added. Single leg cone reaches were added specifically to improve the patient's ability to reach for things on the ground, an activity that often exacerbated her symptoms. She was instructed to hinge at her hips and reach toward 3 different cones place near her feet. Initially, she demonstrated decreased dynamic postural control with this activity and required HHA. After two sessions of performing this exercise she demonstrated significant improvement in her ability to hinge at her hips and reach down for objects without any onset of symptoms. The agility ladder was used to encourage increased body awareness by using various stepping patterns without allowing patient to fixate her eyes on her feet.

**Week 8:** No new interventions were added during week 8. The patient continued to show progress with balance activities but still had some difficulty with horizontal head turn while side-stepping. After eight weeks of treatment, the

primary author had discontinued working at the physical therapy clinic and the remaining three weeks of care was carried out by another physical therapist. Interventions during the final three weeks of treatment remained the same but were adjusted accordingly in regards to volume and intensity based on patient tolerance. The patient was forced to decrease the frequency of physical therapy to once per week during the final three weeks due to financial reasons. The patient was compliant with HEP throughout the entire course of treatment, based on subjective report.

## 6. Outcomes

Every four weeks, progress notes indicating the patient's response to physical therapy treatment were completed. A final discharge note was written after the eleventh week of treatment due to the patient's decision to discontinue physical therapy based on financial reasons. In the context of the ICF framework, the patient demonstrated mild improvement in body structure-function impairments and significant improvements in her activity limitations and participation restrictions as outlined below. Specific objective outcomes based on patient goals from initial evaluation can be found in **Table 6**.

**Table 6.** Patient progress toward goals.

<b>Outcome Measure</b>	<b>Initial</b>	<b>4 Weeks</b>	<b>8 Weeks</b>	<b>11 Weeks</b>	<b>Status</b>
Lower Extremity Functional Scale	43/80	38/80	52/80	58/80	100% Met
Dynamic Gait Index	19/24	22/24	19/24	24/24	100% Met
Dizziness Handicap Inventory	86/100	74/100	74/100	68/100	90% Met
Sharpened Romberg	2 seconds	>30 seconds, no sway	>30 seconds, no sway	>30 seconds, no sway	100% Met
<b>Patient Reported Functional Limitations</b>	<b>Initial</b>	<b>4 Weeks</b>	<b>8 Weeks</b>	<b>11 Weeks</b>	<b>Status</b>
Playing Flute	Unable to Perform	5 - 10 minutes	15 - 30 minutes	Up to 2 hours, mild-moderate symptoms	70% Met
Lower Extremity Dressing	Severe Limitation, falls	Difficult, needs support	Needs support	Less support required	90% Met
Driving	<30 minutes	30 minutes	1 hour	45 minutes	20% Met
Stairs	1 at a time, needs railing, head down	Needs railing, head down	No railing ascending, needs railing down	No railing	80% Met

Note: Normative value for the sharpened Romberg test is >30 seconds [9].

### **6.1. Body Structure Function Impairments**

After eleven weeks of physical therapy treatment, the patient demonstrated a decrease in her frequency and duration of headaches. She continues to experience occasional dizziness with head rotation and lateral eye movement, but she reports that the severity of her symptoms has decreased tremendously. She also continues to experience increased sensitivity to loud noises and bright lights, but she has learned strategies to manage her symptoms. She reports that physical therapy has allowed her to understand the specific triggers for her symptoms and has taught her strategies manage those symptoms better.

### **6.2. Activity Limitations**

The patient has learned strategies to complete activities she was previously unable to complete without experiencing symptoms. She is now able to perform LE dressing tasks with only minimal handheld support and no onset of symptoms. Although she is still unable to play her flute without symptoms, she does report her symptoms have lessened as she has learned strategies to minimize symptoms during this activity. She can tolerate playing her flute for up to 2 hours. She can drive a maximum of one hour before experiencing symptoms, but she reports the gaze exercises she learned in physical therapy have helped improve her ability to drive.

### **6.3. Participation Restrictions**

The patient made the most notable progress in regards to her participation restrictions. Before starting physical therapy, she was unable to participate in social gatherings or go to church. She is now able to participate in both of those activities and has learned how to prevent and manage her symptoms during. She often keeps earplugs in her purse and finds that wearing them can help decrease her symptoms when they come on in social situations. She is now able to walk and play with her dogs without any onset of symptoms. She is still unable to participate in teaching flute lessons.

### **6.4. Subjective Outcomes of Patient**

Overall, the patient reported she was 50% better as a result of physical therapy interventions. She was overall pleased with her improvement and felt as if she had gained the appropriate knowledge and skills for her to manage her condition successfully upon discontinuation of physical therapy services. She stated that physical therapy has taught her many strategies to understand her body better and manage her symptoms. Despite the improvement made from conservative management of the patient's condition, she continues to experience symptoms that interfered with her quality of life and does plan to seek surgical intervention for her condition in the future from a surgeon specializing in SSCD.

## **7. Discussion**

The purpose of this case report is to describe the effects of physical therapy in-

volving vestibular rehabilitation exercises such as gaze stabilization, sensory reweighting, adaptation, and proprioceptive training in the treatment of a patient diagnosed with bilateral SSCD. With eleven weeks of physical therapy emphasizing vestibular rehabilitation, the patient demonstrated mild improvement in her body structure/function impairments, and significant improvements in her activity limitations, and participation restrictions. The most significant improvements for this patient were in her ability to participate in social gatherings, play with her dogs, and drive with minimal to no symptoms. This case report is one of few pieces of literature describing the effects of physical therapy services on a patient diagnosed with bilateral SSCD.

The initial treatment focused on educating the patient on the pathophysiology of her condition and helping her understand the relationship among the visual, vestibular, and somatosensory systems. This early education allowed for increased patient compliance in the program. The next priority in treatment was to initiate gaze stabilization exercises and sensory reweighting exercises to facilitate vestibular adaptation. The therapist taught all VOR gaze stabilization exercises to the patient so that the patient could complete these as part of her HEP. The patient progressed well through all interventions and demonstrated improvement from session to session.

When treating a patient with SSCD, it is important to understand the treatment options available for that patient. A thorough understanding of the surgical approaches available, as well as the success rates and associated risks with each procedure is crucial. There is a limited research of patients with SSCD who choose to decline surgery. However, one study concluded that most patients diagnosed with SSCD who declined surgery did not experience symptoms of hyperacusis, oscillopsia, or autophony [4]. The presence of autophony in persons with SSCD may warrant the decision to pursue surgery because of its effect on quality of life. Other symptoms that were apparent in almost all patients who chose surgical intervention include pressure induced vertigo, and hyperacusis in response to a tuning fork applied to the extremities [4]. This information is important to share with patients who inquire about surgical intervention.

Because balance and posture are critical functions of human life, patients with vestibular dysfunction are more likely to experience psychological distress such as anxiety, depression, withdrawal, avoidance, and loneliness [9]. In this particular case, the patient did report that her quality of life was affected but did not show any signs of depression. Although her social life was limited, she appeared happy and reported that she was still able to maintain positive relationships with her family and friends. When working with any vestibular patient, it is important for clinicians to inquire about their overall quality of life and be aware of this phenomenon to know when to refer patients to the appropriate resources.

The amount of variation in treatment interventions is a primary limitation of this case report. With a physical therapy approach that involves interventions targeting multiple bodily systems, it is difficult to determine which interventions were most effective. Another limitation of this case report is the fact that treat-

ment was interrupted by the patient's personal vacation. A lapse in physical therapy management may have hindered the progress of the patient. A third limitation of this case report was the patient's availability of financial resources. After she had completed her first twelve visits, her insurance no longer covered physical therapy treatment and she was forced to pay cash, which further limited her attendance. Lastly, the patient was obliged to drive herself to physical therapy appointments, which is one of the activities that exacerbated her symptoms. Often, her ability to complete all interventions was limited by an increased baseline of symptoms from driving to the clinic.

There are possible alternative explanations for the patient's decrease in symptoms and improvements in functional mobility. The improvements made by this patient could be attributed to factors other than the physical therapy interventions such as time, social interaction, or the effects of neuroplasticity. Another factor that may have contributed the patient's overall improvement is the dandelion root tea she drank daily. Dandelion root extract has been shown to act as a diuretic, serve as an antioxidant, and decrease inflammation [29] [30]. The diuretic effects of the dandelion root tea may have contributed to normalizing the pressure balance of endolymph and perilymph in the semicircular canals, but more research needs to be conducted to support this hypothesis [29] [30]. In retrospect, this case could be improved by limiting treatment variables to determine which intervention was most effective.

A possible explanation for the patient's decreased score on the DGI and DHI at the eight-week interval is that she was participating in more activities than she previously was which may have caused her to be more aware of her limitations. As her symptoms decreased, she was more active in social situations, which may have informed her of new activity limitations that she was previously unaware of because she had not attempted them. Other outcome measures could have been added to the plan of care to better identify the patient's progress with sensory reweighting. A recommended outcome measure to use in further studies of patients with SSCD is the Clinical Test of Sensory Interaction and Balance (CTSIB) because of its ability assess balance in a variety of conditions. The CTSIB allows the tester to infer which sensory systems are most dysfunctional based on the patient's ability to tolerate each condition [31].

Although successful conservative management for SSCD is not well established in the literature, this case report provides evidence to support the effectiveness of gaze stabilization and sensory re-weighting exercises in the clinical management of patients with SSCD. The current clinical practice guidelines for vestibular hypofunction suggest that a supervised vestibular rehabilitation program can improve patient outcomes, quality of life, and psychological well-being [32]. The treatment program outlined in this case report can be practically applied in a clinical setting. Physical therapists and other healthcare professionals can use these gaze stabilization and sensory re-weighting exercises with their patients to help improve function and restore any activity and participation restrictions.

Successful results of vestibular rehabilitation in the treatment of vestibular hypofunction are well supported in the literature [9] [22] [32]. However, more research is warranted to determine confidently the specific interventions that produce positive outcomes in patients diagnosed with SSCD. Further research should also be conducted to identify certain patient characteristics that may provide insight as to which patients will respond best to conservative management of SSCD and which patients should consider surgical intervention. A successful physical therapy treatment program for SSCD should consider all patient impairments, activity limitations, and participation restrictions. The results of this case cannot be generalized to all patients with vestibular hypofunction, but it does provide a viable treatment protocol for patients diagnosed with unilateral or bilateral SSCD. All patients seeking physical therapy management should be thoroughly evaluated and treated via an individualized physical therapy program tailored to individual impairments.

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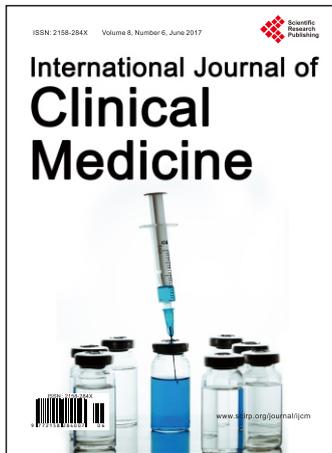
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- Clinical and Experimental Otorhinolaryngology
- Clinical and Experimental Pathology
- Clinical and Experimental Pharmacology and Physiology
- Clinical and Molecular Allergy
- Clinical and Translational Oncology
- Clinical Anesthesia
- Clinical Apheresis
- Clinical Autonomic Research
- Clinical Biochemistry and Nutrition
- Clinical Biomechanics
- Clinical Cardiology
- Clinical Case Studies
- Clinical Child Psychology and Psychiatry
- Clinical Chiropractic
- Clinical Densitometry
- Clinical Effectiveness in Nursing
- Clinical Endocrinology and Metabolism
- Clinical Epidemiology
- Clinical Forensic Medicine
- Clinical Gastroenterology and Hepatology
- Clinical Genetics
- Clinical Haematology
- Clinical Hypertension
- Clinical Imaging
- Clinical Immunology
- Clinical Implant Dentistry and Related Research
- Clinical Interventions in Aging
- Clinical Laboratory Analysis
- Clinical Linguistics & Phonetics
- Clinical Lipidology
- Clinical Microbiology and Antimicrobials
- Clinical Microbiology and Infection
- Clinical Microbiology and Infectious Diseases
- Clinical Molecular Pathology
- Clinical Monitoring and Computing
- Clinical Neurology and Neurosurgery
- Clinical Neurophysiology
- Clinical Neuropsychology
- Clinical Neuroradiology
- Clinical Neuroscience
- Clinical Nursing
- Clinical Nutrition
- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

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