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REVIEW ARTICLE OPEN ACCESS

Ultrasound as A Viable Option in the Diagnosis of Pelvic Congestion Syndrome

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The Pelvic Congestion Syndrome is a disease that manifests usually with chronic pelvic pain, impairments in daily activity due to pain severity, dyspareunia, and dysmenorrhea. It affects mainly women in premenopausal stages. The gold-standard procedure for diagnosis is venography, which has an invasive character. This syndrome is underdiagnosed, partly because women tend not to report symptoms to their doctors, but also because of the tendency to delay or deny invasive procedures until there is a severe alteration in the quality of life. Transabdominal and transvaginal ultrasound examination can detect pelvic vein insufficiency, which is the main cause of pelvic congestion syndrome. Vein diameter, the grade of reflux, velocity, and extension of affected vessels are among the parameters that can be assessed. Implementing a diagnosis scheme using only ultrasound parameters could lead to an increase in the number of diagnosed patients.

Keywords: Pelvic congestion syndrome, pelvic pain, ultrasonography

Introduction

Pelvic congestion syndrome (PCS) represents a cause of chronic pelvic pain (CPP). CPP is defined as a non-cyclic pelvic pain which occurs for a period of time usually longer than 6 months, mainly in premenopausal women. The pain can generate functional disabilities and is not relieved by standard pain medication. Beside the CPP which worsen after prolonged hours of standing or sitting, symptomatology can include dyspareunia, depression, rectal discomfort, dysmenorrhe and urinary frequency (1, 2). Risks factors associated with PCS include women at premenstrual period, multiparity, hormonal impairments, polycystic ovaries and inferior limb varices (3). Also, during pregnancy there is an increased volume of blood flowing through the ovarian vein which in turn dilates. These changes can persist after giving birth and can contribute to the venous insufficiency (3).

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The causes of PCS are still debatable. Several factors are thought to be implicated. Some patients present with congenital absence of valves at the level of the ovarian veins. Because of anatomical reasons, the left ovarian vein is more frequently affected in terms of dilatation and reflux then the right vein. It drains into the left renal vein which in turn drains into the inferior vena cava compared to the right ovarian vein which drains directly into the inferior vena cava (4).

Golden standard diagnosis is attributed to venography. Findings include a larger diameter of the ovarian vein (>6mm), ovarian venous reflux, delay in contrast clearance, presence of pelvic tortuous collaterals. Other investigations that can contribute to the diagnosis are ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) (1).

The aim of the present review is to present the implications and potential use of US in diagnosis of PCS.

Materials and Methods

We searched MEDLINE for reports in English from Jan 1, 2000, to March 01, 2020. We used the search terms "pelvic congestion syndrome diagnosis", "pelvic congestion syndrome ultrasound", "pelvic vein insufficiency diagnosis", "ovarian vein ultrasound". Relevant articles were reviewed, and the ones in which detailed ultrasound procedures were preferably cited. Additional reports were identified from the reference lists of the selected articles.

Results

In general US is the first procedure performed as it is non-invasive, quick, requiring 5-7 minutes for experienced doctors and instantly gives a view about possible diagnosis. Examination with the Doppler mode can give valuable information about the dynamics of the blood flow (1, 5).

Transvaginal US (TVU) examination should take place in a private environment, at a warm temperature, and should preferably be performed by the gynecologist following up the patient. Informed consent should be obtained from the patient before the examination. TVU can be performed at 45-degree Fowler position or in a semi upright position (on the edge of the examination bed with feet on the floor) (5,6).

A wand-shaped transducer is used for this approach, with a frequency of 5-9 MHz and 2D/3D features. The probe is covered with enough ultrasound gel to act as an acoustic window and also not to incommode the patient. A thorough analyzation of the uterus, myometrium, adnexa and pelvic viscerae should be performed to rule out any other possible diagnosis. Special attention should be devoted to the local vascularization, especially venous circulation, bilaterally. Ovarian, internal iliac, uterine vein should not be missed (7).

Transabdominal US can also be used for assessing the pelvic area. A transductor with the frequency of 7-15 MHz can be used. It is advised for the patient to have their bladder full in order to have a better visualization of the pelvic viscerae. Investigation for vascularization should be carried out starting from the inferior vena cava and the left renal vein to rule out any possible compression of the two (8,9).

In the literature, criteria for diagnosis of varicosities using US and Doppler include: dilated ovarian veins (>4 mm), tortuous arcuate veins in the myometrium that communicate with varicose pelvic veins, venous blood reflux and slow blood flow (<3 cm/second) (1,10,11). It

has been long thought that the diameter of the ovarian vein is directly correlated with the grade of venous reflux, but in a recent study Dos Santos et al. proved the contrary (5). A group of patients underwent US examination of the ovarian and internal iliac vein assessing vein diameter and existent reflux. Patients with identified reflux underwent venography. Results showed no correlation between the two parameters, reflux potentially being found in veins of lower or larger caliber than 8 mm (which was considered the cut-off value) (5).

A study from 2016 evaluated the efficacy of transvaginal US (TVS) in detecting pelvic venous reflux. Ovarian vein, internal iliac vein and para-uterine veins, bilateral, were assessed. Patients were examined in supine position and semi upright position, with and without Valsalva maneuver. A reversed flow of blood persistent for more than 0.5 seconds was considered to define venous incompetence. Results showed benefits of performing TVS in both positions. In some cases, the reflux present in supine position was absent in semi upright position, demonstrating the implication of the gravity in maintaining valves closed. Another finding that supports the previous study from 2015 is the lack of evidence supporting correlations between the vein diameter and presence of reflux (6).

In Table 1, we present the basic US parameters that we consider should be examined in all patients that undergo this procedure, even at regular visits.

Discussion

PCS is an underdiagnosed disease, for a number of reasons. Premenopausal women, up to 15%, have pelvic vein varicosities, although symptomatology is not present in all cases (3). However, when PCS tends to be symptomatic, many patients do not seek up medical care, especially if their quality of life is not severely affected. Although women tend to do regular gynecological check-ups during which an US examination could raise the suspicion of pelvic vein insufficiency, many refuses to undergo invasive procedures for a certainty diagnosis.

TVU and transabdominal US can give a broad image of the pelvic anatomy and circulation patterns, due to Doppler mode and Power Doppler. Reflux, diameters, blood velocity, overall appearance of principal veins and their collaterals can all be assessed. Also, using both US approaches gives the possibility to perform a differential diagnosis. The old belief of correlating vein diameters with the presence or severity of reflux should be abandoned as no statistical significance has been found, in multiple recent studies (5,6). Another crucial detail when evaluating vein reflux is to examine at rest and under Valsalva maneuver. When performing TVU, the position of the patient can influence the grade of reflux. It is recommended not to limit the examination in the classical lithotomy or 45-degree Fowler positions, but also examine in a semi upright position, for assessment in presence of a higher gravitational force (6).

Treatment options include medical, surgical and interventional approaches. As the vast majority of patients prefer the interventional option, that by default includes the use of venography. US could be used to determinate which patients actually can benefit from this form of treatment in order to avoid undergoing unnecessary radiations and contrast agent administration. PCS presents similarities to the varicocele, affecting male patients. US and physical examinations are used for diagnosis

and treatment options following the same principles. However, the downside of PCS is that presence of inguinal or inferior limb varices can lead to assumption of pelvic vein insufficiency and that US assessment is more difficult r given that all the vessels are situated more profound compared to varicocele.

Conclusion

US could have the potential of becoming a trusted procedure for diagnosis of PCS. Awareness should also be raised upon this particular pathology. This would increase the rate of diagnosed patients, without significant additional costs or investigations.

Conflict of Interests

The authors have no conflicts of interests to declare for the present review article.

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REVIEW ARTICLE OPEN ACCESS

Diagnostic Dilemma of Sinus Headache and Migraine

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This review article aims to clarify and elucidate how to diagnose correctly sinus headache by discussing sinus headache as regards to its epidemiology, clinical picture, radiological investigations, as well as its medical and endoscopic management. The article also will clarify the relationship between a sinus headache and other co-morbidities, namely migraine, facial pain, and allergy, and the differential diagnosis of sinus headache. That sinus headache is not indicating life-threatening health problem, not a common disease, and usually is overrated. Usually the patient and sometimes the physician will attribute the patient's facial pain to a sinus headache, while in fact it is caused by another pathological condition. Sinus headache is better to be diagnosed by exclusion and to be confirmed by nasal endoscopy before rushing into its treatment. Although it is neither sensitive nor specific in cases of chronic rhinosinusitis, plain X-ray is beneficial in the diagnosis of acute rhinosinusitis. Computed tomography (CT) is recommended, but it is not conclusive and it is important to know that a CT scan may remain abnormal even after endoscopic sinus surgery. Magnetic resonance imaging (MRI) is excellent and it is the choice option wherever possible. Pharmaceutical treatment of sinus headache should be addressed first before adopting surgery option; and if functional endoscopic sinus surgery (FESS) is chosen, which is the most common type of surgery used, preoperative assessment is very important to reduce complications.

Keywords: Headache, sinus, migraine, clinical picture, facial pain

Introduction

The Sinus headache is a common term used by patients and primary health care providers to describe a sort of headache that feels like pain of sinusitis. It is felt like pressure sensation in the forehead, cheeks and nose, and is associated with symptoms of sinusitis (1). There is no specific definition of the sinus headache, even in the International Classification of Headache 2013. It concluded that the term "sinus headache" is outmoded because it refers to both primary and secondary headache. Headache is considered as a symptom of rhinosinusitis (RS or true sinus headache) (2), which is defined by the Sinus and Allergy Health Partnership Task Force as a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses. Acute rhinosinusitis usually is preceded by acute upper respiratory tract infection then the patient develops fever, unilateral severe facial

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pain and nasal obstruction. One of the common complaints at the oto-rhino-laryngology clinics is the difficulty of diagnosis of sinus headache as usually sinus headache is a misinterpreted migraine (3). Acute sinusitis is characterized to endure for four weeks as a maximum, while chronic sinusitis duration could be endured for twelve weeks or more (4).

Classification of Headache Disorders

Headaches attributed to both acute and chronic rhinosinusitis have been classified by The International Classification of Headache Disorders (ICHD-3) (2). The international society of headache (HIS) has classified headache syndromes depending on diagnostic criteria. Other non-sinogenic facial pain that mimic sinus headache is several and either primary headache such as migraine, tension headache, cluster headache and trigeminal cephalagia, or secondary headache which is uncommon, such as psychiatric illness, vascular pathology, infection or injuries of cranial nerves (5).

Rhinogenic Headache

Rhinogenic headache is a pain syndrome affecting the face and is caused by impinging mucosal surfaces in the nose and sinuses. Symptoms most probably affect the area surrounding the orbit, the medial canthus and superiorly, or the zygomatic-temporal region and are one-sided, even if both sides may be affected in some cases, usually the pain is affecting the patient in paroxysmal attacks. Three features must be present in cases of rhinogenic headache: an area of mucosal impingement, confirmed endoscopically or radiologically; infiltrating the suspicious area with local anesthesia should abolish nociception for 5 minutes; and the pain should disappear within a week (5).

Tension Headache

The tension headache is the most common type of headache that 78% of the world's population experienced it. It is described as band like pain of the whole vertex. It can be misdiagnosed as sinus headache as it overlaps the frontal sinus area (4).

Trigeminal Neuralgia

Trigeminal neuralgia is a unilateral pathology caused by irritation of the trigeminal nerve leading to acute sharp pain like electric shock which is felt in area supplied by trigeminal nerve and the pain will cease abruptly. This unique character of pain differentiates it from sinus headache easily, but the patient may undergo nasal endoscopy just to be convinced (6).

Giant Cell Arteritis

Giant cell arteritis is the synonym of temporal arteritis. Usually a unilateral, but may be bilateral disorder. It affects females in seventies more. It is commonly presented with unilateral facial pain on chewing with jaw claudication. Usually the investigations show raised ESR and CRP and diagnostic temporal artery biopsy (6).

Pneumocephalus

Pneumocephalus is a condition occurs because of collection of air in the spaces inside the skull such as intraparenchymal, intraventricular, extradural, subdural and sub arachnoid spaces. It may be associated with increase in the air pressure during diving or valsalva. Also, it may result from petrous bone dehiscence, post-traumatic, post-surgical or associated with tumor. It may be misdiagnosed as sinus headache, but the key difference in pneumocephalus is the relation of pain to change in the air pressure especially if accompanied with any one of the previously mentioned cases (7).

Sinonasal Anatomy

Rhinosinusitis is not the only nasal cause of daily headache. Contact between the mucosal surfaces in the nose which will stimulate the nocireceptors. Deviation of the nasal septum, enlarged nasal turbinates, and nasal septal spur may cause the patient to suffer from chronic daily headache that may be attributed to sinus headache (8).

Nerve Related Conditions

There are rare causes of facial pain that may be misinterpreted as sinus headache such as glossopharyngeal neuralgia, occipital neuralgia, nervus intermedius and supraorbital neuralgia (5).

Medication Overuse Headache

Medication overuse headache is difficult to be diagnosed and is easily misdiagnosed as sinus headache. The patient will be resistant to treatment as most probably the patient has a primary headache that will be diagnosed once he stops the overused medication (9). Katsarava and Obermann (2013) showed three features of medication overuse headache identification: as it is the result of continuous overuse for three months or less using one or more medication which is taken for acute and/or treatment of headache; the headache has markedly worsened during the overuse of medications; the headache will disappear or returns to its former pattern within two months of stopping the overused medication (10).

Sinogenic and Non-sinogenic Headache

De Corso et al. (2018) described the severity of pain of sinogenic headache as a mild to moderate of a pressure sensation or congestion which continue for more than 72 hours, mostly unilateral, depending on the sinus of origin. The triggers of sinogenic headache vary in relation to atmospheric pressure changes (e.g. diving, flying, skiing); frequently associated with congestion, nasal blockage, or discharge, in addition to Reduction and in sometimes loss of smell. The non sinogenic headache is characterized being moderate to severe of tightening nature or pulsatile not exceeding 72 hours; its location is either unilateral or bilateral with poor interrelationship between the site of facial. The triggers of non sinogenic headache including some foods (e.g. cheese, chocolate), some exercises' types, menstrual cycle. The non sinogenic headache is frequently associated with vomiting, nausea, photophobia or phonophobia., in addition to unilateral conjunctival injection (5).

The ear, nose and throat (ENT) examination of sinogenic headache include mucosal oedema, nasal congestion, and purulent nasal discharge. Nasal endoscopy examination of sinogenic headache may revealed purulent nasal discharge, mucosal oedema, nasal polyps, occlusion of osteomeatal complex and/or spheno-ethmoidal recess.

Computed tomography of sinogenic headache showed sinuses opacification; osteomeatal complex and/or spheno-ethmoidal recess occlusion. While The non sinogenic headache showed no abnormalities or nasal mucosal congestion in the ENT examination, nasal endoscopy or computed tomography (5).

Headache Attributed to Rhinosinusitis

Chronic rhinosinusitis/chronic recurrent rhino sinusitis are the most common nasal condition seen in oto-rhino-laryngology OPD which has enormous economic burden and significant morbidity on general population (11). The headache attributed to rhinosinusitis is characterized by being a frontal headache pain accompanied by pain in one or more regions of

the face, ears, or teeth; with a clinical picture, nasal endoscopic examination, CT and/or MRI, and/or laboratory evidence of acute or acute on top of chronic rhinosinusitis. The pain also develops simultaneously with onset of rhinosinusitis or its acute exacerbation, and resolve within seven days after remission or successful treatment of acute on top of chronic rhinosinusitis (12).

The acute sinusitis should be diagnosed by clinical, nasal endoscopic, and/or radiological; the evidence of causation is confirmed by two headache symptoms of the following: developed in relation to the onset of rhino sinusitis; worsened with worsening of the rhinosinusitis; significantly improved or resolved with improvement in or resolution of the rhinosinusitis; exacerbated by pressure over the paranasal sinus. In the case of unilateral rhinosinusitis, headache is limited to the affected side**.**

While the chronic or recurrent sinusitis should be diagnosed by clinical, nasal endoscopic, and/or radiological proof of current or previous infection or other inflammatory process within the sinuses; the evidence of causation is confirmed by two headache symptoms of the following: developed in temporal relation to the onset of chronic rhinosinusitis; its waxes and wanes with the degree of sinus congestion and other symptoms of the chronic rhinosinusitis; exacerbated by pressure over the paranasal sinuses. In case of unilateral rhinosinusitis, headache is limited just to the affected side (6).

Involvement of the frontal sinuses will cause tenderness on the medial side of the orbital floor, while the maxillary sinusitis will result in unilateral facial and dental pain (13). Chronic rhinosinusitis is often painless (6), but sometimes it results in chronic facial pain which predispose the patient to experience migraine and increase the morbidity (14). Sometimes it is difficult to correlate the site of pain to the affected sinus such as acute sinusitis of the sphenoid sinuses, in which the pain may affect the vertex, temporal bone or even the whole head (6).

Clinical Association with Migraine

It is a great challenge to physicians to achieve a correct accurate diagnosis of sinus headache. It is a common complaint at the oto-rhino-laryngology clinics, but actually this is not the true story. Usually sinus headache is a misinterpreted migraine. i.e.: the patient is suffering from migraine, but wrongly assumes it as sinus headache because of associated symptoms (3). It was found that migraine is misdiagnosed as sinus headache in about 42 % of patients having sinus headache (15) while other studies suggest that about 90% of sinus headache cases are actually experiencing migraine (16, 17) There is no specific diagnostic code for sinus headache in the international classifications of diseases, 9th edition, but all types of headache are coded as ICD-9 code 784 (3). It is given to all types of headache including migraine, tension headache and sinus headache (which are commonly difficult to be differentiated) and includes all other types of headache as well.

There are a lot of factors contribute to this conflict. First of all, there is a possibility that migraine and allergy are comorbidities and are commonly associated together (18). This may add to the difficulty to distinguish between them. A patient who is having chronic allergic sinusitis is expected to experience pain and pressure sensation over any of the affected sinuses, and if he suffers from migraine that is unilateral pain in the head, he will attribute his

pain to sinusitis rather than to migraine, especially if associated with sense of pressure and nasal blockage (5).

Another factor related to this conflict is about the pathogenesis of migraine. Migraine stimulates the trigeminal nerve, which supplies both meninges and paranasal sinuses; so that the patient will experience symptoms related to both and got confused between both. Continuing with factors contributing to the strong relation of both diseases, sometimes migraine resembles sinusitis and be associated with nasal congestion, nasal block or rhinorrhea due to its vascular component. Again, this confuses the patient: which was the first event? (3). Patient with migraine may feel pain over the site of one of the sinuses which will be assumed to be caused by the underlying anatomical structure (the sinus), rather than migraine, which further leads to under-diagnosis of migraine (6). Some patients who were thought to have sinus headache had good response to the treatment by migraine medications rather than nasal decongestants and other common cold and sinusitis medications (3).

Jackson and Dial (2004) found that 49 out of 100 patients visited otolaryngology clinic complaining of sinus headache had an undiagnosed migraine. Among the 49 patients with migraine, 19 had allergic rhinitis as well, 11 had sinusitis, and 6 had allergic rhinitis and sinusitis (19). Thus, migraine and allergy are often co-morbidities, and both are frequently seen by the otolaryngologists. Whether or not two diseases are linked remains controversial. A study conducted in 1952 reported that half of the study group of patients complaining of migraine, had recovered from migraines attacks after restriction of some allergenic food elements such as chocolate and wheat and that most of the patients with migraine already had positive history to allergic rhinitis and sinusitis (20). More recent studies failed to confirm the association between migraine, allergy and so the sinus headache (21). However, there is a theory attributing migraine to allergy. This theory can explain the common association between allergy, rhinosinusitis and migraine. According to this, migraine is caused by hypersensitivity of intracranial pain receptors; so, its pathogenesis is due to degranulation of the intracranial mast cells which induces prolonged state of excitation of the meningeal nocireceptors and activation of the trigeminal nucleus as well (18,22). Gelfand (2004) had noted migraine-related elevation of serum prostaglandin D2 and F2, interleukin-1, tryptase, histamine, and TNF-α; and compared between different mediators in migraine and allergic rhinitis (23). Another supporting study was conducted United Kingdom General Practice Database in 2008. It showed a relative risk of having asthma in patients with migraine is 1.3 compared with patients who are not suffering from migraine. It showed the common association between the two entities, but diagnosis of migraine is not meaning an increased risk of asthma. This was concluded after a thorough case control analysis which showed an adjusted OR of only 1.17 (24).

The association between migraine and sinusitis is further confirmed by Eross et al. (2007) who noticed that many of patients suffering from migraine are developing an attack of migraine secondary to exposure to triggering factors such as weather changes (83%), seasonal changes (73%), and exposure to allergens (62%) (25). Schreiber et al. (2004) involved 2991 patient were self-reported or diagnosed by their physicians as having sinus headache. They

were subjected to the international headache society criteria. The study resulted in a fact that migraine should be included as a first differential diagnosis of sinus headache, as 88% of the study patient met the criteria of migraine rather than of sinus headache (16).

Moreover, another study done by Alpay et al. (2010) evaluated 30 patients with migraine for IgG antibodies against 266 food antigens then used the information to do food exclusion or inclusion in a crossover study design. The elimination periods were found to provide a statistically significant reduction in the number of headache days and the number of migraine attacks (26).

This common overlap between sinus headache and migraine has a lot of drawbacks such the patients and physicians are misdiagnosing migraine as sinus headache, which in turn leads to the overdose of antibiotics and nasal decongestants. The patient may even undergo endoscopic sinus surgery without actual need or benefit (3). This overlap between sinusitis and its pain and headache from one side, and migraine is not just at the level of the misinterpretation of the complaints; it extends to the radiological investigations. The patient may have a concomitant radiological sign of sinusitis which will further harden the differentiation. The location, variation, pattern of the headache can guide us towards the correct diagnosis (11).

Diagnosis of Sinus Headache

It needs careful detailed history, examination of the head and neck then nasal endoscopy and imaging studies. There are several diseases that lead to facial pain and pressure sensation and are misdiagnosed as sinus headache other than rhinosinusitis and migraine. Those clinical problems are: tension headache, cluster headache, paroxysmal hemicrania medication overuse headache, temporal arteritis, temporo mandibular joint dysfunction, trigeminal neuralgia, and hemicrania continua (6). Patel et al. (2013) divided factors of diagnosing sinusitis to major and minor factors; the major factors included facial pain or pressure associated with another major factor, facial congestion or fullness, nasal obstruction or blockage, hyposmia/anosmia, nasal discharge or drainage, and fever in acute conditions. While minor factors of diagnosing sinusitis included headache, fever associated with another major nasal symptom, halitosis, fatigue, dental pain, cough, ear pain or pressure or fullness sensation (1).

Thus, because of the similarity of symptoms of rhinosinusitis such as lacrimation, rhinorrhea and nasal congestion, it is easily misinterpreted by the patient suffering from migraine. These symptoms are caused in migraine due to activation of trigeminal-autonomic reflex, while in sinusitis they occur due to local pathology. The same symptoms are experienced by patients suffering from tension headache. A recent observational study was conducted by Petersen et al. (2019) to detect the association between headache and sinus headache in patients who were self or physician reported as having sinus headache. This was to determine wither neck pain is a co-morbid symptom in self-reported sinus headache cases or not. The authors defined cervical musculoskeletal dysfunction that may be suffered by self-reported sinus headache patients as any reduced neck muscle function, reduced range of cervical movement and painful cervical segmental joint dysfunction. Thus the authors concluded that neck pain is a common co-morbidity in patients with self-reported sinus

headache, and as a result, they assumed to be troublesome in patients who are treated at physiotherapist as having just neck pain, which found to be difficult to correlate this neck pain to the rhinosinusitis in the suffering patients. So endoscopic evaluation is essential; it shows hyperemia of the sino-nasal mucosa with purulent discharge (2).

Radiology and Imaging of Sinus Headache

Plain X-ray: is beneficial in the diagnosis of acute rhinosinusitis, but is neither sensitive nor specific in cases of chronic rhinosinusitis.

Computed tomography (CT): is recommended, but it is not conclusive same way as nasal endoscopic study. It shows the anatomy and pathology of the nose and sinuses. Sometimes CT scan remains abnormal many weeks after resolution of the sinusitis. Unfortunately, CT may give an impression of abnormal sinus features in normal persons. 30% of normal people show thickened mucosae and increased opacification on their CT (5). The CT scans use variable methods of scoring didn't succeed in improving the correlation. There was a weak association between CT appearances as scored using Lund-Mackay and the degree of chronic rhinosinusitis (27,28). It is important to know that a CT scan may remain abnormal even after endoscopic sinus surgery, even there might be CT features of chronic sinusitis while the patient is clinically free Those patients are not in need of treatment.

Magnetic Resonance Imaging (MRI): Magnetic resonance imaging is excellent to visualize the soft tissues and the anatomy of the nose and paranasal sinuses. It offers excellent visualization of the nasal mucosa. It can differentiate between bacterial, viral and fungal infection. Also, it is able to identify area of bone erosions (29).

Laboratory Tests of Sinus Headache: Some laboratory tests such as sedimentation rate, white blood cell counts, and C-reactive protein levels are reported by some researchers to be used to help of acute sinusitis diagnosis (30). But the practical experiences showed that those tests appear to have little value for helping in clinical findings in the sinusitis diagnosis. So, cultures should not routinely obtain for evaluation of acute sinusitis but should be obtained in a patient in intensive care or with immunocompromised patients, in children not responding to appropriate medical management, and in patients with complications of sinusitis. Because the nose is colonized with multiple nonpathogenic species of bacteria, care must be taken when evaluating culture results (31).

Treatment Approach of Sinus Headache

Pharmaceutical Treatment of Sinus Headache

Rhinosinusitis is like other upper respiratory infections, usually results from a viral infection. Despite this, antibiotics are overused for its treatment which may predispose to emergence of widespread antibiotic resistance (32).

Broad spectrum antibiotics are used for the treatment of acute on top of chronic bacterial exacerbation of rhinosinusitis. Amoxicillin and its combination with clavulanic acid are the first antibiotics of choice (33). Long course of low-dose macrolides also may be used.

Fluoroquinolones are used for treatment of upper respiratory tract infections for its effect effectiveness against wide variety of bacteria responsible for upper respiratory infections (34).

The physician should treat the underlying cause of rhinosinusitis at first. Oral anti-histamines may be needed for patients with known allergy, but there is little evidence of their efficacy in chronic rhinosinusitis even in cases of nasal polyps. Another group of medications are proton pump inhibitors. They have great benefit for the patients with gastroesophageal reflux disease associated with chronic rhinosinusitis (35).

Finally, environmental factors or allergic factors may predispose individuals to chronic rhino sinusitis. In these patients, It is beneficial to avoid their exposure to pollution, cigarette smoke, dust, moulds, or other environmental and chemical irritants.

Physicians usually describe nasal decongestant to patients having from chronic rhinosinusitis. It was notice that there is a transient effect of the nasal decongestants on the inferior and middle turbinates with no shrinking of maxillary and ethmoid linings after using xylometazoline.

There are no enough studies as regards the use of capsaicin and ipratropium bromide for managing with chronic rhinosinusitis (36).

Surgical Treatment of Sinus Headache *(Nasoendoscopy)*

Functional Endoscopic Sinus Surgery (FESS)

It is a modality of treatment chronic rhino sinusitis and is a common method to treat mucosal contact point headache that was used successfully over the past 20 years. It has been used as a safe and effective treatment for paranasal sinus disorders.

Contact point is a site where opposing mucosal surfaces touch each other inside the nasal cavity, which may result from deviated nasal septum, nasal septal spur or abnormal position of the superior and middle nasal turbinates. The problem of contact mucosal points as a cause of sinus headache was discussed in many literatures and is much debated, and is controversial (1). The target of functional endoscopic sinus surgery is to remove the tissue obstructing the Osteo Metal Complex (OMC) thus facilitating the drainage of secretions in the paranasal sinuses. This removal is done while conserving the normal non-obstructing mucous membrane and with preservation of the intranasal anatomy. This endoscopic surgery is performed through the nasal cavity and results in no external scars. It has with low incidence of associated complications (37).

Indications of Endoscopic Sinus Surgery

The functional endoscopic sinus surgery (FESS) was indicated at first at 1980s and early 1990s to resolve the chronic sinusitis allowing drainage of the mucous accumulated in the paranasal sinuses, thus hinder its infection and reliefs the sensation of compression and fullness of the sinuses felt by the patient. Patients who followed medical treatment and that medical treatment had failed to relief his symptoms are suitable to undergo this sinus surgery. The benefit of this endoscopic surgery is not limited to the treatment of rhinosinusitis, but extends to the eyes like orbital decompression of thyroid orbitopathy, lacrimal obstruction, optic nerve decompression, traumatic loss of vision, and pituitary tumor surgery (38).

Procedure of Endoscopic Sinus Surgery

The endoscopic sinus surgery is better to be done under local and topical anesthesia for safety concerns especially if done for ocular purpose (38). The fiberoptic nasal telescope provides optimum visualization of the osteo-meatal complex. Television monitor is allowed during the surgery. There are microdebriders

that excise only the diseased tissue from the nasal mucosa (39). However, there is a risk of developing some complications. The cutting instrument is thought to be safe around the skull base and lamina papyracea, but this sense of safety is undermined by the information that this cutting tool can grasp and cut free edges of the bone. The extent to which the surgeon widens the ostium of inferior turbinate is crucial. Excessive anterior extension carries a risk of damaging the nasolacrimal duct and should be avoided. If there is ethmoiditis and orbital edema or subperiosteal abscess located lateral to the lamina papyracea, it is better to use the endonasal approach of this surgery. There are other indications of FESS like repair of defects of the skull base, and excision of benign and some malignant nasal tumors (37).

Complications of FESS

Functional endoscopic sinus surgery was having a lot of complications in earlier years of its discovery, but the new technology of instrumentation had reduced the incidence of these complications (37). An example of such a complication includes nasal hemorrhage, extraocular muscle injury, optic nerve damage, intraorbital, cerebrospinal fluid leak, meningitis, orbit nasolacrimal duct damage, intracranial hemorrhage, and emphysema. Any delayed complications may occur, but in the young it is expected that even limited endoscopic sinus surgery can affect the development of the face. The formation of mucocele, due to scarring in the frontal recess, is difficult to resolve rapidly, as it takes long time to be formed. All of the major of endoscopic, external or conventional intranasal ethmoidectomy show incidence of major complications is less than 1%. It was found that both intranasal ethmoidectomy and endoscopic sinus surgery resulted in more complications in the right side which is suspected to be related to the right-handed ness of the surgeons or may be due to anatomical variations (40).

Means of Reducing Incidence of Complications

Physicians should take a detailed history prior to the surgery to verify any potential risk of bleeding, which may not be mentioned by the patient unless asked for. It is recommended that the patient don't undergo surgery for chronic rhinosinusitis and/or nasal polyposis until an adequate course of medical therapy was administered. This medical treatment may include antibiotics, steroids or short courses of systemic steroids for some cases of nasal polyps; this will optimize the condition of the nasal mucosa before surgery. The visual status of the patient should also be checked before surgery and the discussion and informed consent should be taken after clarifying all the expected complications (40). The patient should be instructed not to blow his nose during first 48 hours postoperatively because there is a risk of orbital surgical emphysema. Also, the surgical emphysema can extend sometimes to the face and cranial cavity (37).

Outcomes of FESS

Tosun et al. (2000), conducted a prospective study. They included patients suffering from chronic headache lasting at least 3 months. Evidence of contact points by endoscopy, CT, or both; non response to medical treatment of the headache; disappearance of headache after applying local anesthetic to the contact points; and remaining of contact points even after decongestion, all were the inclusion criteria. They excluded cases with observed features of inflammation on ENT examination including nasal endoscopy and CT scan, and the presence of any prominent cause of headache

(including migraine) after a complete examination physician of different related specialties. After surgery directed to contact points to patients, they noticed good response in 91% of patients, 43% experienced complete relief and 47% showed significant relief (41). Another study was conducted by Welge-Luessen et al. (2013), who included 20 patients who had a long history cluster headache or migraine not responding to treatment but they had a positive result of endoscopy as regards to presence of mucosal contact points. The study patients underwent surgeries to correct it. The patients were followed up for 112 months. The success rate of the surgery was 65%, 6 out of the 20 patients showed complete disappearance of pain, while 7 patients showed partial improvement and last 7 patients had never improved (42).

In addition to FESS which is considered as the most common sinus surgery, there are other techniques such as FEDS, image-guided surgery (FESS done with an image-guided system that uses computed tomography (CT) scans to aid the surgeon in identifying the anatomy and removing as little tissue as necessary). In addition to other procedures used for more serious sinus problems such as Caldwell-Luc operation, endoscopic skull base surgery, turbinate reduction surgery, balloon sinus ostial dilation (BSOD). The decision for using sinus surgery technique is based upon many factors, including the type and extent of inflammatory disease, patient anatomy and patient preferences.

Endoscopic Dilatation Sinus Surgery (FEDS)

Functional endoscopic dilatation of the sinuses (FEDS) is a new technique of sinus ostial balloon dilatation and is specifically aimed at restoring the patency of sinuses without removing any tissue thereby decreasing morbidity. Cadaver studies confirm the potential use of this method in rhinosinusitis (43). Clinical trials in the USA have also shown the safety and effectiveness in selected patients with rhinosinusitis. Some studies anecdotally reported that FEDS effectively relieves sinus ostial obstruction with less post-operative pain, scarring and bleeding than typically seen with traditional instruments (44). Achar et al (2012) reported that FEDS is as effective as FESS in treatment of chronic rhinosinusitis, and can be considered an additional tool in endoscopic surgery and has the potential to be undertaken as a day procedure (45).

Conclusion

Sinus headache is not a common disease, but is overrated due it similarity and proximity to paranasal sinus and the common association between allergy and migraine. Most of sinus headache cases are actually experiencing another disorder such as migraine or other causes of primary and secondary headache; so, it should be investigated comprehensively before rushing into diagnosis. This will improve the patient's quality of life and satisfaction and will avoid the side effects of prolonged treatment that is not hitting the target. Although it is neither sensitive nor specific in cases of chronic rhinosinusitis, plain X-ray is beneficial in the diagnosis of acute rhinosinusitis. Computed tomography (CT) is recommended, but it is not conclusive and it is important to know that a CT scan may remain abnormal even after endoscopic sinus surgery. Magnetic resonance imaging (MRI) is excellent and it is the choice option wherever possible. Pharmaceutical treatment of sinus headache should be addressed first before adopting surgery option; and if functional endoscopic

sinus surgery (FESS) is chose, preoperative assessment is very important to reduce complications. We recommend paying more attention to the cases allaying to have sinus headache and take enough time to get a detailed history and examination associated with nasal endoscopic examination to identify the cause accurately. This will protect the patient from side effects and complications of wrong medication and surgeries without actual benefits.

Conflicts of Interest

The author has declared no conflict of interest for the present article.

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ORIGINAL ARTICLE OPEN ACCESS

Evaluation of Lipid Profile and Atherogenic Indices of Automobile Workers Before and after Green Tea Supplementation

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Introduction: The various toxic chemicals automobile workers (AMW) are exposed to may predispose them to some adverse cardiovascular outcomes by alteration of lipids and lipoproteins. However, dietary strategies may be useful in preventing this undesirable outcome.
Materials and Methods: The study aimed to assess the lipid profile and atherogenic indices of automobile workers. 78 male subjects aged 18 to 54 years, 33 automobile workers (AMW), and 45 control subjects were recruited for this study. 28 out of the 33 automobile workers received 150 ml of green tea daily for two months. 3ml of fasting blood samples were collected before and after one and two months of intervention. Total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), and triglyceride (TG) were measured enzymatically while low-density lipoprotein cholesterol (LDLc) and atherogenic indices (Castelli's risk index (CRI) 1 and 2, atherogenic coefficient (AC), atherogenic index of plasma (AIP), non-HDLc (nHDLc) were calculated.
Results: The median values of TC, LDLc, TG, CRI-1, CRI-2, AC, AIP, and nHDLc were significantly higher in the automobile workers when compared to the control ($p<0.05$), however, the median HDLc level was not significantly different in both groups ($p=0.083$). TC, LDLc, TG, CRI-1, CRI-2, AC, AIP, and nHDLc decreased significantly after one and two months of green tea intake whereas HDLc level increased significantly after two months of intake ($p<0.05$).
Conclusion: This study suggests that automobile workers are at higher risk of developing cardiovascular disorders, however, green tea supplements may possess anti-atherogenic properties for attenuating cardiovascular risk in these worker.

Keywords: Green tea, supplementation, atherogenic indices, cardiovascular disease, lipid profile

Introduction

Automobile workers are group of workers found in the automobile repair workshops including the car mechanics, panel beaters, spray painters, welders and auto electricians. Present in the automobile workshops are significant amounts of toxic substances or chemicals which the workers are exposed to on a daily basis. These toxic chemicals include but are not limited to metal dusts and fumes, polycyclic aromatic hydrocarbons and toxic metals. Exposure to toxic chemicals at workplaces may account for higher cases of the occupational exposure-related conditions

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including hypertension, cancers, oxidative stress, dyslipidemia, infertility, and more.

Occupational exposure to toxic metals like lead has been shown to alter lipids and lipoprotein levels (1), thus increasing the risk of developing cardiovascular diseases (CVD) which is one of the leading causes of death worldwide. Despite the reported dyslipidemia associated with toxic metal exposure, a number of lipid parameters may be apparently normal leading to flawed rulings. Therefore, for a better representation of atherogenic potential of lipid profile, the lipid parameters have been incorporated as calculated or mathematical fractions of cholesterol ester and triglyceride-rich lipo proteins (2) often referred to as atherogenic indices or lipid ratios. These indices or ratios include Castelli risk index 1 and 2, atherogenic co-efficient and atherogenic index of plasma with CV risk predictor values of >3.5, >3.0, >3.0 and >0.1 respectively as well as non-high density lipoprotein cholesterol (non-HDLc).

Green tea made from the plant *Camellia sinensis* is a commonly consumed beverage which is beneficial to human health including protection against cancer (3), oxidative stress (4), diabetes and hypertension (5) and metal chelating (6) effects. These positive effects of green tea have been linked to its high content of bioactive constituents particularly polyphenols often referred to as catechins.

In view of the known adverse health condition associated with occupational exposure as well as the beneficial effect of green tea, it has become necessary to employ dietary strategies aimed at mitigating the undesirable health conditions. This study therefore assessed the lipid profile and atherogenic indices of automobile workers and the subsequent effect of green tea supplementation.

Materials and Methods

Subjects

A total of seventy eight (78) male subjects aged between 18 and 54 years comprised of 33 automobile workers (AMW) and 45 control subjects in Emene, Enugu were randomly enrolled in this study after a written informed consent was obtained. 28 out of the 33 automobile workers received 150ml of green tea (Unilever, Nigeria) daily for a period of two months while the remaining 5 of the automobile workers could not complete the intervention study. The green tea supplement was prepared by soaking two (2) tea bags in freshly boiled water for 5 minutes.

Three milliliters (3ml) of fasting blood samples was collected from all participants before and after one and two months of intervention. The blood samples were dispensed into plain tubes, separated by centrifugation at 3000 rpm for 10 minutes, and sera obtained used for analysis of total cholesterol (TC), high density lipoprotein cholesterol (HDLc) and triglyceride (TG). Apparently healthy non-obese male volunteers aged 18 to 54 years were included in the study whereas those with any history of heart disease or on lipid lowering drugs were excluded from the study. Approval for this study was obtained from Nnamdi Azikiwe University Teaching Hospital Research Ethics Committee (NAUTHREC), and conformed to all the ethical requirements of the Helsinki declaration.

Methods

TC, HDL and TG were determined by enzymatic colorimetric method as described by Roeschlaw *et al*. (7), Grove (8) and Fossati and Prencipe (9) respectively. LDLc and atherogenic indices were estimated by calculation according to Friedewald *et al*. (10) and Bhardwaj *et al*. (11) respectively.

The atherogenic indices were calculated thus;

- Castelli's Risk Index 1 (CRI-1)=TC/HDLc
- Castelli's Risk Index 2 (CRI-2)=LDLc/HDLc
- Atherogenic Coefficient (AC)=TC-HDLc/HDLc or nHDLc/HDLc
- Atherogenic Index of Plasma (AIP)=Log(TG/HDLc)
- Non-HDLc (nHDLc)=TC-HDLc

Non-HDL (nHDL) was estimated by calculating the difference between TC and HDL.

Table 1. Lipid profile and atherogenic indices of control and automobile workers

Parameters	AMW *(n:33)*	Control *(n:45)*	P value
TC *(mmol/l)*	5.13±0.89	4.24±0.6	0.0001*
HDLc *(mmol/l)*	1.16±0.09	1.2±0.09	0.094
LDLc *(mmol/l)*	3.54±0.8	2.69±0.51	0.0001*
TG *(mmol/l)*	0.92±0.32	0.80±0.16	0.03*
CRI-1	4.46±0.99	3.53±0.3	0.0001*
CRI-2	3.08±0.86	2.23±0.29	0.0001*
AC	3.46±0.99	2.53±0.3	0.0001*
AIP	0.24±0.16	0.15±0.08	0.02*
nHDL*(mmol/l)*	3.97±0.92	3.04±0.52	0.0001*

Abbreviations. TC: Total Cholesterol, TG: Triglyceride HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AIP: Atherogenic index of plasma, CR1-2: Castelli Risk Index

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS, v 23.0, SPSS Inc, Chicago, IL, USA). Data were tested for normality, and nonormally distributed variables were expressed as median (range). The Mann Whitney U and Wilcoxon tests were used to assess the difference between two unrelated and related variables, and the significance was considered at $p<0.05$.

Results

The median levels of TC, LDLc, TG, CRI-1, CRI-2, AC, AIP and nHDLc were significantly higher in the automobile workers when compared to the control ($p<0.05$), but there was no significant difference in the median HDLc level in both groups ($p=0.083$) as shown in table 1.

In table 2 and figures 1 and 2, the median levels of TC, LDLc, TG, CRI-1, CRI-2, AC, AIP and nHDLc decreased progressively from baseline to two months of green tea intake ($p<0.05$). The median HDLc level after one month of green tea supplementation did not differ significantly from the baseline value ($p=0.202$), but increased significantly after two months of

Table 2. Lipid profile and atherogenic indices of automobile workers following green tea supplementation.

Parameters	Baseline *(n:28)*	One Month *(n:28)*	Two Months *(n:28)*
TC *(mmol/l)*	5.13±0.85[a,b]	4.62±0.67[a]	4.23±0.7
HDLc *(mmol/l)*	1.17±0.07[a]	1.18±0.07[a]	1.20±0.06
LDLc *(mmol/l)*	3.55±0.77[a,b]	3.07±0.65[a]	2.71±0.68
TG *(mmol/l)*	0.90±0.27[a,b]	0.81±0.21[a]	0.73±0.19
CRI-1	4.42±0.89[a,b]	3.94±0.59[a]	3.55±0.56
CRI-2	3.07±0.79[a,b]	2.62±0.58[a]	2.27±0.56
AC	3.42±0.89[a,b]	2.94±0.59[a]	2.55±0.56
AIP	0.23±0.12[a,b]	0.18±0.10[a]	0.13±0.11
nHDL*(mmol/l)*	3.96±0.86[a,b]	3.45±0.66[a]	3.04±0.68

Abbreviations. TC: Total Cholesterol, TG: Triglyceride HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AIP: Atherogenic index of plasma, CR:Castelli Risk Index. [a] Significant when compared with 2 Months, [b] Significant when compared with One Month

supplementation when compared to its values at one month and baseline (p=0.029 and p=0.031 respectively).

Discussion

This study assessed the lipid profile and atherogenic indices of automobile workers and the subsequent effect of green tea supplementation. The automobile workers had markedly elevated levels of total cholesterol, LDLc and TG with normal HDLc. This alteration may be attributed to up-regulation of plasma cholesterol and triglyceride concentrations by toxic metals (12) which these workers are exposed to, possibly by enhancing HMG CoA (3-hydoxy 3-methylglutaryl coenzyme A) reductase activity. The deranged lipids and lipoprotein levels in these workers may as well play a significant role in the progression and development of cardiovascular diseases and atherosclerosis. The findings from this study correspond with the earlier studies of Sharma *et al*. (13) and Obi-Ezeani *et al*. (1) who reported similar increase in total cholesterol, LDLc, triglyceride and normal HDLc levels in India and Nigeria respectively. Adejumo *et al*. (14) however reported lower total cholesterol level in spray painters and lower HDLc levels in car mechanics, battery chargers and spray painters in Benin City.

In addition to the lipid profile parameters, the atherogenic indices CRI-1, CRI-2, AC, AIP and nHDL which can be used in cardiovascular risk assessment beyond the routinely measured lipid profile were also estimated. It was observed that the automobile workers had higher values of these indices which were well above the cut-off values for cardiovascular risk prediction than in the control, and this may point to a higher risk of cardiovascular disorders in the workers. AIP may be useful in predicting atherosclerosis with values of -0.3 to 0.1, 0.1 to 0.24 and >0.24 associated with low, medium and high CV risk respectively (15). The pro-atherogenic nHDLc has also been shown to be a better predictor of CVD than LDLc, and is a valid surrogate to apolipoprotein B100 (Apo-B) (11).

Despite the normal HDLc level in automobile workers, they still had higher CV risk based on the values of the atherogenic indices, which further supports the use of these indices in predicting the risk of developing CV events (11) and effectiveness of therapy (Dobiasova *et al*., 2011) even when the conventional lipid parameters are supposedly normal. Adejumo *et al*. (16) however observed lower CRI-1 and 2, AC and AIP in automobile workers in Benin City.

In the intervention study, green tea supplement was found to improve lipid parameters as well as atherogenic indices in the automobile workers by reducing total cholesterol, LDLc, Triglyceride, CRI-1 and 2, AC, AIP and nHDLc and increasing HDLc level. Green tea supplementation for one month reduced total cholesterol, LDLc and triglyceride levels, and the values of CRI-1 and 2, AC, AIP and nHDLc, the reductions in these parameters as well as elevated HDLc level were equally observed after two months of green tea intake. This improvement in lipids, lipoprotein fractions and atherogenic indices suggests that green tea has a positive effect on cardiovascular health which may be linked to the ability of green tea catechins to reduce intestinal lipid absorption (17) and enhance fecal excretion (18). Green tea in an in vitro study was reported to reduce cholesterol synthesis by inhibiting HMG-CoA reductase (19) which is the rate limiting enzyme in the mevalonate pathway. Additionally,

green tea polyphenols have also been shown to simultaneously inhibit three enzymes (mevalonate kinase, mevalonate diphosphate decarboxylase and farnesyl pyrophosphate synthase) in the mevalonate pathway (MVP) of cholesterol biosynthesis (20). Zhou *et* al. (21) reported similar reductions in serum levels of total cholesterol, LDLc, triglyceride, and elevated serum level of HDLc after green tea supplementation. However, Senger *et al*., (22) observed no improvement in lipid profile parameters after green tea supplementation, though this study was on elderly subjects with metabolic syndrome.

The limitation of the study was the small sample size, as only consenting participants were enrolled. Additionally, some participants did not complete the intervention study.

This study therefore suggests that automobile workers are at higher risk of developing cardiovascular disorders, however, green tea supplements may possess anti-atherogenic properties for attenuating cardiovascular risk in automobile workers.

Ethical Statement

Approval for this study was obtained from Nnamdi Azikiwe University Teaching Hospital Research Ethics Committee (NAUTHREC), and conformed to all the ethical requirements of the 1975 Helsinki declaration.

Conflicts of Interest

The author has declared no conflict of interest for the present article.

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ORIGINAL ARTICLE OPEN ACCESS

The Effect of Monthly Vitamin D Replacement on Bone Turnover Parameters and Inflammation Parameters in Hemodialysis Patients

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Introduction: Vitamin D replacement is recommended for chronic kidney patients as vitamin D prevents the development of secondary hyperparathyroidism. However, the optimal vitamin D level or dosage is controversial. In this study, we investigated the basal vitamin D levels in patients undergoing hemodialysis, and effects of high dose vitamin D supplements on serum Vitamin D, parathormone (PTH), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), C-reactive protein (CRP), and albumin test levels.

Materials and Methods: 61 patients who have been in the routine hemodialysis program for at least six months in Usak University Training and Research Hospital included in the study. The demographic characteristics of the patients, 25(OH) vitamin D, PTH, Ca, P, ALP, albumin, CRP levels collected from the patient records before and after three months of high dose vitamin D (150.000-300.000IU) replacement. The data obtained in this study analyzed with SPSS 21 package program.

Results: 31 of the patients were female, 30 were male. The mean age of the patients was 63.39±13.76. Vitamin D level was insufficient or deficient in 95.2% of the patients. Only there was a statistically significant correlation between basal vitamin D levels and dialysis duration ($p<0.05$). There was no significant difference between the PTH, Ca, P, ALP, and CRP levels of patients before and after vitamin D replacement, but there was a significant difference in serum albumin and vitamin D levels ($p<0.005$).

Conclusion: Although vitamin D treatment is necessary for chronic kidney patients undergoing dialysis, more clinical studies are needed to bring standardization regarding the dosage and duration of administration.

Keywords: Hemodialysis, vitamin D, bone turnover

Introduction

Vitamin D is a soluble steroid prohormone. It is produced in the skin as a result of contact with sunlight, and with various metabolic changes in the body, it turns into a hormone known as calcitriol, which plays a significant role in calcium and phosphorus metabolism (1). There are two forms of vitamin D: Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The first step in the synthesis of vitamin D_3 is the conversion of provitamin D, which is found in the skin, to vitamin D_3 (cholecalciferol) with the

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effect of sun or ultraviolet rays. Then, they transport to target organs by binding to vitamin D-binding proteins (DBP). Another source of vitamin D is intestinal absorption. Dietary vitamin D transport in chylomicrons after being absorbed from enterocytes. Therefore, diseases associated with fat malabsorption can cause vitamin D deficiency. Chylomicrons reach the liver through portal circulation. Here, vitamin D hydroxylated by the 25-hydroxylase enzyme, and 25-hydroxyvitamin D (25OHD) formed. In mitochondria in the proximal tubules of the kidneys, advanced hydroxylation of 25OHD to 1.25-dihydroxyvitamin D (1.25OHD) takes place. 1,25OHD is a physiologically active form of vitamin D (2). As chronic kidney disease (CKD) progresses, 1-α hydroxylase activity decreases in the kidney, calcitriol production decreases, and parathormone levels increase. It thought to be due to decreased residual renal mass, hyperphosphatemia, metabolic acidosis and uremic toxins suppressing 1-α hydroxylase activity (3).

The synthesis of 1,25-OH vitamin D regulates parathormone (PTH), serum calcium, and phosphorus levels. However, its effect is not limited to calcium and phosphorus regulation. It has also shown in several studies that it attains maximum muscle strength and it prevents type-1 diabetes, multiple sclerosis, rheumatoid arthritis, cardiovascular heart disease, hypertension, various cancers with its anti-inflammatory, antiproliferative, immune modulator properties (4).

Based on this information, the use of cholecalciferol or ergocalciferol is necessary for patients with advanced chronic renal failure and dialysis patients. Also, recent studies show that the effectivity of vitamin D supplementation is not only in maintaining renal osteodystrophy control but also against inflammation in the patients with chronic renal failure (5). However, there is no consensus about which dose of vitamin D to use, the dose adjusted according to the level of serum vitamin D. It has not known whether this dose is sufficient to achieve the immunomodulating effect of vitamin D in dialysis patients with vitamin D deficiency (6). The half-life of active vitamin D supplements is less than 4-6 hours. It is possible that this will not have a lasting effect. In normal physiological conditions, the active source of vitamin D is 25-hydroxy vitamin D. It can produce active vitamin D at any time according to the body's needs. Due to the short half-life of active vitamin D drugs, it may not be possible to achieve the same effect continuously.

Based on these studies, we determined basal vitamin D levels in patients and we applied monthly high dose vitamin D supplements to increase the drug compliance in patients undergoing hemodialysis , then we investigated the effect of this monthly dose of vitamin D on PTH, Ca, P, ALP, CRP and albumin levels.

Materials and Methods

Sixty-one patients who have been in routine hemodialysis program for at least six months in Usak University Training and Research Hospital included in the study. Demographic features of the patients such as gender, age, height, weight, body mass index (BMI), duration of dialysis obtained from the patient file records. Serum calcium, phosphorus, ALP, albumin and CRP levels analyzed by a spectro photometric method in Architect c8000 auto analyses (Abbott Diagnostic, Lake Forest, IL, USA); Serum intact PTH test analyzed by chemiluminescence immunoassay method in Centaur XP analyses (Siemens Healthcare United Kingdom). The test results obtained

from the from the medical records of the patients. The difference between 25(OH)vitD, PTH, Ca, phosphorus, ALP, albumin and CRP levels examined before and after the vitamin D treatment (300,000 IU for patients with vitamin D <20 ng/mL - 150,000 IU for patients with vitamin D level >20 ng/mL). The relationship between these tests and age, gender, duration of dialysis, and BMI is analyzed. The data obtained in this study analyzed through SPSS 21 package program. The relationship between the variables is analyzed with correlation analysis. The difference between two groups is analyzed by Mann-Whitney U test fort the variables which are not normally distributed and Kruskall-Wallis H test is used in more than two-group comparisons. The difference between the related groups is analyzed by Wilcoxen sign test. A p value <0.05 was used as the level of significance.

Results

31 (50.2%) of the patients were females, 30 (49.8%) were males. The mean age of the patients was 63.39±13.76, ranged between 30-84 years. The mean duration of hemodialysis of the patients was 42.34 months, and the average BMI of 51 patients that we could reach the body mass index (BMI) data was 26.89 kg/m^2 (Table 1).

Table 1. Basic characteristics of the patients

Variables	n(%)	Mean	Min	Max	SD
Age *(year)*	61	63.39	30	84	13.76
Duration of dialysis *(month)*	61	42.34	2	144	35.5
BMI *(kg/m²)*	51	26.89	17.6	40.8	5.83
Waist circumference *(cm)*	51	97.04	55	151	19.71

BMI: Body mass index

If the patients are examined according to their gender; 31 (50.2%) were females and 30 (49.8%) were males of 61 patients. The etiology of chronic kidney diseases (CKD) is not known in 44% of patients and the most common cause of chronic kidney diseases is diabetes mellitus. The most common disease accompanying kidney diseases is hypertension with a rate of 57.4% (Table 2).

Table 2. Patients' gender, concomitant disease, vascular access type, ethiology of CKD

Variables		n	%
Gender	Male	30	49.2
	Female	31	50.8
	Total	61	100
Vascular Access Type	Catheter	26	42.6
	Arteriovenous Fistul	35	57.4
	Total	61	100
Ethiology of CKD	Unknown	27	44.3
	Hypertension	11	18
	Diabetes Mellitus	19	31.1
	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	1	1.6
	Glomerulonephritis	1	1.6
	Stone	2	3.3
	Total	61	100
Concomitant or Comorbid Disease	None	11	18
	Hypertension	35	57.4
	Diabetes Mellitus	3	4.9
	Coroner Artery Disease	3	4.9
	Chronic Obstructive Pulmonary Disease	2	3.3
	Heart Failure	1	1.6
	Malignity	2	3.3
	Cerebrovascular Disease	1	1.6
	Dementia	2	3.3
	HIV	1	1.6
	Total	61	100

Vitamin D level was insufficient or deficient in 95.2% of the patients (Table 3). There was no relationship between age, gender, BMI, presence of diabetes and basal vitamin D levels (Table 4), but a low level of statistically significant relationship with dialysis duration was found ($p<0.05$; $r=0.287$). Average vitamin D levels of patients increased significantly with 3-month vitamin D treatment. Although there was no statistically significant difference between PTH, Calcium, phosphorus, ALP, CRP levels analyzed before and after vitamin D replacement, a difference was observed in serum albumin ($p<0.05$) (Table 5).

Table 3. Classification according to Vitamin D levels

Vitamin D Level	n	%
Sufficient (>30 ng/mL)	3	4.9
Insufficient (21-29 ng/mL)	6	9.8
Defficient (<20 ng/mL)	52	85.2
Total	61	100

Table 4. Correlation between basal vitamin D levels and age, weight, height, BMI, WC, duration of dialysis(month), blood pressure (systolic), blood pressure (dyastolic), comorbid disease

Correlations		Age	Weight	Height	BMI	WC*	Duration of Dialysis (month)	Blood Pressure (systolic)	Blood Pressure (dyastolic)	Comorbid Disease
Basal Vitamin D	r	-0.01	-0.096	0.06	-0.042	0.118	0.287	-0.068	-0.03	0.013
	p	0.937	0.461	0.678	0.77	0.413	0.025	0.603	0.819	0.922
	N	61	61	51	51	50	61	61	61	61

*Waist circumference

Tablo 5. Comparison test results before and after vitamin D replacement

Variables	n	Mean	Median	Minimum	Maximum	SD	z	p
$Albumin_1$	61	3.54	3.6	2.4	4.5	0.42	-2.08	0.037
$Albumin_2$	61	3.63	3.7	2.3	4.4	0.4		
$Calcium_1$	61	8.5	8.5	6.7	10.4	0.69	-1.8	0.068
$Calcium_2$	61	8.67	8.8	7	9.8	0.61		
$Phosphorus_1$	61	4.56	4.6	1.5	7.8	1.38	-1.47	0.141
$Phosphorus_2$	61	4.86	4.8	2.5	8.3	1.22		
PTH_1	61	500.59	344	29.8	1900	481.39	-0.347	0.728
PTH_2	61	465.49	362	6.2	2000	454.79		
ALP_1	61	124.25	99	46	442	79.8	-0.143	0.886
ALP_2	61	122.89	95	53	529	81.18		
CRP_1	61	29.24	12.9	0.1	147.4	40.4	-0.75	0.453
CRP_2	61	28.23	11	0.1	529	70.66		
Vitamin D_1	61	11.54	8.51	4.2	39.95	8.2	-5.1	0.0001
Vitamin D_2	61	25.28	25.32	4.2	75	13.74		

Wilcoxon sign test was used for all variables. $Albumin_1$: basal albumin levels, $Albumin_2$: albumin levels after vitamin D thearapy; $Calcium_1$: basal calcium levels, $Calcium_2$: calcium levels after vitamin D thearapy; $Phosphorus_1$: basal phosphorus levels, $Phosphorus_2$: phosphorus levels after vitamin D thearapy; PTH_1: basal PTH levels, PTH_2: PTH levels after vitamin D thearapy; ALP_1: basal ALP levels, ALP_2: ALP levels after vitamin D thearapy; CRP_1: basal CRP levels, CRP_2: CRP levels after vitamin D thearapy; Vitamin D_1: basal vitamin D levels, Vitamin D_2: vitamin D levels after vitamin D thearapy

Discussion

Vitamin D is the only synthesized vitamin in the human body. Vitamin D and its metabolites have an important clinical role in calcium balance and bone metabolism. It is estimated that around one billion people in the world have vitamin D deficiency. (7). In previous studies, the prevalence of vitamin D deficiency shown to be vary between 40% and 100% in Turkey (8). This prevalence increases in chronic kidney patients. Causes and risk factors of 25 (OH) vitamin D deficiency/insufficiency in chronic kidney disease are age, adiposity, proteinuria, female gender, decreased vitamin D receptor, tubular reabsorption peritoneal dialysis, of 25(OH) D and deterioration of hydroxylation vitamin D (9).

Vitamin D deficiency/insufficiency is associated with secondary hyperparathyroidism and bone cycle markers seen in CKD, low bone mineral density, atherosclerosis, weakened immunity, the progression of kidney disease and mortality results (10,11). Vitamin D deficiency causes a decrease in intestinal absorption of calcium and phosphorus value. Hypocalcemia induces hyperparathyroidism, and hence phosphaturia develops. According to the K / DOQI guidelines, (12) vitamin D replacement recommended if patients with CKD stages 3 and 4 have hyperparathyroidism. Although there is a low risk of toxicity at the recommended dose, vitamin D replacement therapy is the first-line therapy in patients with secondary hyper parathyroidism with vitamin D deficiency (13).

In this study, we used oral high dose vitamin D synthetic preparations for hemodialysis patients for three months. A cut off value of 30 ng/ml is considered as optimal vitamin D level. Although the vitamin D median value of the patients increased significantly within three months after treatment, some of the patients could not reach the optimal vitamin D levels. This condition may be due to the short duration of using vitamin D and need for the higher loading dose in some patients .

The post-treatment CRP level which is a marker for inflammation, the Ca, P, ALP, and iPTH levels we looked to evaluate bone turnover did not change significantly. In the study conducted by Tokmak et al. (14) They did not determine a statistically significant difference in Ca-P balance and PTH levels although they used longer duration (9 months) and a higher dose (20000 IU/day) cholecalciferol to 64 hemodialysis patients. Tentori et al compared the groups who received and did not receive vitamin D treatment in 8000 hemodialysis patients but found no significant difference in Ca levels (15). Body mass index control is associated with nutrition and inflammation, and in our study, the mean BMI of the patients was within normal limits. However, we found that albumin levels, which are negative acute phase markers but also show nutritional status, increased significantly. The presence of chronic inflammation and protein-energy malnutrition are the main factors responsible for mortality in patients with CKD. Therefore, increasing albumin and decreasing CRP is an indicator of a good prognosis. As a result, although vit D doses (150.000 IU and 300.000 IU) used for supportive treatment in chronic kidney patients are sufficient to decrease inflammation, they are insufficient for bone remodeling.

Conclusion

We hope that the results of these studies will clarify the dose and the duration of limits of vitamin D treatment in the future. The limitations of our study are being retrospective, limited number of patients and being a single

center study. Multicenter, prospective studies with higher number of patients are needed to be conducted. The followup of patients receiving dialysis is multifactorial. Precautions should be taken by following nutritional status, presence of inflammation, disorders related to bone turnover imbalance, and heart diseases. The patients on dialysis are on high pill burden which makes their medical treatment more difficult and high dose vitamin D supplements used once monthly or longer intervals may improve the compliance of the patients to the vitamin D replacement treatment.

Ethical Statement

The Ethical Committee and Institutional Review Board of Usak University Faculty of Medicine, where the study was conducted, approved the study design.

Conflicts of Interest

The authors declared no conflict of interest.

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ORIGINAL ARTICLE OPEN ACCESS

Adult Medulloblastoma: Clinical Profile and Treatment Result of 25 Patients

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Introduction: The study aimed to discuss the clinical presentation of radiological findings, surgical treatments, and postoperative complications as well as the radiotherapy and chemotherapy options for adult patients with medulloblastoma.

Materials and Methods: A total of 25 patients (14 males and 11 females) between the ages of 17 and 63 who underwent an operation at our clinic between 2006-2016 are discussed in this article. The degree of resection in the patients and tumor sizes after radiotherapy (RT) and chemotherapy (Cht) was compared using the patients' preoperative and postoperative magnetic resonance (MR) images.

Results: The average age of the patients was 30.9 years. Gross total resection was achieved in 20 patients, whereas subtotal resection was achieved in the remaining 5 patients. Three patients developed hydrocephalus during the 6th month after resection, which was treated with a V-P shunt. Another four patients developed a cerebrospinal fluid (CSF) fistula. Among the five patients who only achieved subtotal resection, two died during the 24th month of the post-operative period, and the other three died during the 18th month. Eleven patients presented pathology of the desmoplastic type, and 14 patients presented classical medulloblastoma. Spinal metastasis was detected in three patients during the pre-operative follow-up and in three patients during the post-operative follow-up. The average survival rate of the cohort was 60% during the 3 to 5-year follow-up period.

Conclusion: Medulloblastoma development is a risk not only for children and adolescents but also for adults. Maximum tumor removal during treatment affects patient outcomes, and RT and Cht administration during the post-operative period can extend the life span of these patients.

Keywords: Resection, desmoplastic medulloblastoma, adult medulloblastoma, chemotherapy, radiotherapy, survival

Introduction

Medulloblastomas are malignant tumors that often metastasize locally to the posterior fossa and occupy significant regions within the central nervous system of children (1). However, approximately 20% of individuals diagnosed with medulloblastoma are over 16 years of age. Although adult medulloblastomas are similar to pediatric medulloblastomas, they differ from the pediatric subtype via a higher incidence of the desmoplastic variant and more frequent lateral localization (2). Patients with desmoplastic histology always have better survival rates than those with either classical or

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large-cell histology. Additionally, the lateral (i.e., non-vermian) location of the tumor allows for a greater likelihood of total resection. However, there is no prominent consensus related to the treatment of medulloblastomas in adolescents and adults, and there is no complete consensus on the application of chemotherapy (Cht) for adult medulloblastoma because of the high risk of toxicity associated with Cht and reduced number of cases requiring an emergency decrease in the craniospinal radiotherapy (RT) dosage (3-5). Notwithstanding these factors, administering Cht for adult medulloblastoma can delay relapse and inhibit systematic metastasis (6-8).

The purpose of this article is to discuss the treatment and follow-up of adult medullo blastoma patients based on the findings of 25 cases monitored at our clinic.

Materials and Methods

Data from 25 adult medulloblastoma patients followed in our clinic between 2006 and 2016 were evaluated in this study. The average age of the patients was 30.9 years old (range 17-63); 11 of them were female, and 14 of them were male. The most frequent reason for seeking clinical consultation was headache followed by complaints of nausea, vomiting, and ataxia. Craniospinal imaging was performed on all the patients during the pre-operative period.

Table 1. Summary of the demographic and clinical characteristics of the patients

No.	Age	Sex	Degree Of Resection	Tumor Localization	Pathology	Metastasis
1	29	f	Gross Total	Median	Classical	None
2	35	m	Gross Total	Median	Classical	None
3	53	m	Gross Total	Mediolateral	Classical	None
4	19	m	Gross Total	Mediolateral	Classical	Spinal (Pre Op)
5	34	m	Sub Total	Median	Desmoplastic	None
6	23	m	Gross Total	Median	Classical	None
7	19	m	Gross Total	Lateral	Classical	None
8	30	m	Gross Total	Lateral	Desmoplastic	Spinal (Post Op)
9	26	f	Gross Total	Lateral	Desmoplastic	None
10	17	f	Gross Total	Lateral	Desmoplastic	None
11	30	m	Subtotal	Lateral	Classical	Spinal (Pre Op)
12	29	m	Gross Total	Mediolateral	Desmoplastic	None
13	53	m	Gross Total	Mediolateral	Classical	Spinal (Post Op)
14	23	f	Subtotal	Lateral	Desmoplastic	None
15	23	f	Gross Total	Median	Classical	None
16	36	f	Gross Total	Lateral	Classical	None
17	19	m	Gross Total	Lateral	Desmoplastic	None
18	25	f	Gross Total	Lateral	Desmoplastic	None
19	63	m	Gross Total	Median	Classical	None
20	37	f	Subtotal	Lateral	Classical	Spinal (Post Op)
21	43	m	Gross Total	Median	Classical	None
22	38	f	Gross Total	Median	Classical	None
23	47	f	Gross Total	Lateral	Desmoplastic	None
24	53	f	Subtotal	Lateral	Desmoplastic	Spinal(Pre Op)
25	29	m	Gross Total	Median	Desmoplastic	None

Metastasis, tumor localization, intensity and the presence of hydrocephalus was evaluated using imaging of the patients. All the patients were placed in a sitting position during surgery. Subtotal resection was achieved in 5 patients, whereas gross total resection was achieved in 20 patients. Two of the patients who achieved subtotal resection underwent the second operation 1 year later. Craniospinal imaging of patients was performed during the post operative follow-up period. The amount of resected tissue, instances of relapse, and metastasis were evaluated using follow-up imaging. All the patients received RT and Cht.

Results

Computerized brain tomography (CBT) of the lesions revealed a generally iso-hypodense appearance (Fig. 1). The lesions were generally iso-hypodense in the T1-weighted images and hyperintense in the T2-weighted images; In addition, pre-operative magnetic resonance image (MRI) showed prominent homogeneous contrast (Fig. 2). Among 25 lesions, 9 were at the midline, 4 were lateral from the midline, and 12 were laterally localized. Hydrocephalus was observed in 10 patients, and spinal metastasis was detected in 3 patients (Table 1).

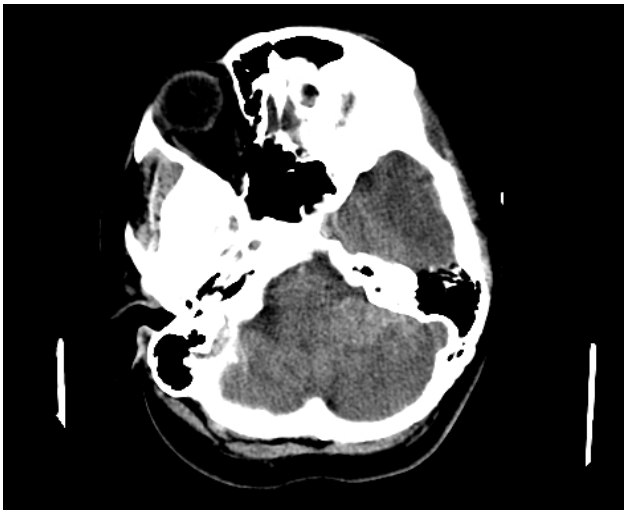

Figure 1. Pre-operative CBT image of a patient.

While in the post-operative recovery unit, one of the patients developed a hematoma within 6 hours after surgery completion, which qualified as an early-period complication. The patient underwent surgery again to drain hematoma. On a postoperative day 3, another 3 patient developed hydrocephalus, which was treated with a V-P shunt. Cerebrospinal fluid (CSF) leakage from the incision site was observed in four patients within the first week during the post-operative period; these patients underwent repair of the incision site and dura. Two of the patients who achieved subtotal resection underwent a second tumor resection 1 year

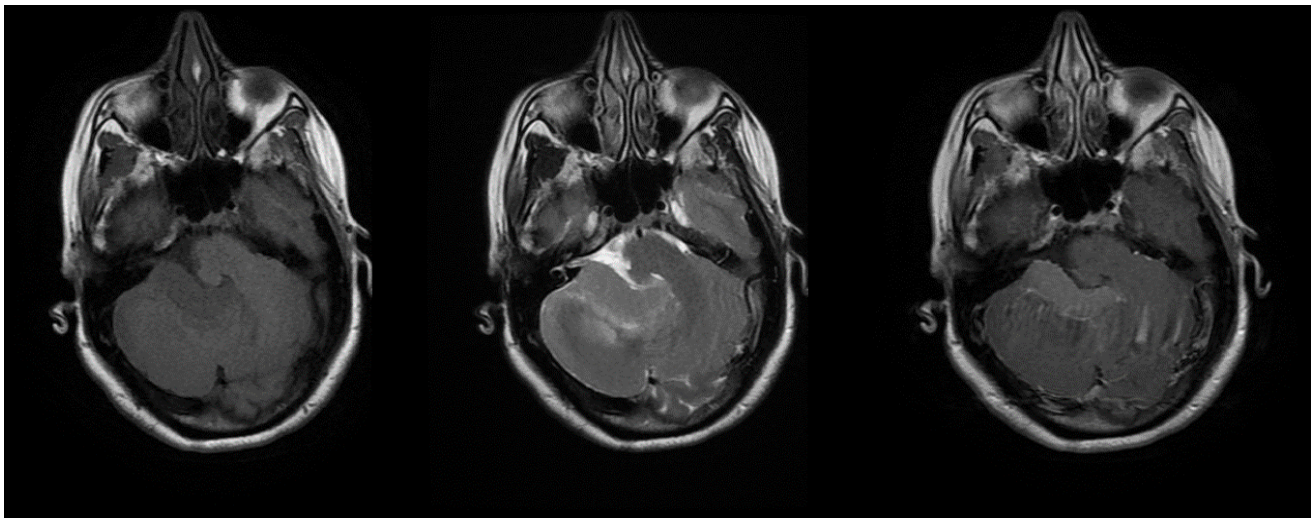

Figure 2. T1, T2-weighted and T1-weighted contrasted images from the pre-operative MRI of a patient

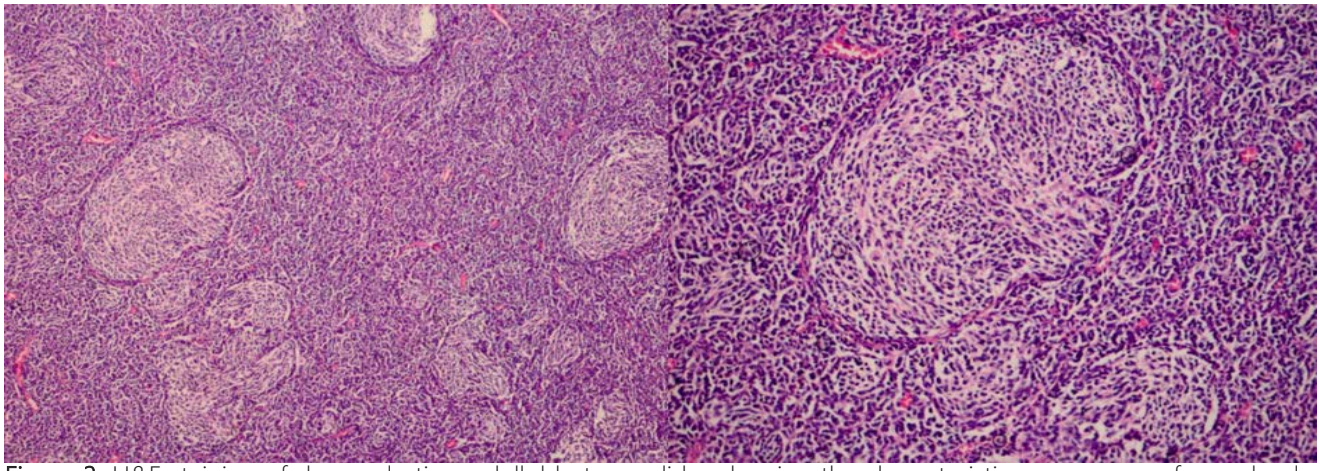

Figure 3. H&E staining of desmoplastic medulloblastoma slides showing the characteristic appearance of round pale nodules in a pale fibrillary background (left panel, magnification 10×). One the paler tumor nodules presents uniform round cells (right panel, magnification 20×).

after the initial surgery. The pathology results of 14 patients showed classical type medullo blastoma, whereas the pathology of the remaining 11 indicated desmoplastic medullo blastoma (Fig. 3). The average survival rate of the cohort was 60% during the 3 to 5-year follow-up. Three patients developed spinal metastasis during the post-operative period. 2 patients who achieved subtotal resection and underwent a second operation died in the 24th month of the post-operative period after the first surgery, and the other 3 patients who only achieved subtotal resection died in the 18th month of the post-operative period.

Discussion

Medulloblastoma is a tumor that is mostly observed during childhood and originates from transient undifferentiated neuroepithelial cells in either the cerebellum or the roof of the 4th ventricle (1). These cells can differentiate into astroglial or neuroblastic subtypes. The embryonic origin of these cells is the primary reason that medulloblastoma is frequently observed in childhood; additionally, it is the second most frequently observed tumor of the central nervous system in childhood.

Many features of adult medulloblastomas are similar to those in pediatric medulloblastomas; however, adult and pediatric medulloblastomas have different demographic, morphological, and molecular characteristics. Medulloblastoma is categorized based on gene expression profiles and can be divided into 4 subgroups: Wingless (WNT), Sonic hedgehog (SHH), Group 3, and Group 4. Among these groups, the WNT subtype has the best patient prognosis. The SHH and Group 4 subtypes have mediocre prognoses, and Group 3 has a poor prognosis (9). A meta-analysis showed that the majority of patients in the SHH subgroup (57%) were in the adult group. The percentage of adults within the other subgroups was 13% for WNT, 4% for Group 4, and 2% for Group 3 (10-12). Using cytogenetic analyses, Northcott et al. (9) showed that the frequency of deletions on chromosome 10q was lower among adult SHH patients than among pediatric patients. These four subgroups also differ in the prognosis rates among pediatric and adult patients. The prognosis of adult Group 4 and WNT patients is worse than that in corresponding pediatric patients. In the SHH subgroup, both pediatric

and adult groups have similar prognoses. Among pediatric patients, metastasis is more frequent in Group 3 and Group 4 patients, whereas adult patients in each subgroup exhibit similar metastasis rates; however, metastasis in adults, groups do not affect prognosis (10).

Adult medulloblastoma is less prone to metastasis; additionally, pulmonary metastasis is more common in adult medulloblastoma, whereas liver metastasis is more commonly observed in pediatric medulloblastomas (12,13). Metastasis is less frequent in the desmoplastic and lipomatous medulloblastoma, melanotic medulloblastoma, medullomyoblastoma, and large cell medulloblastoma subtypes but is more commonly observed in classic medullo blastoma type (14). The desmoplastic subtype has reduced metastasis compared to classical medulloblastoma with a better clinical course.

The observation frequency of medulloblastoma among primary brain tumors in adults is approximately 1%. It is most often diagnosed between 45-50 years of age and is rarely observed after the 5th decade (4,5,15). It is male dominant in adults as well as in children (3,6). The patients in our series were between 17 and 63 years old with an average age of 30.9. There was a pattern of male dominance within our cohort, which is following the literature.

Performing a craniospinal MRI on patients is significant for determining the optimal surgical strategy for the patients, examining the patient, and detecting spinal metastasis. Although the MRI findings of adult medulloblastomas do not reveal distinctive characteristics, studies reporting these findings indicate that medullo blastomas in adults tend to develop more laterally compared to the localization observed in children. No prominent distinguishable characteristics regarding the intensity and contrast relating to the tumor were detected. Generally, isodense regions are observed in T1-weighted images, and hyperdensity is observed in T2-weighted images. Contrast of the tumor may be homogeneous or inhomogeneous. The fact that the tumor may contain cystic or necrotic areas may affect the specified findings. In a study of 13 patients conducted by Bezircioğlu et al., (16) T1-weighted imaging was hypointense in 4 patients and isointense in 9 patients; however, all the patients showed hyperintense lesions in T2-weighted images. Contrast involvement was homogeneous in 5 of the patients and inhomogeneous in 8 of them. In 5 of the patients, the lesion was located in the midline. In 5 of the patients the lesion was located in lateral to the midline and in 3 of the patients was located in lateral (16). In a cohort of 12 patients published by Koci et al. (17), 8 patients showed lateral tumor localization, 2 were medial to lateral and 2 were medial. In our series, 9 of the lesions in the patients were at the midline, 4 of them were lateral across the midline and 12 of them were laterally localized. Homogeneous involvement was observed after performing iso-hypointense contrast in T2-weighted images and hyperintense contrast in T2-weighted images. Spinal metastasis was observed in 3 patient, and hydrocephalus was observed in 8 patients.

The percentage of resected tumor is an important parameter in the study of cancer patients. According to the risk criteria set by the University of California San Francisco, resections below 75% constitute a significant risk factor for poor prognosis. However, it should be noted that sequelae, which may occur while performing resection, can affect the study outcomes. In the long-term study of 27 patients by Riffaud et al. (18), the 5-year survival rate was

85% for patients who achieved total resection and 67% for patients who either experienced subtotal resection or only underwent a biopsy. In a study conducted by Jiang et al.,(19) the 5-year survival rate within a cohort of 33 patients was approximately 50-60% among patients who underwent gross total resection and 25% among patients who only achieved subtotal resection (15). In a report by Lai et al. (20) that evaluated the prognosis of a cohort of 454 adult patients with medulloblastoma at 17 centers, gross total resection was revealed to be among the best prognostic factors. In our study, we achieved a gross total resection in 20 of the 25 patients and subtotal resection in the remaining 5 patients. Among the latter patients, two underwent a second operation 1 year later; unfortunately, these patients died 24 months after the first operation. The other three patients who only achieved subtotal resection died 18 months after the operation. The average 3 to 5-year survival rate was calculated as 60%.

As common as the classical medulloblastoma subtype is observed among pediatric patients, the desmoplastic variant is observed more frequently among adults. The desmoplastic type tends to develop in a more lateral location than the classical subtype. Although lateral localization of classical medulloblastoma often plateaus at a rate of 12%, approximately 71% of desmoplastic cases exhibit lateral localization (2). The term desmoplasia is used based on the observation of excessive collagenases within the connective tissue surrounding the tumor. The tumor tissue is macroscopically observed as a benign limited lobule leptomeningeal mass. A 13-patient study by Bezircioğlu et al. described 2 patients classified with classical medulloblastoma and 11 patients classified with desmoplastic medulloblastoma (2). In a A 27-patient study by Riffaud et al. (19), 21 patients were identified with classical disease, and 6 patients were classified as desmoplastic medulloblastoma. In a larger cohort, Lai et al. stratified their cohort of 454 patients with medulloblastoma as follows: 397 patients with classical medulloblastoma; 52 patients with desmoplastic medulloblastoma; 2 patients with medullomyoblastoma; and 3 patients with large cell medulloblastoma (20). The cohort described by Jiang et al. included 17 patients with classical medulloblastoma, 13 patients with desmoplastic type medulloblastoma, and 3 patients with anaplastic medulloblastoma. The frequency of the desmoplastic type compared to that of the classical type differs in the various studies of adult medulloblastoma. In our study, 14 of the 25 patients were classified as classical type and the remaining 11 had the desmoplastic type.

RT application is highly recommended for patients during the post-operative period. In a study conducted by Abacıoğlu et al. of 30 patients with adult medulloblastoma, low dosages of RT were observed to control the tumor occurrence in the posterior fossa (3). RT administered during the post-operative period minimizes the development of residual lesions as well as prevents spinal metastasis. The main subject under discussion is the requirement of administering Cht to these patients. Because the toxicity of established Cht agents is higher in adults than in children, there is increased risk in administering Cht. The recent discovery of agents such as temozolomide, which has low toxicity, minimizes these associated risks. In the studies performed, adjuvant Cht delays recurrence among patients who are at high risk for recurrence. The prospective study conducted by Brandes et al. (7) reported that

among patients who underwent only RT during the postoperative period, the incidence of recurrence increased prominently over a 7.6-year follow-up period. In a meta-analysis conducted by Kocakaya et al. (21) on 907 patients, adult medulloblastoma patients who were administered Cht had an increased long-term prognosis. We administered RT and Cht to all the patients in our study during the post-operative period. The average survival rate of our cohort was 60% during the 3 to 5-year follow-up. Additionally, three patients suffered from spinal metastasis during the postoperative follow-up period.

Conclusion

Although medulloblastoma is more commonly observed during childhood, they also affect 1% of adults with central nervous system tumors. They primarily tend to settle in the lateral region, which is different from the tumors that develop in children. The desmoplastic variant of medulloblastomas was observed more frequently among adults than among children. Achieving total resection is critical in terms of treatment, and administering RT to patients during the postoperative period is important in terms of eliminating residue lesions and preventing spinal metastasis. Additionally, CT significantly reduces relapse rates. Finally, scanning the spinal region of patients during the postoperative follow-up period is essential to identify spinal metastasis.

Ethical Statement

The Ethical Committee and Institutional Review Board of Adana City Training and Research Hospital, where the study was conducted, approved the study design.

Conflicts of Interest

The authors declared no conflict of interest.

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ORIGINAL ARTICLE OPEN ACCESS

The Relationship between the Amount of Epicardial Adipose Tissue Measured on Echocardiography and Decreased Heart Rate Recovery in Exercise Stress Test in Patients with Metabolic Syndrome

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Introduction: In this study, the impact of the epicardial adipose tissue (EAT) thickness on the heart rate recovery (HRV) was investigated by comparing the HRV values in the second minute of the recovery phase of the exercise test applied to metabolic syndrome (MS) patients and the healthy control group.

Materials and Methods: A total of 78 people, 30 of them healthy control group, and 48 of them diagnosed with MS for the first time were included in the study which was carried out in a Uludağ University's Medical Faculty Hospital in Turkey. The study was designed prospectively. The EAT thickness measurement was performed and recorded for all individuals. All patients underwent a symptom-limited exercise test following the Bruce protocol. The relationship between known risk factors of coronary artery disease of the EAT thickness measured by echocardiography and decreased HRV index in the recovery phase in the exercise stress test was investigated.

Results: Metabolic syndrome group was found out to have a significantly thicker EAT thickness ($p<0.01$). Recovery 2^{nd}-minute heart rate change was determined to be statistically different between the two groups ($p<0.05$). The triglyceride levels went up, so did the EAT thickness. Within the MS group, ones having an LDL>160 mg/dl level had a significantly thicker EAT than the ones with an LDL<160 level. The group with an HDL level<40 mg/dl had a significantly thicker EAT thickness. In the cases included in the study, the most important variable affecting the recovery 2^{nd}-minute heart rate variation (HRV_2) was determined to be the EAT ($p<0.01$).

Conclusion: The routine measurement of the EAT might be a good indicator of the coronary artery diseases before the apparent ischemic findings emerge, which is supported by the findings of the present study.

Keywords: Epicardial fat, heart rate recovery, metabolic syndrome, echocardiography, exercise stress test

Introduction

Metabolic Syndrome (MS) is a modern life disease in which multiple fatal systemic disorders such as glucose intolerance starting with insulin resistance or diabetes mellitus, obesity, hypertension, and coronary artery disease blend with each other. NHANES III study, carried out in the USA, reported MS incidence in the population of over 20 years of age was 34% and it was three-fold in the 40-59 age group compared to the 20-39 age (1).

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According to TEKHARF study data, general MS prevalence is 49.6% in males and 54.5% in females in the over 40 years age group in Turkey (2). It has been demonstrated that there is excess epicardial adipose tissue in MS patients and that it is associated with coronary artery disease (CAD)(3).

Heart Rate Recovery (HRR) is defined as the post-exercise decrease in heart rate (4). HRR is observed as a rapid decline in the first 30 seconds following exercise. Many researchers have evaluated abnormal HRR at various times of exercise tests. Cole et al. reported that the risk of death for any reason during the six years was approximately 4 times higher in individuals with first-minute HRR≤12 beats than those with >12 beats (4). In the Lipid Research Clinics Prevalence study, after 12 years of follow-up, mortality was reported to be 2.58 times higher in patients with HRR<43 beats in the second minute after exercise test than those with HRR>43 beats (5). As corroborated by many studies, HRR is a significant predictor of all-cause mortality, independent of the severity of atherosclerosis in coronary arteries, left ventricular function, and exercise capacity.

This study aims to investigate the impact of the epicardial adipose tissue (EAT) thickness on the HRR by comparing the heart rate recovery in the second minute (HRR 2^{nd}-min) of the recovery phase of the exercise test in MS patients and the healthy control group.

Materials and Methods

A total of 78 people were included in the study. 48 were patients diagnosed with MS for the first time in Uludağ University's Medical Faculty Hospital in Turkey and 30 were the healthy control group. The study group was initially planned as 100 participants, however, 22 participants were excluded due to such reasons as not achieving the exercise test, having a history of drug use due to DM, HT, HL, having ischemic heart disease, rheumatic valve disease, congenital heart disease, the pericardial disease in anamnesis or echocardiographic findings. The study was designed prospectively. Special attention was given to form the patient and control groups similar in terms of age, gender, and risk factors. Demographic, blood biochemistry, exercise stress test and echo cardiography data of the participants were recorded. ATP III criteria were used in metabolic syndrome diagnosis. Patients who met at least 3 MS criteria and whose waist circumference was over 88 cm in females and over 102 cm in males were admitted to the study. The relation ship between known risk factors of CAD of EAT measured by echocardiography and decreased heart rate recovery index in the recovery phase in the exercise stress test was investigated.

In epicardial fat thickness measurement; para sternal long-axis and parasternal short-axis images at the end of 3 cardiac cycles, using 2-D and M-Mode techniques areas adjacent to the right ventricular free wall, near the ventricular basal 1/3 section of the echo-free area between myocardium and visceral peri cardium perpendicular to the aortic annulus at end-diastole and average of all measurements were recorded.

All patients underwent a symptom-limited exercise test following the Bruce protocol. During the exercise stress test, the systolic and diastolic blood pressures of the patients were measured manually at the beginning of the test and the second minute of each stage. The exercise stress test was ceased in case the patients had fatigue and maximal heart rate was reached. After the test was over, 3 minutes of recording was taken during the recovery phase.

Systolic, diastolic, and heart rate values were recorded every minute during the recovery phase. Second-minute heart rate recovery (HRV_2) was found by subtracting the recovery second-minute heart rate from the peak heart rate. An $HRV_2 \leq 43$ was considered to be a decreased heart rate recovery.

We used Statistical Package for Social sciences (SPSS) 15 (Inc., Chicago, Illinois, USA) software for statistical analysis. The one-sample Kolmo gorov-Smirnov test was used in assessing the normal distribution of the samples. The One-Way ANOVA test, Student t-test, Man Whitney and Ki-Square was used in the analysis. Pearson correlation test and Linear Regression was also used for data. The findings were stated as percentages and frequencies for categorical variables and as mean±standard deviation (SD). P<0.05 was accepted as statistically significant in all the analyses.

Results

Seventy-eight cases were included in the study. They were 48 patients diagnosed with metabolic syndrome and 30 cases consisting of the control group. The metabolic syndrome group consisted of 27 females and 21 males (48.2% 44,8% respectively) and the control group consisted of 15 females and 15 males (50% and 50% respectively). The respective average ages of the MS and the control groups were 45.31±5.48 and 37.9±5.56. Respective BMIs of the metabolic syndrome and the control groups were calculated as follows: 33.2±5.36 (52.2-26) ve 25.56±2.78 (32.3-2) kg/m^2. Of the cases admitted to the study, heart disease history in the family was 35.4% in the MS group and, 36.7% in the control group, which didn't constitute a statistically significant difference (p>0.05). The percentage of smokers was 56.2 in the MS and 30 in the control, which was a significant difference (p<0.01). Besides, statistically significant results for hypertension and hyperlipidemia parameters were also determined between MS and control (Table 1).

Table 1. Basic characteristics of the patients and control

Variables	Metabolic syndrome (n:48)	Control (n:30)	P value
Gender (Male/Female)	21/27	15/15	0.59
Age (years)	45.3±5.4 (31-50)	37.5±5.56 (27-50)	0.698
BMI (kg/m^2)	33.2 (26-52.2)	25.56 (20-32.3)	0.45
Hypertension (n,%)	22 (45.8%)	1 (3.3%)	<0.001
Hyperlipidemia (n,%)	38 (79.2%)	6 (20%)	<0.001
Family history	17 (35.4%)	11 (36.7%)	0.91
Smoking (n,%)	27 (56.2%)	9 (30%)	0.005
Obesity (n,%)	47 (97.9%)	13 (43.3%)	<0.001
Waist circumference	104.4±9.4	89.5±8.73	0.455

BMI: Body mass index

While TSH, hemoglobin, HDL cholesterol, and creatinine values weren't significantly (p>0.05) different in both groups, fasting blood sugar, total cholesterol (p<0.01), LDL cholesterol, and triglyceride (p<0.05) of the MS group were found out to be statistically higher (Table 2).

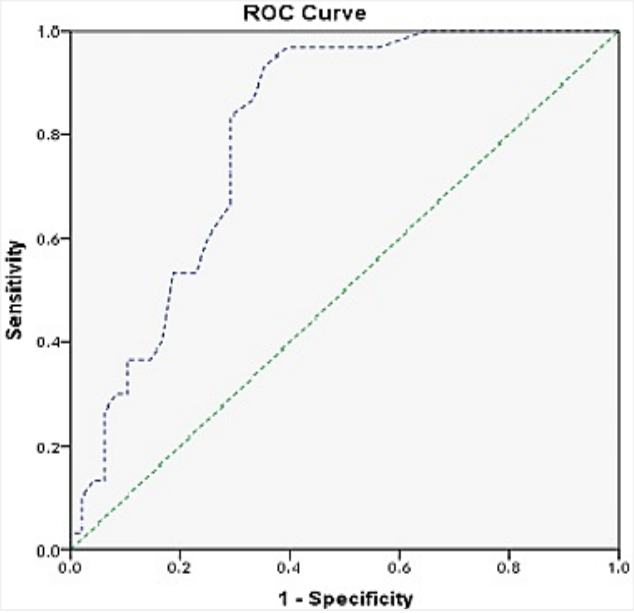

Figure 1. Recovery cut-off evaluation for 2nd-minute heart rate change

MS group was found out to have a significantly thicker EAT (p<0.01) (Table 2). MS and control group recovery HRV_2 was found by subtracting recovery 2nd-minute heart rate from peak heart rate. The cut-off value for the MS and control groups was determined as ≤43 by using a ROC Curve (Area under the curve=0.802; p<0.001) (Figure 1).

Table 2. Laboratory characteristics of patient and control

Variables	Metabolic syndrome (n:48)	Control (n:30)	P value
Fasting Blood Sugar (mg/dl)	122.08±67.3	85.8±10.05	<0.001
Creatinine (mg/dl)	0.81±0.17	0.79±0.12	0.2
T. Cholesterol (mg/dl)	218.1±49.8	191.1±35.7	0.007
HDL (mg/dl)	39.7±8.99	44.67±10.2	0.37
LDL (mg/dl)	141.6±49.3	120.8±28.8	0.02
Triglyceride (mg/dl)	231±280.4	134.3±90.4	0.03
Hemoglobin (g/dl)	13.98±1.4	14.29±1.62	0.3
TSH	1.56±0.89	1.48±0.71	0.62
Epicardial Adipose Tissue Thickness (mm)	6.11±1.69	3.7±0.67	0.001

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein, TSH: Thyroid-Stimulating Hormone

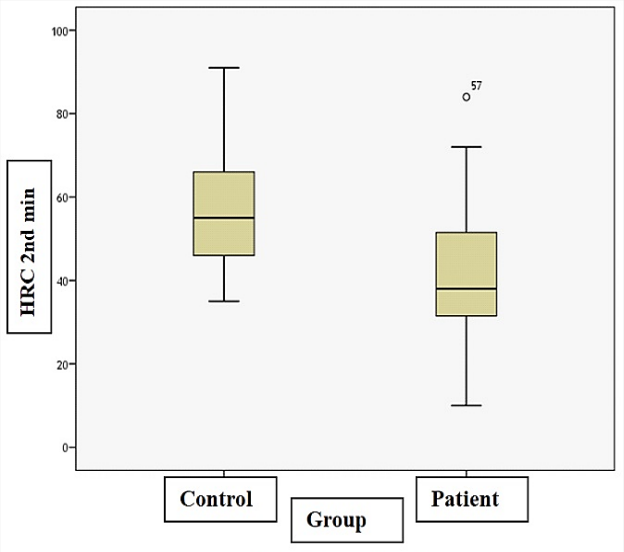

Figure 2. Recovery 2nd-minute heart rate change

Recovery 2nd-minute heart rate change was determined to be statistically different between the two groups (p<0.05) (Figure 2). MS group triglyceride, total cholesterol, LDL, and fasting sugar levels were determined as significantly higher. It was observed that as the triglyceride levels went up, so did EAT thickness. No correlation was observed between the HRV and the triglyceride level.

Within the MS, ones having an LDL>160 mg/dl level had a significantly thicker EAT than the ones with an LDL<160 level, however, no difference was determined in its effect on the HRV. The group with HDL<40 mg/dl had a significantly thicker EAT, however, the group with HDL>40 mg/dl didn't have a difference in terms of HRV. Considering all the results, triglyceride, total cholesterol, LDL, HDL levels and BMI didn't have an impact on the heart rate recovery independent of the EAT. In the cases, epicardial adipose tissue was determined to be important variable affecting the recovery 2nd-minute HRV_2 at the level of p<0.01 (Table 3).

Table 3. Relationship between heart rate variability and epicardial adipose tissue

Variables	HRR 2	n	Epicardial Adipose Tissue Thickness (mm)	P value
In All Cases	≤43	39	6.17±1.6	0.001
	>43	39	4.2±1.42	
Patient	≤43	34	6.52±1.4	0.007
	>43	14	5.11±1.9	
Control	≤43	5	3.76±0.7	0.83
	>43	25	3.68±0.68	

Discussion

Fatalities due to coronary artery disease are still high despite developing treatment options. Appropriate risk categorization should be performed to ascertain the appropriate treatment options for each patient (7). The main research areas of cardiology are preventing the

catastrophic consequences of coronary artery disease and finding out the trigger factors, biomarkers, and therapeutic molecules.

EAT is a component of visceral adipose tissue located between the heart and pericardium, especially in the atrioventricular sulcus, lateral to the right ventricle, and around the coronary arteries (8). Many researchers have shown that the increased EAT is associated with insulin resistance, metabolic syndrome, adiponectin, LDL, and increased blood pressure. Iacobellis et al. reported in their research that EAT could be measured via echocardiography, computerized tomography, and magnetic resonance. Among such modalities, echocardiography seems to be the most practical approach in that it is practical, cost-effective, and does not contain radiation (9).

Researches on EAT determined that some paracrine and autocrine cytokines secreted by EAT were important factors of inflammation and atherogenesis responsible for main physio pathological mechanisms of the CAD. EAT was found out to be associated with plasminogen activator inhibitor-1, proatherogenic and pro inflammatory adipokines, visfatin, monocyte chemoattractant protein-1, and increased CRP. All these findings support the idea that EAT has important effects on CAD (10).

Metabolic syndrome is a collection of many risk factors associated with CAD. Many studies are showing that EAT is increased significantly in a person with MS (11-13). The present study has determined that EAT in the MS group is significantly increased compared to the control group. Post-exercise decreased HRV is an important symptom of autonomic dysfunction and is associated with all-cause mortality (14). We have focused especially on the post-exercise 2nd-minute heart rate recovery and epicardial adipose tissue relationship. Results of the Lipid Research Clinics Prevalence study demonstrated that patients with decreased post-exercise 2nd-minute heart rate recovery had a four-fold mortality risk (5). In this study, we have examined the relationship of the epicardial adipose tissue, an early marker of the CAD, which is an important cause of mortality in patients with MS, and also a good non-invasive indicator of exercise capacity in obesity treatment, with the decreased heart rate recovery (15).

In our study, we have determined that EAT is associated with decreased heart rate recovery regardless of the other risk factors important for the CAD, which indicates that EAT is not only a patch of fat but also has important physiological effects (16). An increasing number of studies on EAT demonstrate that this parameter, which would be examined during the routine echocardiographic examination would be very beneficial in the prognosis determination. Sengul et al, similar to our study, found out EAT to be associated with decreased heart rate recovery (17). This study aimed to find simple approaches that would be useful in early diagnosis of the CAD, in patients with MS. When CAD progresses, its cost as well as its mortality rate increase. Studies focus on non-invasive and simple prognostic identifiers. We believe that routine measurement of the EAT might be a good indicator of the CAD before the apparent ischemic findings emerge, which is supported by the findings of the study.

Ethical Statement

The study was approved by the University Ethics Committee for Clinical Research Studies and all the patients were informed about the study.

Conflicts of Interest

The authors declared no conflict of interest.

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ORIGINAL ARTICLE OPEN ACCESS

The Profile of Healthy Adults in Istanbul Province: Investigation of Dietary Habits and Biochemical Parameters

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Introduction: Although the beneficial effects of a healthy diet and increased physical activity are well-known, it is not always easy to follow such a life style. In this study, eating habits and physical activity of the healthy adult population in Istanbul province were investigated.

Materials and Methods: A total of 202 subjects who underwent a health check-up program were enrolled in our study. The demographic characteristics and exercise habits of the subjects were recorded. All participants filled out a self-administered questionnaire to determine their dietary profile. Biochemical analysis, complete physical examination, electrocardiogram, and 2-D echocardiography of each subject were performed.

Results: The mean age, weight, height, and BMI of the study population were 40.05±11.76 years, 72.9±15.31 kg, 167.6±9.2 cm, and 25.73±5.12 kg/m^2, respectively. The prevalence of high LDL, TG and low HDL were 32.6%, 40.6% and 49.5%, respectively. Majority (57.9%) of the subjects consumed >5 gr/day salt daily. Only 36.6% of the subjects consumed vegetables more than 3 times a week. 21.3% of the subjects seldom consumed fish. There were relationships between age and fast food consumption (x^2=34.86; p<0.001) and between age and soft drinks (x^2=26.67; p<0.001). Subjects who were doing exercise regularly had lower BMI than the subjects doing exercise irregularly or not at all. There was an inverse relationship between BMI and education level of the subjects. Eating vegetables and fish were associated with better lipid profile; whereas eating red meat and fast food were associated with worse lipid profile.

Conclusion: The majority of our study population did not follow healthy eating recommendations. It is imperative to increase the awareness of the public about beneficial effects of diet, healthy eating habits, and lifestyle changes.

Keywords: Healty diet, lifestyle, eating habits

Introduction

One important factor in protection and sustainability of health is assurance of sufficient and well-balanced diet as well as gaining healthy nutrition habits. Due to processes brought by today's conditions, eating habits are affected and hence various problems arise. One leading problem is progress of chronic illnesses. In recent studies, chronic illnesses such as cardiovascular disease and eating habits have been shown to be correlated (1). Cardiovascular

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disease (CVD) is the leading cause of death for both men and women. In 2015, the number of people who died from CVD was more than 17 million, representing as much as 30 percent of all global deaths, of which 7.4 million were due to coronary artery disease and 6.7 million due to stroke (2). A number of risk factors are related to CVD such as age, sedentary lifestyle, hypertension, hyperlipidemia, smoking, obesity, and diabetes mellitus. Many of the risk factors are modifiable, diet and lifestyle modifications play a crucial role in managing the individual's risk profile. It is well-known that DASH (Dietary Approaches to Stop Hypertension) diet which is rich in vegetables, fruits, low-fat dairy products, whole grains, fish, dietary fibre, potassium and calcium that contains only small amounts of sweets, and sugar containing beverages lower not only the blood pressure in subjects with or without hypertension but also the risk of CVD, coronary heart disease, heart failure and stroke (3, 4). Improved adherence to nonsmoking, healthy dietary patterns, moderate physical activity and alcohol consumption is associated with reduced cardiovascular mortality (5).

While there is a good evidence base for lifestyle interventions involving dietary change and increased physical activity have a positive impact on individuals and communities, it is not always easy to follow a healthy diet. In a world where the unhealthy and processed food readily available, poor eating habits would be heard to change. In this study, we aimed to evaluate lifestyle, eating habits and physical activity of the general adult population in Istanbul province.

Materials and Methods

This study was undertaken between May and September 2018 and a total of 202 subjects who underwent health check-up program were enrolled. Patients with ischemic heart disease, congestive heart failure, valvular heart disease, hypertension, abnormal ECG, liver rhythm-conduction disorders, disease, cerebrovascular accident, diabetes mellitus, renal dysfunction, and hypo-hyper thyroidism were excluded from the study.

The study was conducted according to the declaration of Helsinki. The study was approved by the ethic committee of Sakarya University (date: 02.04.2018 number: 71522473/050.01.04/65) and the patients gave informed consent prior to participation. Demographics of the population such as age, gender, occupation, educational and income levels were recorded. Body mass index (BMI) in kg/m^2 was calculated from self-reported height and weight. Exercise were classified as never/rarely, occasionally and regularly. All participants filled out self-administered questionnaire to determine their dietary profile. Participants were asked to select one option that represented their average weekly consumption of fruits, vegetables, dairy products, whole grains, red meat, fish, poultry, junk food and high calorie drinks (never/seldom [Group 0], once a week [Group 1], twice a week [Group 2], ≥3 times a week [Group 3]). They were asked about their eating speed, overeating episodes and whether they ate their meals regularly. Eating speed was self-recorded into slow, medium and fast. Overeating was defined as consuming food more than usual or even after feeling satiety. Consumption of spicy food was assessed as never, once a week, more than once a week. Daily coffee intake (none, once a day, 2-3 times a day, more than 3 times a day) and salt consumption (saltless, <5 g/day, 5-10 g/day, ≥10 g/day) were also recorded.

Alcohol consumption was classified as never/seldom, light drinking (at least one serving per

month), moderate drinking (1 serving every day) and heavy drinking (more than 2 serving per day). After an overnight fast blood samples blood samples were collected from antecubital vein: serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), fasting glucose levels were measured using an chemistry analyzer (COBAS c311, Roche Diagnostics, Germany). Low HDL-C level was defined as <40 mg/ dl, high LDL and TG levels were defined as ≥130 mg/dl and ≥150 mg/dl, respectively.

All subjects underwent complete physical examination, 12-lead electrocardiogram, and chest radiography. The 2-dimentional echo cardiographic examinations were performed using Vivid 3 prosystem (GE Vingmed Ultra sound AS, Horten, Norway) according to the recommendations of the American Society of Echocardiography (6).

SPSS (version 20) software programme was used for the data analysis. In order to determine whether the sample was coming from normally distributed population we used Shapiro-Wilk tests. Since data was not normally distributed, we used non-parametric tests. Kruskal-Wallis tests were used for group comparisons, where as sub-group analyses were conducted using Kruskal-Wallis pairwise comparisons test. A p of <0.05 was considered as statistically significant.

Results

The mean age, weight, height and BMI of the study population were 40.05 years, 72.90 kg, 167.61 cm, and 25.73 kg/m^2, respectively. All participants had normal electrocardiogram, chest x-ray and 2-D echocardio examination. Clinical and demographic characteristics of the study population are given in Table 1.

Table 1. Clinical and demographic characteristics

Parameters	Value
Male / Female	85 (42.1%) / 117 (57.9%)
Age *(years)*	40.05 (16 - 68 - 18)*
Weight *(kg)*	72.9 (50 - 120 - 21)*
Height *(cm*	167.61 (150 - 192 - 12)*
BMI *(kg/m^2)*	25.73 (17 - 43 - 7)*
Smoking	
▪ 0	150 (74.3%)
▪ 1	31 (15.3%)
▪ 2	21 (10.4%)
Alcohol Consumption	
Never/seldom	159 (78.7%)
Light drinking	33 (16.3%)
Moderate drinking	4 (2%)
Heavy drinking	6 (3%)
Heredity	
▪ 0	167 (82.7%) 83,2
▪ 1	35 (17.3%) 16,8
Education	
▪ Elementary	47 (23.3%)
▪ Middle/high	93 (46%)
▪ College	62 (30.7%)
Income Level	
▪ Lower	36 (17.8%)
▪ Middle	126 (62.4%)
▪ Upper	40 (19.8%)
Occupation	
▪ Housewife	48 (23.8%)
▪ Private company	78 (38.6%)
▪ Government officer	15 (7.4%)
▪ Minimal wage	28 (13.9%)
▪ Unemployed	11 (5.4%)
▪ Student	9 (4.5%)
▪ Retired	13 (6.4%)
Marital Status	
▪ Single	56 (27.7%)
▪ Married	129 (63.9%)
▪ Divorced	17 (8.4%)
Exercise Habits	
▪ Never/rarely	48 (23.8%)
▪ Occasionally	94 (46.5%)
▪ Regularly	60 (29.7%)

*"min"-"max"-"IQR", respectively. 0: Seldom; 1: Once Per Week; 2: Two Times Per Week 3: Times Per Week

Biochemical parameters of the subjects are given in Table 2. The majority of the study subjects ate 3 meals per day and had regular meal patterns. The percentage of slow, normal and fast eaters were 31.2%, 42.6%, and 26.2%, respectively. Participants consumed spicy food (never/seldom: 8.4%, once a week: 36.6%, twice a week: 35.6%, and three times a week: 19.3%). 31.7%, 33.7%, 25.2% and 9.4% of the subjects had overeating episodes never/seldom, once a week, two times a week and three times a week, respectively. Majority of the study population consumed coffee once a day(37.6%), remainder consumed two cups a day (34.1%), 3 cups a day (9.9%), or rarely (18.3%). Salt consumption of the study population were; 18.3%, 23.8%, 38.6% and 19.3% for saltless, normal, salty, too salty, respectively.

Table 2. Biochemical parameters of the subjects

Parameter	Mean	Min	Max	IQR
Total cholesterol *(mg/dl)*	195.94	119	340	50
Triglyceride *(mg/dl)*	158.58	41	530	92
HDL *(mg/dl)*	33.38	23	74	13
LDL *(mg/dl)*	118.74	40	200	53
Fasting glucose *(mg/dl)*	93.12	68	126	14
RDW *(%)*	13.96	11	136	1
Hb *(g/dl)*	14.24	9	17	2
MPV *(fl)*	9.10	4	16	1
Neutrophil count *($10^3/mm^3$)*	4.69	0	12	2
Lymphocye count *($10^3/mm^3$)*	2.27	0	5	1

HDL: High Density Lipoprotein Cholesterol, LDL: Low Density Lipoprotein Cholesterol, RDW: Red Cell Distribution Width, Hb: Hemoglobin, MPV; Mean Platelet Volume

Table 3. Eating habits of the study population

Parameters	N	%
Number Of Meals		
▪ Once A Day	4	2
▪ Twice A Day	49	24.2
▪ Three Times A Day	140	69.3
▪ Four Times A Day	9	4.5
Regular Meals		
▪ Regular	98	48.5
▪ Mostly Regular	82	40.6
▪ Irregular	22	10.9
Eating Speed		
▪ Slow	63	31.2
▪ Normal	86	42.6
▪ Fast	53	26.2
Overeating Episodes		
▪ Never/Seldom	64	31.7
▪ Once A Week	68	33.7
▪ Twice A Week	51	25.2
▪ Three Times A Week	19	9.4
Spicy Food		
▪ Never/Seldom	17	8.4
▪ Once A Week	74	36.6
▪ Twice A Week	72	35.6
▪ Three Times A Week	39	19.3
Coffee		
▪ Never/Seldom	37	18.3
▪ Once A Day	76	37.6
▪ Twice A Day	69	34.1
▪ Three Times A Day	20	9.9
Salt Consumption		
▪ Saltless	37	18.3
▪ Normal	48	23.8
▪ Salty	78	38.6
▪ Too Salty	39	19.3

Frequency of food types were described as never/seldom, once a week, twice a week, and three times or more than three times a week. The results are shown in Table 3 and 4. We found relationships between age and fast-food consumption ($KW(x^2)=34.86$; $p<0.001$) and between age and soft drinks ($KW(x^2)=26.67$; $p<0.001$); further analysis showed the difference

Table 4. Eating habits of the study population

Parameters	N	%
Vegetable		
▪ 0	5	2.5
▪ 1	28	13.9
▪ 2	95	47.0
▪ 3	74	36.6
Fruit		
▪ 0	5	2.5
▪ 1	32	15.8
▪ 2	85	42.1
▪ 3	80	39.6
Whole Grains		
▪ 0	1	0.5
▪ 1	40	19.8
▪ 2	116	57.4
▪ 3	45	22.3
Meat		
▪ 0	29	14.4
▪ 1	87	43.1
▪ 2	55	27.2
▪ 3	31	15.3
Fish		
▪ 0	43	21.3
▪ 1	95	47.0
▪ 2	60	29.7
▪ 3	4	2.0
Poultry		
▪ 0	17	8.4
▪ 1	72	35.6
▪ 2	81	40.1
▪ 3	32	15.8
Dairy Products		
▪ 0	1	0.5
▪ 1	10	5.0
▪ 2	76	37.6
▪ 3	115	56.9
Junk Food		
▪ 0	122	60.4
▪ 1	46	22.8
▪ 2	30	14.9
▪ 3	4	2.0
Soft Drinks		
▪ 0	78	38.6
▪ 1	57	28.2
▪ 2	41	20.3
▪ 3	26	12.9

0: Seldom; 1: Once/Week; 2: 2 Times/Week 3: 3 Times/Week

was made by group 0, indicating that subjects who seldom consumed fast-food and soft drinks had higher average age than the others. There were no significant relationships between fast-food consumption and income level and education of the subjects (p=0.256 and p=0.227, respectively). Subjects who ate junk food at least 2 times a week had statistically significantly higher TC, LDL and TG than those who seldom consumed such food ($KW(x^2)$= 10.07; p=0.01, $KW(x^2)$=9.81; p=0.02 and $KW(x^2)$ =10.41; p=0.01, respectively) (Table 5).

The BMI of the participants were differed according to their exercise habits ($KW(x^2)$=50.11; p<0.001). Subjects who were doing exercise regularly had lower BMI than the subjects doing exercise irregularly or not at all. There was an inverse relationship between BMI and education level of the subjects ($KW(x^2)$= 31.12; p<0.001). Subjects who had irregular and fast eating patterns had significantly higher BMI compared to that of the subjects who had regular, mostly regular and slow and normal eating pattern ($KW(x^2)$=7.12; p=0.028 and ($KW(x^2)$=12.11; p=0.002. Similarly, BMI who had overeating episodes were higher relative to the subjects who had no overeating episodes ($KW(x^2)$=61.38; p<0.001). Eating vegetables more than 3 times a week was associated with lower BMI compared to less frequent consumption ($KW(x^2)$=11.11; p=0.025). Further analysis showed that subjects who were eating vegetables more than 3 times a week had lower BMI compared to that of subjects who were eating vegetables only once a week. Subjects who were doing exercise regularly had statistically significantly lower TC and TG levels and higher HDL levels than the subjects who were doing exercise occasionally or rarely ($KW(x^2)$=53.82; p<0.001, $KW(x^2)$=42.42; p<0.001

and KW(x^2)=13.31; p=0.004, respectively). Eating vegetables at least 3 times/week was associated with lower TC and LDL (KW(x^2)=37.48; p<0.001, KW(x^2)=45.02; p<0.001 and KW(x^2)=20.97; p<0.001, respectively). Participants who ate red meat more than 2 times a week had significantly higher TC and LDL levels than that of the participants who consume less amount of meat (KW(x^2)=25.94; p<0.001 and KW(x^2)=39.25; p<0.001, respectively). On the contrary, eating fish more than once a week was associated with lower TC, LDL and TG levels (KW(x^2)=24.31; p<0.001, KW(x^2)=19.52; p<0.001 and KW(x^2) =13.96; p=0.003, respectively. The increased number of overeating episodes was correlated with higher LDL levels (KW(x^2) =85.97; p<0.001). The pairwise analysis demonstrated that the difference was significant between all groups except between subjects who had overeating episode once a week (Group 1) and twice a week (Group 2). Overeating episodes were also associated with increased glucose levels (KW(x^2) =55.94; p<0.001). Further analysis showed that the difference was between all groups except between subjects who had overeating episodes once and twice weekly. When we analyzed the glucose levels of the participants, we found that participants who were doing exercise regularly had lower glucose levels than the participants who were not doing exercise regularly or not at all (KW(x^2) =56.53; p<0.001). Table 6 shows the comparison of the eating habits of the subjects with other parameters. There was an association between TG levels and alcohol consumption. (KW(x^2)=10.65; p<0.014). Heavy drinkers had higher TG levels compared to light and seldom drinkers. It was found that as the salt intake increases, the TC also increases KW(x^2)=44.66; p<0.001). Further analysis showed that the difference was significant between all groups, except between group 0 (saltless consumer) and 1 (normal salt consumer).

Table 5. Comparison of fast food and soft drink consumption with other parameters

Fast Food Consumption					
Variables	Seldom	Once a week	Two times a week	Three times a week	p
Age (years)	43.95	35.93	18.01	27.5	p<0.001
TC (mg/dl)	199.4	207.34	226.03	238.25	p=0.01
LDL (mg/dl)	123.56	135.15	144.9	142.25	p=0.02
TG (mg/dl)	164.07	198.21	221.6	224.25	p=0.01
Income Level (n)					
Lower	28	4	4	0	p=0.256
Middle	71	31	20	4	
Upper	23	11	6	0	
Education (n)					
Elementary/middle/high	91	28	19	2	p=0.227
College	31	18	11	2	
Soft Drink Consumption					
Age (years)	44.6	40.08	36.9	31.34	p<0.001

LDL: Low density cholesterol, TC: Total cholesterol, TG: Triglyceride

Table 6. Comparison of eating habits and education of the subjects with other parameters

Exercise Habits	Never/rarely	Occasionally	Regularly		P Value
BMI (kg/m^2)	30.66	28.50	25.68		p<0.001
TC (mg/dl)	233.29	210.25	177.3		p<0.001
TG (mg/dl)	235.89	189.14	126.29		p<0.001
HDL(mg/dl)	40.83	42.39	46.98		p=0.004
Glucose (mg/dl)	98.85	93.41	87.3		p<0.001
Education	Elementary	Middle/High	College		
BMI (kg/m^2)	29.88	28.46	24.90		p<0.001
Regular Meals	Irregular	Mostly Regular	Regular		
BMI (kg/m^2)	27.43	26.14	25.12		p=0.028
Eating Speed	Slow	Normal	Fast		
BMI (kg/m^2)	26.59	27.13	30.07		p=0.002
Overating Episodes	Never/Seldom	Once a Week	Twice a Week	Three Times a Week	P Value
BMI (kg/m^2)	24.79	27.12	29.31	35.56	p<0.001
LDL(mg/dl)	102.89	128.94	143.19	186.94	p<0.00
Glucose (mg/dl)	87.32	93.69	95.53	104.10	p<0.001
Vegetables					
BMI (kg/m^2)	27.51	29.73	28.71	25.94	p=0.025
TC (mg/dl)	221.52	220.85	221.07	182.04	p<0.001
LDL(mg/dl)	140.25	148.21	141.85	108.33	p<0.001
Red Meat					
TC (mg/dl)	186.89	194.29	215.89	238.77	p<0.001
LDL(mg/dl)	111.10	119.31	139.05	159.93	p<0.001
Fish					
TC (mg/dl)	221.67	212.98	185.95	169.25	p<0.001
LDL(mg/dl)	138.65	136.66	113.53	112.75	p<0.001
TG (mg/dl)	198.51	196.55	149.58	124	p=0.003

BMI: Body mass index, HDL: High density cholesterol, LDL: Low density cholesterol, TC: Total cholesterol, TG: Triglyceride

Discussion

Our study provides important insights about the dietary habits of the adult population in Turkey. It also gives information on how dietary habits of the subjects affected their biochemical parameters.Most of the subjects had three main meals per day, regular meal pattern and normal eating speed. The majority consumed salty or too salty food, drank coffee once a day and had overeating episodes at least once per week. The average BMI of the sample was 25.73±5.12 kg/m^2, indicating overweight. Eating vegetables and red meat was found to be related better and worse lipid profiles, respectively. Subjects who had high consumption of fish had better blood lipid levels.

Obesity and overweight are growing public problems with serious medical consequences such as diabetes mellitus, hypertension and cardiovascular disease, sleep apnea (7, 8). Over the past four decades, the prevalence of obesity in the world has doubled, with a higher rate

of increase in childhood obesity (9). According to Turkish Health Ministry, BMI of the Turkish adult population was 26.6 kg/m^2 (women: 26.8 kg/m^2, men: 26.1 kg/m^2) (10). A high prevalence of high-LDL, TG and low HDL (29.1%, 36.5% and 46.1%, respectively) have been reported in our country which remains a major health concern for cardiovascular diseases (11). In our study, the prevalence of high LDL, TG and low HDL were 32.6%, 40.6% and 49.5%, respectively. Our results were in agreement with the above-mentioned results, emphasizing the importance of life style changes for better overall health.

Several studies have found a clear association between lower socioeconomic and educational level and high BMI in developed countries (12-14). This may be due to the characteristics of local food environment, less consumption of fruits and vegetables and prices of the food (15). The reverse may be true; for example, higher BMI might be related to lower self-esteem, weaker job prospects, lower income and educational levels (16, 17). However studies performed in developing countries showed just the opposite; thus reflecting the changes in eating habits and occupational patterns (18, 19). According to Turkish Health Ministry data prevalence of obesity was the highest among people with no education (10). Similarly in our study, we found an inverse relation between BMI and education. Our results have shown, one more time, the pivotal role of education for healthy diet and life.

Eating frequency has been offered as one of the factors which influence BMI. However studies conducted on this topic revealed conflicting results. EPIC project and SEASONS study showed higher eating frequency was associated with lower LDL and obesity risk even after adjustment for confounding factors (20, 21).16-year follow up study indicated that eating one or two times a day increased the risk of type II diabetes compared to more frequent eating (22). Conversely, other studies reported lower BMI in subjects who ate less frequently and had long overnight fast (23, 24). BMI is appeared to be affected by eating time. Eating in a short time lower the response to the satiety hormones, resulting in overeating, high calorie intake and insulin resistance (25,26). We did not find any association between number of meals and BMI of the subjects. However, subjects who had regular meals and slow eaters had lower BMI compared to subjects who had irregular meals and fast eaters.

Much evidence showed that high salt intake is a key factor for developing high blood pressure (27). The World Health Organization (WHO) proposed reduced salt intake as a cost-effective and practical way of reducing cardio vascular disease prevalence (28). Although salt consumption in Turkey has decreased in recent decades, it is still high and has been reported as 14.8 gr/day (29). Bread represented the main source of salt, followed by the salt added during cooking, prepackaged food and the salt added after cooking (29). More than half of the study population consumed salt >5 gr/day, emphasizing the importance of raising the awareness of population about consumption of salt and its effects on health.

Less intake of fruits and vegetables has been linked to various chronic diseases, namely, cardiovascular diseases, diabetes mellitus and some kinds of cancer (30). WHO recommends 400 gr or five portions of fruit and vegetable intake every day (31). The fruit and vegetable consumption of our study group was lower than the recommended level substantially.

Excess red meat intake has been found to be related to various diseases (diabetes, stroke, cardiovascular diseases, cancer) and increased mortality (32). There has been several studies regarding the effect of red meat intake on blood cholesterol. Results of these studies showed that processed meat and fatty meat, not lean red meat, had adverse effects on serum TC and LDL levels because of their high saturated fatty acid content (33). In the present study, we only asked our target population about their red meat consumption, we did not ask whether it was processed meat, fatty meat or lean read meat. Probably because of that we found significant associations between red meat consumption and blood cholesterol and LDL levels. As expected, consuming a diet rich in fish and vegetables was associated with better blood lipid profile. Junk food, because of its lower cost and easy availability, has been preferred especially by younger population. Since its high saturated fat and glycemic index, it has deleterious effects on blood lipid and glucose profile (34). In our study, fast-food and soft drinks were preferred by young subjects, but we did not find any relationship between fast food consumption and socioeconomic status or education levels of the subjects.

The US Dietary Guidelines Advisory Committee has recommended at least 2 servings of sea food per week as a part of heathy and balanced diet, since it is a good source of proteins, vitamins and long chain n-3 polyunsaturated fatty acids (35). Fish intake of our population is far less than the expected, although Turkey has surrounded by 4 seas. Almost one fifth of our study population consumed fish seldom and only one third of the subjects consumed at least twice per week. With the given health benefits of fish consumption, it is one of the major public health concern in Turkey.

Conclusion

In conclusion, adopting healthy diet and lifestyle changes are crucial for maintenance of health. Majority of our study population did not follow healthy eating recommendations. As in other countries, obesity and overweight are becoming an increasing problem in our country. Public campaigns and activities should be implemented, aimed at awareness of people about the fabulous benefits of healthy diet, healthy eating habits and lifestyle changes.

Ethical Statement

The study was conducted according to the declaration of Helsinki. The study was approved by the ethic committee of Sakarya University (date: 02.04.2018 number: 71522473/050.01.04/65) and the patients gave informed consent prior to participation.

Conflicts of Interest

The authors declared no conflict of interest.

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ORIGINAL ARTICLE OPEN ACCESS

Outcomes of Two Years Follow-Up after Loop Electrosurgical Excision Procedure in a University Hospital

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Introduction: We aimed to determine our experience on Loop electrosurgical excision procedure (LEEP) in patients with cervical preinvasive lesions in an academic hospital in two years follow-up period.
Materials and Methods: Data from 64 patients with cervical preinvasive lesion who underwent LEEP were analyzed retrospectively. Human papillomavirus (HPV) status, cytological outcomes of patients before LEEP, and after 2 years follow-up period were documented.
Results: Prior to LEEP, 94.52% of patients were positive in terms of HPV status. HPV positivity rate was detected as 13.89% after LEEP. The most common detected HPV type in residual lesions was HPV 16. 67.19% of patients who underwent LEEP have negative cytology after two years follow-up period. The other cytological outcomes at this period were as follows; 21.88% of patients had ASCUS, 9.38% of the patients had LSIL and 1.56% of patients had HSIL cytology. Surgical margin status was positive in 6.25% of LEEP specimens. There were 3 patients who underwent re-LEEP in two years follow-up period for HSIL.
Conclusion: The LEEP procedure was applied to patients with HSIL and ASC-H with satisfactory recurrence rates in two years follow-up period.
Keywords: Leep, HSIL, HPV, LSIL, cervical cancer, preinvasive lesion

Introduction

The majority of cervical cancer cases are composed of women who have not been screened or not screened sufficiently for cervical cancer. Moreover 50% of patients diagnosed with cervical cancer have not previously had cervical cytology. Among the screening methods, Hpv and pap-smear tests are widely used (1).

Cervical cytological abnormalities and cervical cancer may develop in a small portion of high-risk Hpv positive cases. Hpv can cause temporary or persistent infection (2). Generally, temporary infections cause LSIL and persistent infections cause HSIL. Women with persistent infection may progress to HSIL or cervical cancer within 1 or 2 years (3). Cervical preinvasive

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lesions are classified histologically as benign, LSIL (CIN-I), HSIL (CIN-II and CIN-III).In addition, if CIN-II and CIN-III are not treated, it can progress to cervical cancer in 10-20 years (4). Therefore, histologically confirmed cases of CIN-II and CIN-III require treatment. For this purpose, there are 3 treatment options applied generally. These are cryotherapy, loop electro surgical excision procedure (LEEP) and cold conization. There is no consensus on which of these methods is superior. However, LEEP and cold conization procedures seems advantageous in terms of follow-up since pathological material is obtained (5). In addition, there are randomized controlled studies showing the risk of premature birth. In recent years, smear test and HPV test have been increasing in our outpatient clinic for cervical cancer screening both alone and as a co-test. The application of the LEEP procedure is also increasing due to increasing abnormal cervical pathology results. This study aims to reveal the 2-year follow-up outcomes of patients who underwent LEEP in our clinic.

Materials and Methods

This retrospective study was approved by the local ethics committee for clinical research of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey. Between January 2015 and January 2017, data from patients who underwent LEEP with the diagnosis of cervical preinvasive lesions were retrospectively analyzed.

Inclusion criterions were as follows: patients over the age of 18 with biopsy or endocervical curettage (ECC) proven ASC-H/HSIL/CIN2/3 with LEEP. The exclusion criterions of the study were as follows; the ones with prior LEEP history, diagnosed or underwent treatment of any type of malignancy, suspicious adnexial mass, and cognitive limitations, and, incomplete records due to missing data or loss to follow-up. LEEP procedures in Mugla are done in operating room with sedation and anesthetics. Immediately prior to LEEP, Lugol's solution is used to identify the transformation zone and a LEEP electrode is selected to best fit the targeted tissue to be excised. An endocervical curettage (ECC) is subsequently performed. In follow up visits, targeted biopsies and ECC are used when clinically appropriate without use of anesthetic or sedation.

Cervical cytologies were prepared using liquid based tools and slides were examined using thin-prep procedure. Cervical cytology reports were determined according to 2001 Bethesda System; negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells-unspecified (ASC-US), low grade squamous intraepithelial lesion (LSIL), atypical squamous cells-high grade not excluded (ASC-H), high grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). The results with ASCUS and above accepted as abnormal cytology. The Bethesda system was conducted by pathology experts while cytopathological examination of the cervicovaginal material collected from patient for Pap-test. Histological diagnoses were determined as benign, LSIL (CIN-I), HSIL (CIN-II and CIN-III), and SCC.

We used a commercial kit; digene HC2 HPV DNA Test (Qiagen Germantown, Inc., MD, USA) for HPV typing. This kit can detect 13 types of high-risk HPVs(16,18,31,33,35,39,45,51,52,56,58, 59,68) and 5 types of low-risk HPVs (6,11,42, 43,44). Patients characteristics such as age, gravida, parity, BMI (body mass index), history of smoking, diabetes mellitus and hypertension, indication for LEEP, HPV status before LEEP,

need for re-LEEP, surgical margin status of LEEP specimen and cytological outcomes after 2 year follow-up period were recorded. The necessary information was obtained from colposcopy forms, pathology and operative reports, and hospital database.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software, version 23 (SPSS, Inc., Chicago, IL). The data were expressed as the mean and range for continuous variables, and binary variables were reported as counts and %. Descriptive statistics were used to summarize baseline characteristics and follow up details.

Results

During this period, 74 patients underwent LEEP by one surgeon with advanced experience on cervical preinvasive diseases. Among those patients, 2 had pathologic confirmation of microinvasive cervical cancer on LEEP pathology specimen. Medical records of eight patients could not be found and were lost to follow up. A total of 64 patients who underwent LEEP were included. The baseline descriptive statistics of the patients are listed in Table 1.

Table 1. Descriptive statistics of studied group

Variable	LEEP patients
Age	39.96±7.39 (26-59)
BMI	28.12±2.51 (23-34)
Gravidy	2.32±1.03
Parity	1.90±0.81
Smoking, n(%)	24 (37.5)
Diabetes, n(%)	6 (9.4)
Hypertension, n(%)	13 (20.3)
LEEP indication, n(%) ▪ HSIL ▪ ASC-H	 61 (95.31) 3 (4.69)
Re-LEEP n (%)	3 (4.69)
Margin positivity, n(%)	4 (6.25)

The average age of 64 patients who underwent LEEP was 39.96±7.39 years. The mean BMI of patients was 28.12±2.51. The mean gravidy and parity of those patients were 2.32±1.03 and 1.90±0.81, respectively. In 64 patients, 37.5% have smoking, 9.4% have diabetes mellitus and 20.3% have hypertension history. Indications for LEEP were HSIL in 61 patients and ASC-H in 3 patients.

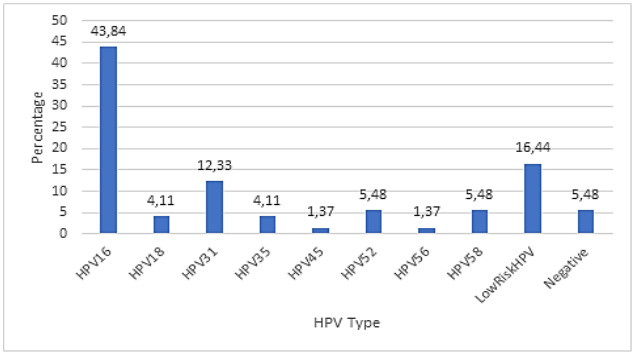

Figure 1. Disrtibution of HPV types before LEEP

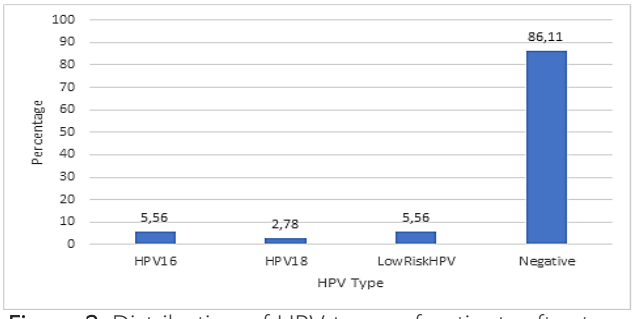

Figure 2. Distribution of HPV types of patients after two years follow-up for LEEP

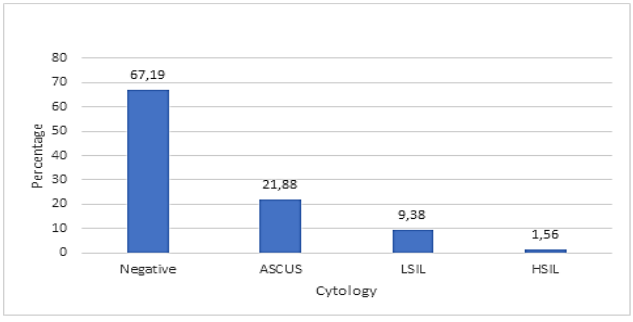

Figure 3. Cytological outcomes after two years follow-up

Distribution of HPV types of patients before LEEP are shown in Figure 1. The most common detected HPV type was HPV 16 (43.84%) before

LEEP. HPV 31 was the second common high risk HPV type seen before LEEP. Of the 4 patients, there was no HPV type detected before LEEP. Distribution of HPV types of patients after two years follow-up for LEEP are shown in Figure 2. Of the 35 patients, 86.11 % of patients was negative for HPV after two years follow-up. The most common detected HPV types were HPV 16, low risk HPV types and HPV 18, respectively.

The cytological outcomes outcomes of the study group after two years follow-up were documented in Figure 3. 67.19% of patients who underwent LEEP have negative cytology after two years follow-up. 21.88% of patients have ASCUS, 9.38% of the patients have LSIL and 1.56 % of patients have HSIL cytology after two years follow-up. Four of 64 LEEP specimen (6.25%), surgical margin status were positive. There were 3 patients who underwent re-LEEP in two years period for HSIL. All of the patients who underwent re-LEEP were positive in terms of surgical margin status. One patient of the studied group underwent bilateral salpingo opherectomy laparoscopic hysterectomy and for abnormal uterine bleeding in the sixth month of follow-up period.

Discussion

In this research, we evaluated the two years follow-up outcomes of patients who underwent LEEP procedure for HSIL/ASC-H proven histo pathologically. According to this report, it was revealed that LEEP procedure was an effective surgical option in the management of high grade cervical preinvasive diseases. Indeed, there were detected satisfactory outcomes and regression in cytopathological and HPV status of patients after two years follow-up period of LEEP.

In the present study, 1.56% of patients with pre-operative CIN 2/3 in colposcopic biopsy showed persistance of the CIN 2/3 lesion. We observed resolution of the disease in 67.19% of patients with preoperative CIN 2/3. However, nearly 98% of the patients showed regression after LEEP. There was a dramatic regression after LEEP in two years follow-up period. Our study demonstrates a very high efficacy of LEEP for the treatment of CIN 2/3 with persistent disease in only 1.56% of patients and no recurrence in two year follow-up period. Previously published recurrence rates after LEEP procedure were 1.5, 2.2, 9.1 and 11.9% for CIN 2/3 (6–9). According to the results of these studies, there were much more margin positive cases than those in our study. We think that low margin positive cases may have a major role in lower recurrence rate of our study.

Papalia and his colleagues used laser ablation in combination with LEEP and reported lower recurrence rates as 3.2% (10). In our hospital, we did not have laser ablation technology. Although we did not used laser in this study, recurrence was not seen in any patient.

After LEEP operations, follow-up of HPV status of patients is very important. Kim et al reported 85% of patients after LEEP showed HPV clearance in the six month follow-up (11). Jing et al. reported HPV positivity of the patients as 95.6% before LEEP and 29.8% after LEEP in two years follow-up period (12). Bae et al. reported HPV status as 93% before and as 35.1% after LEEP and they concluded that detection of HPV status after conizaiton may help to identify treatment failure or recurrence (13). In our study, we observed that the ratios of HPV negative patients increased from 5% to 86% after LEEP. Although the follow-up time was longer as two years, HPV clearance rate was similar to Kim et al.'s study. In this context, our study conforms that HPV clearance rate

increases gradually after LEEP. But the strict follow-up of HPV status of patients is necessary after operation for HPV persistence, especially for high risk genotypes. Some authors had reported that high-risk HPV status after LEEP is a better predictor of CIN recurrence than colposcopy or cytology results (11,14). However, some authors stated that high-risk HPV load prior to conization serves as a causative agent for recurrence(9).

In the study of Jing et al., 71% of patients who underwent LEEP were surgical margin positive (12). In our study, only 4 (6.25%) patients were positive in regard of surgical margin. Surgical margin status of LEEP patients is a major risk factor for recurrence or persistence of cervical intraepithelial neoplasia (15). Patients with positive surgical margin after LEEP have more likely experience recurrent CIN (16). In the literature, there are recurrence rates as high as 47% for patients with positive margin (17). In our study population, three of 4 patients with positive margin underwent LEEP again. Of these 3 patients, all of them were positive for HPV 16 subtype. Spontaneous regression was seen in one patient and HPV clearance was detected in her follow-up period. These findings of our study emphasizes the critical importance of persistence in high-risk HPV subtypes especially for HPV 16 at the follow up period of margin positive cases. Moreover, Bruno et al. reported that 40% of the relapsing cases in their study were seen in margin negative cases with persistent HPV 16 infection (18). We strongly agree with this opinion. If HPV 16 persistency is seen at the follow-up, a crucial attention must be given even the pathology report is margin negative.

The limitations of our study were having the retrospective design and small sampling size with lack of a comparative group. The strength of our study was the completeness of cytological data and the low lost-to-follow-up rate. In future, researches may be planned as in prospective nature designed to evaluate adverse events, oncological findings and the quality of life of patients.

CIN recurrency may be encountered mostly within the subsequent two years follow-up period of LEEP. The rate of recurrence after LEEP is higher in HPV positive. Therefore, these patients necessitates careful monitorization. In identification of residual lesions or recurrencies, Pap-smear and HPV testing have a central role at the follow-up strategies. However, recommendation favoring the use of more effective follow-up strategies for the margin positive patients should be supported with researches involving longer follow-up periods and larger patient series.

Ethical Statement

This retrospective study was approved by the local ethics committee for clinical research of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey.

Conflict of Interests

The author declared no conflicts of interests.

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ORIGINAL ARTICLE OPEN ACCESS

Female Gender and Polypharmacy Results in An Increased Risk of High-Energy Trauma Associated With Falls in Elderly People

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Introduction: Falls represent a major clinical problem in the elderly population. Accordingly, prevention of falls is clinically important in this vulnerable population. The aim of the present study was to evaluate the clinical characteristics associated with falls and to define a patient subgroup that is at increased risk.

Materials and Methods: Consecutive patients aged ≥65 years, who presented with falls at Emergency Department of American Hospital, Istanbul, Turkey, from 01/02/2014 to 01/02/2015, were included in this cross-sectional study.

Results: A total of 166 (17%) patients met the study inclusion criteria, comprising 110 (57.2%) females and 56 (33.7%) males. The mean age was 86.2±7.6 (66-105) years. The incidence of high-energy trauma was significantly higher in individuals aged ≥80 years (t=6.71; p=0.0054). Female gender was associated with an increased risk of high-energy trauma (x^2=9.51; p=0.003). The frequency of angiotensin-converting enzyme inhibitors and polypharmacy was significantly higher in high energy trauma group (p<0.001).

Conclusion: Women aged ≥80 years are at an increased risk of falls. Moreover, polypharmacy is associated with falls that lead to high-energy trauma. Healthcare providers should pay particular attention to this patient group to prevent high-energy falls that may lead to temporary or permanent injuries.

Keywords: Elderly, women, falls, injury, trauma

Introduction

The life expectancy of the world's population has markedly increased over recent decades. Therefore, the proportion of elderly people in populations has increased. In 2000, there were 605 million people aged ≥60 years worldwide; however, this number is estimated to reach 2 billion in 2050 (1). In accordance with the World Health Organization definition of "elderly," which includes individuals with a chronological age of ≥60 years, the majority of developed countries and geriatric sciences have adopted the threshold of 60 years of age (2). Among many other age-related diseases, falls represent a major clinical problem in this population of individuals, with millions of older adults suffering falls every year.

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The incidence of falls among elderly population living in the community is approximately 30-40%; however, this number may reach up to 60% for those living in nursing homes, i.e., almost twice the incidence of falls among the elderly living in the community (3, 4). Falls may lead to temporary and permanent deficits requiring frequent hospitalizations, thereby increasing the burden on healthcare systems. Fractures, such as hip fractures, are the most common and most expensive non-fatal injuries associated with falls. Moreover, fractures account for 61% of all non-fatal costs, despite comprising only a third of non-fatal injuries (5). In addition to temporary injuries, falls may cause permanent disability and even death. The injuries to internal organs are responsible for almost 28% of fall deaths and account for 29% of costs (6). Accordingly, the prevention of falls in clinically important is this high-risk group of individuals.

Risk factors should be identified and eliminated to prevent falls. Certain factors, such as gait disorders, depression, female gender, arthritis, the use of assistive devices and a history of stroke, incontinence, orthostatic hypotension, visual disorders, muscle weakness, as well as the use of medications for concurrent diseases, in addition to polypharmacy (i.e., the concurrent use of ≥4 drugs) have been shown to predispose elderly individuals to falls (7-9). Pharmacological agents that may increase the risk of falls include neuroleptics, benzo diazepines, tricyclic antidepressants, serotonin uptake inhibitors, antiepileptics, Class 1A anti-arrythmics, diuretics and digoxin (10, 11).

The present study aims to evaluate the clinical characteristics associated with falls and to define a patient subgroup that is at increased risk.

Materials and Methods

Consecutive patients aged≥65 years, who presented with falls at Emergency Department of American Hospital, Istanbul, Turkey, from 01/02/2014 to 01/02/2015, were included in this retrospective study. Ethical Committee permission was obtained from the local ethics committee (Protocol date and number: 12.01. 2015/2015.011.IRB2.005). A fall was defined as an event resulting in an individual suddenly and inadvertently coming to rest on the ground or a lower position. Medical records of included patients were retrieved from the archives and analysed. All falls, regardless of setting, were included in the present study. Analysed data included the demographic and health characteristics of patients, such as age, gender, concomitant diseases and medications. The residential status of patients, such living alone in their own home, with others or in a residential home, was recorded from the files.

High energy trauma (HET) was defined as trauma caused by a fall, which resulted in brain injuries, cervical fracture, thoracic trauma, abdominal trauma, lower extremity fractures or dislocations, facial fractures, aortic rupture, diaphragmatic rupture, spleen and liver rupture or pelvic and acetabular fractures (12). Low energy trauma (LET) was defined as a trauma, which resulted in minor injuries other than HET. Recurrent falls were defined as >2 falls within the last 6 months. The index event was defined as the fall leading to hospital admission. Patients were assigned to two groups as HET (Group 1) or LET (Group 2). The exclusion criteria of the present study were as follows: falls related to being pulled or pushed; any medical condition that may predispose to falls, such as myocardial infarction or ischemia, cognitive impairment; stroke or neurological

impairment, the being bedridden and visual impairment; alcohol intoxication or gastro intestinal bleeding.

The impact of variables on falls was analysed using Pearson Chi-square and Student's t-test. Further analyses were performed using Pearson Chi-square, the one-way analysis of variance (ANOVA), post-hoc analysis and Tukey's honest significant difference method. The impact of gender on the evaluation of falls was assessed using Pearson Chi-square and Student's t-test. The effect of retirement duration was evaluated using Pearson Chi-square, ANOVA and post-hoc analysis.

Results

A total of 976 patients with falls were admitted to the emergency department of the hospital during the study period. There were 166 (17%) patients aged >65 years who met the inclusion criteria. Of the 166 patients, 110 (66.3%) were female and 56 (33.7%) were male. The mean age of included patients was 86.2±7.6 (66–105) years. There were 98 (59%) patients with hyper tension, 10 (6%) with ischemic heart disease, 10 (6%) with valvular heart diseases, 8 (4.8%) with arrhythmia, 7 (4.2%) with chronic obstructive pulmonary disease, 6 (3.6%) with non-limiting dementia, 5 (3%) patients with cerebrovascular disease, 4 (2.4%) with lung cancer, 1 (0.6%) with metastatic lung cancer and 1 (0.6%) with epilepsy. The demographics of the patients are shown in Table 1.

All patients lived in their own homes, and no patients lived in a nursing home. Ten (6%) patients lived alone and 156 (94%) patients lived with others. There were 42(25.3%) patients who used assistive devices to stand and walk. Group 1 included 67 (40.3%) patients, whereas Group 2 included 99 (59.7%) patients. Elderly individuals aged >80 years were more likely to suffer from HET related to falls. There were 87 (52.4%) patients aged <80 years and 79 (47.6%) aged ≥80 years (x^2=9.48; p=0.00001). The incidence of HET was significantly higher in individuals aged ≥80 years (t=6.71; p=0.0054).

Table-1. Demographic characteristics

Variables		n	%
Gender	Male	56	33.7
	Female	110	66.3
Age	All	80.2±7.51	
	Male	79.5±7.68	
	Female	80.5±7.44	
Disease	Hypertension	98	59
	Ischemic Heart Disease	10	6
	Valvular Disease Of The Heart	10	6
	Arrythmia	8	4.8
	COPD	7	4.2
	Non-limiting Dementia	6	3.6
	CVD	5	3
	Lung Cancer	4	2.4
	Metastatic Lung Cancer	1	0.6
	Epilepsy	1	0.6
Lifestyle	Living Alone	10	6
	Living with Others	156	94
	Using Assisting Device	42	25.3

A strong significant association (p=0.003) was observed between gender and trauma energy. There were 24(14.4%) male and 43(26%) female patients who suffered from HET, and there were 32 (19.3%) male and 67 (40.3%) female patients who suffered from LET. HET risk was increased in the female gender (x^2=9.51; p=0.003).

The use of neuroleptic drugs was significantly higher in Group 2, whilst the use of angiotensin converting enzyme inhibitors (ACEI) and poly pharmacy was significantly higher in Group 1. The rates of drug use are shown in Table 2.

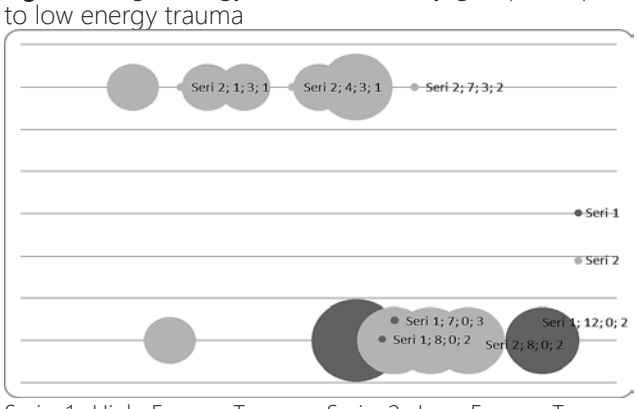
Table-2. Patients medications

Variables	Group 1		Group 2		Chi-square	P value
	%	n	%	n		
Antidepressants	14.6	34	10.1	14	9.61	0.052
Neuroleptics	11.1	35	11.5	36	8.01	0.049*
Other cardiac medicines	20.3	41	21.5	42	9.01	0.062
Polipharmacy	28.1	25	12.5	15	9.78	0.0001*
ACEI**	9.2	32	7.1	28	4.61	0.001*
ARB***	8.1	53	7.9	51	12.6	0.064
β blockers	5.6	21	4.2	15	7.61	0.08

* Statistically Significant Results
** ACEI: Angiotensin Converting Enzyme Inhibitors
*** ARB: Angiotensin Receptor Blockers

There were 76(58%) patients who had recurrent falls. The remaining 99 (42%) patients had no history of falls. The incidence of falls was significantly higher in patients with a history of falls (x^2=3.91, p=0.021). Multilogistic regression analysis identified gender as the only significant risk factor for falls. The risk of falls was five times higher in females than in males (odds ratio, 5.18; 95% confidence interval, 1.1–15; Figure 1). In addition, patients with HET were three times more likely to suffer subsequent falls than those with LET (95% confidence interval, 0.96–4.7).

Figure 1. High energy trauma in elderly group compare to low energy trauma



Serie 1: High Energy Trauma, Serie 2: Low Energy Trauma Hazard Ratios (HR) were estimated using a subdistribution proportional hazards regression model for competing risk analyses. The reference group was the group using more than 4 drugs and they are high density fall ones. Dots represent point estimates for HRs, the width of the horizontal lines represents the 95% CI, upper limits of 95% CIs exceed 3.

Discussion

The resent cross-sectional study found that the prevalence of falls in elderly people aged ≥65 years was 34.8% per year. American Hospital is a private hospital in the city centre of Istanbul with 340 beds. Majority of the patients have middle to high level income, but emergency department welcomes all patients regardless of their economic status, as in Turkey all emergency services are free according to the law. Therefore; we think that this rate reflects the general patient population. This rate is in accordance with the prevalence rates reported by previous studies (13, 14). The incidence of falls is known to be higher among individuals living in nursing homes. We are unable to assess the effect of living in a nursing home as subjects included in the present study lived independently at their own home or with relatives.

The results of the present study demonstrated that the risk of falls was highest in people aged ≥80 years. Moreover, the results demonstrated an association between female gender and falls. The incidence of falls was significantly higher in females than in males. This finding corroborates previous reports(15-19), Stevens et al.(5) showed that women are more likely than men to

be treated for fall injuries in hospitals and emergency departments. Aoyama et al. (17) noticed that women had a higher risk of falling than men. They showed that Motor Fitness Scale may be a significant predictor of falls in older women, Campbell and Robbins submit that there are various intrinsic factors that make women more prone to falls than men. These factors are osteoporosis, self confidence on falling, lower muscle strengh and worse physical performances.

An isolated fall is not always regarded as a sign of major disease or as an increased risk of subsequent falls. However, recurrent falls, defined as >2 falls in the preceding 6 months, is a well-known risk factor. We also observed an increased risk of falls in elderly individuals who had previously fallen more than once. Moreover, this risk was apparently higher in patients with falls resulting in HET (20-25). In our study population, the risk of a subsequent fall was significantly higher in the 67 elderly individuals who had suffered HET related to falls within the last 6 months prior to admission. Hence, we believe that the caregivers at nursing homes should be aware of the increased risk of falls in this population of individuals.

Similarly to many countries, life expectancy in Turkey has also noticeably increased. The expected life span is currently 73.7 years for men, 79.4 years for women and 76.3 years overall (26). An increased life span has led to a higher percentage of elderly individuals in the community and greater numbers of individuals receiving various kinds of medication due to the increased survival among patients with chronic diseases. Thus, the number and duration of pharmacotherapy and concomitant diseases in elderly individuals have concurrently increased. It is estimated that being maintained on one or more medications is a risk factor for falls in the elderly population. Polypharmacy, defined as the use of ≥4 drugs, is accepted as a risk factor for falls (27-28). The present study also found an association between pharmacotherapy and the frequency of falls, with the risk of recurrent falls found to be higher in poly pharmacy. This result confirms that polypharmacy is associated with the risk of falls in this frail population. Nevertheless, drug classes that are associated with falls in the elderly patients remain contro versial. The results of the study indicated an association between the use of antihypertensive drugs and falls.

Antihypertensive drugs may cause unexpected hypotension, thereby precipitating falls (29,30). Of all types of antihypertensive medications, ACEI were the strongest association with falls in the elderly group. However, the mechanisms underlying the association between falls the use of ACEI specifically has yet to be fully elucidated.

Logistic regression analysis identified female gender as the sole risk factor for falls in the elderly population of the present study (odds ratio, 5.18; 95% confidence interval, 1.1–15). This finding demonstrates female gender as an independent risk factor in this population, corroborating the results of previous studies. Nevertheless, not all findings of the present study were consistent with those reported by recent studies. We believe these discrepancies may be the consequence of the small number of patients included in the present study. A drawback of this study was that patients admitted to hospital due to falls were included, and as this was not a population-based study, we may have missed falls that did not lead to injuries necessitating hospital admission.

Conclusion

The risk of falls is particularly high in women aged >80 years and polypharmacy seems to be related to high energy falls. Healthcare providers should be aware of this fact to prevent high-energy falls leading to temporary or permanent injury in this population.

Ethical Statement

The Ethical Committee and Institutional Review Board of Koc University approved the study design with the number: 2015.011.IRB2.005

Conflicts of Interest

The authors declared no conflict of interest.

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List of abbreviations

HET, High-energy trauma
LET, Low-energy trauma
ACEI, Angiotensin converting enzyme inhibitors
ARB, Angiotensin receptor blockers

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Estimation of Residual Tissue with Thyroid Scintigraphy and Thyroglobulin Level in the Pre-ablative Period of Differentiated Thyroid Carcinoma

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Introduction: The aim of the study was to compare the pre-ablative thyroid scintigraphy and serum thyroglobulin (TG) positivity with a therapeutic I-131 scan for the detection of residual tissue.

Materials and Methods: Patients included in the study were those with neck residual tissue only and no residual or metastatic tissue in the ablative radioactive iodine (RAI) scan anywhere in the body. Pre-ablative thyroid scintigraphy for the residual tissue in the neck was obtained from all patients. Ablative TSH, TG and anti-TG levels were measured on the same day or one day before the RAI therapy. The evaluation of neck residual tissue detected with thyroid scintigraphy and TG measurement were made in this study accepting I-131 scan as the gold standard.

Results: The I-131 scan was positive for residual neck tissue in 67 (93.1%) patients and negative in 5 (6.9%) patients. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive values of thyroid scintigraphy were 70.1%, 80%, 70.8%, 97.9%, and 16.7%, respectively. For the high positive predictive value, the kappa value was 0.182, which showed a slight agreement between Tc-99m thyroid scintigraphy and I-131 scan. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive values of TG measurement were 92.5%, 60%, 90.3%, 96.9%, and 37.5%. There was moderate agreement between the TG measurement and I-131 scan.

Conclusion: Negative thyroid scintigraphy should not be noteworthy because of the very low negative predictive value and kappa value. A measurable TG level seems to be more accurate and useful for the detection of residual tissue.

Keywords: Thyroid cancer, scintigraphy, thyroglobulin

Introduction

Differentiated thyroid cancer, papillary and follicular cancer, are usually curable especially if diagnosed early. The treatment algorithm has changed because there are no prospective randomized trials of treatment because of its prolonged course (1). The aim of treatment is to eradicate the primary tumor, prevent local or distant recurrence, treat the metastases and cure the patients with minimal morbidity (2). In low-risk patients after total thyroidectomy and no evidence of abnormal residual tissue or metastatic lymph nodes, patients are not generally given radioactive iodine (RAI) therapy,

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but are followed up with neck USG and the measurement of the thyroglobulin (TG) level because of the excellent response (3). I-131 whole body scintigraphy with the combination of serum TG level and neck USG is commonly applied follow-up procedure for differentiated thyroid cancer (4).

In the patients requiring ablative RAI therapy, it is important to define the residual thyroid tissue. After total or near total thyroidectomy, I-131 uptake may persist in the thyroid bed due to residual thyroid tissue. If the residual tissue is macroscopic, the outcome becomes unfavorable (1). Pre-ablative low dose I-131 whole body scan has been used for many years. Despite the beneficial effect of detecting both thyroid remnant and metastasis, there is a rising trend to avoid this, because of the stunning effect of I-131 (5). Avoiding a pre-ablative scan has been shown to result in better radio-ablation, and reduce cost and time (2).

The aim of this study was to compare pre-ablative thyroid scintigraphy, with serum thyro globulin positivity with therapeutic I-131 scan for the detection of residual tissue after total thyroidectomy in differentiated thyroid cancer.

Materials and Methods

Patients

The study included 72 patients, comprising 63 females (87.5%) and 9 males (12.5%) with a mean age of 41.56±12 years (min: 19, max:71). Only patients with neck residual tissue and no residual or metastatic tissue anywhere in the body were included in the study. Patients with detectable anti-TG levels (>20 IU/ml) were excluded from the study because of the effect on TG levels. All the patients underwent total thyroidectomy and received ablative I-131 treatment for differentiated thyroid cancer. The therapeutic I-131 scan was applied 5-7 days after therapy. Pre-ablative thyroid scintigraphy for the residual tissue in the neck was applied to all patients. Ablative TSH, TG and anti-TG levels were measured on the same day or one day before the RAI therapy. The evaluation of neck residual tissue detected with thyroid scintigraphy and TG were made in this study accepting the I-131 scan as the gold standard. A TG level below the measurable level (0.2 ng/mL) was accepted as zero. All the Tc-99m pertechnetate thyroid scintigraphy scans were made at least 20 days after the operation. Ablative I-131 therapy was given approximately two weeks after thyroid scintigraphy. This retrospective study was approved by the Ethics Committee of Mustafa Kemal University.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows version 21 software (SPSS, Chicago, IL, USA). Descriptive statistics were stated as mean±standard deviation for continuous variables. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of Tc-99m pertechnetate scinti-graphy and TG positivity to detect residual tissue were measured. Tc-99m pertechnetate scintigraphy and serum TG positivity were compared with I-131 scan for the detection of residual tissue with kappa analysis. Interpretation of the kappa test was poor agreement if the value was ≤0.2, fair agreement if 0.21-0.4, moderate agreement if 0.41-0.6, good agreement if 0.61-0.8, and excellent agreement if 0.81-1.

Results

Multifocal tumors were determined in 17 patients. A dose of 50 mCi was given to 5 patients, 75 mCi to 10 patients and 100 mCi

to 57 patients with a mean dose of 93.06±1 4.67 mCi. The mean tumor diameter was 1.55± 0.69 cm (min: 0.7-max: 4.0). The mean TSH value was 108.13±72.32µIU/mL (min:30.54-max: 460.06). Stimulated TG level was 6.68±9.59 ng/mL (min: 0 - max: 52.9) (Table 1).

Table 1. Clinical features of differentiated thyroid carcinoma

Variables	Mean (Min-Max)
RAI dose (mCi)	93.06±14.67 (50-100)
Tumor diameter (cm)	1.55±0.69 (0.7-4)
TSH value (µIU/mL)	108.13±72.3 (30.54-460.06)
Thyroglobulin level (ng/mL)	6.68±9.59 (0-52.9)

The I-131 scan was positive for residual neck tissue in 67 (93.1%) patients and negative in 5 (6.9%) patients. Thyroid scintigraphy was positive in 48 (66.7%) patients and negative in 24 (33.3%) patients. In 1 patient determined as positive on thyroid scintigraphy, there was no residual tissue on the I-131 scan and this case was evaluated as false (+) thyroid scintigraphy. The sensitivity, specificity, accuracy, PPV and NPV of thyroid scintigraphy were 70.1%, 80%, 70.8%, 97.9% and 16.7%, respectively. The high PPV had a kappa value of 0.182 (p=0.022) indicating slight agreement between Tc-99m scintigraphy and I-131 scan.

Table 2. Diagnostic values of thyroid scintigraphy and thyroglobulin level in detection of residual thyroid tissue

Variables	Thyroid Scintigraphy	Thyro-globulin
Sensitivity	70.1%	92.5%
Specificity	80%	60%
Accuracy	70.8%	90.3%
Positive predictive value	97.9%	96.9%
Negative predictive value	16.7%	37.5%

A measurable serum TG (≥0.2) was present in 64 (88.9%) patients and negative in 8 (11.1%) patients. The sensitivity, specificity, accuracy, PPV and NPV of TG measurement were 92.5%, 60%, 90.3%, 96.9% and 37.5%, respectively (Table 2). There was moderate agreement between the TG measurement and I-131 scan (kappa=0.411, p<0.001).

Discussion

Total thyroidectomy, which is the complete macroscopic removal of all grossly apparent thyroid tissue, is applied to the cases of differentiated thyroid carcinoma. However, the postoperative RAI imaging may show incomplete removal of functioning thyroid tissue after total thyroidectomy (6). Following partial thyroidectomy, the risk of malignancy in the residual tissue is high. Tumor multifocality and significant TG elevation are predictive of malignancy in residual tissue (7). Residual thyroid tissue can change significantly based on surgical parameters. Academic centers have reported lower residual thyroid bed uptake on I-131 scans compared to community centers (8). Most patients have some thyroid remnant even after an accurate surgical technique. Salvatori et al. confirmed that 93.1% of patients had thyroid remnant after total thyroidectomy for differentiated thyroid carcinoma with the majority of the remnant tissue observed to be contralateral to the tumor site and outside the thyroid bed. A previous study reported that total thyroidectomy was achieved in 6.9% of patients with negative therapeutic I-131 whole body scan, radioactive iodine uptake <1% and undetectable levothyroxine of TG level (9).

Thyroid USG can visualize the thyroid gland and measure the gland accurately, but in the postoperative period before ablative treatment, granulation tissue and edema cannot be discriminated correctly (10). RAI therapy is used after thyroidectomy to ablate residual tissues, prevent recurrences and increase survival (11). Iodides taken orally are almost completely

absorbed from the duodenum and excreted through kidneys. In addition to accumulation in thyroid follicular cells, extra-thyroid organs such as salivary glands, the stomach, lactating mammary glands and thymus also accumulate RAI (11-13). Beside the therapeutic effect of RAI, it can also be used for whole body scans in the follow up of thyroid cancer. A whole-body RAI scan is very important in the detection of metastases of well differentiated thyroid cancer during follow up. However, careful evaluation is necessary because of misinterpretation of RAI accumulation lesions. Benign thyroid tissue salivary gland inflammation, or thymic uptake may cause a false positive RAI scan (11, 13, 14).

I-131 is also used for the detection of residual thyroid tissue after surgery. RAI planar imaging with I-123 or I-131 is the gold standard imaging method in the follow up after initial surgery (12). Diagnostic I-131 scanning may cause damage to thyroid tissue, thereby impairing the uptake of the therapeutic dose of I-131 which is known as stunning (15). Therefore, because of stunning I-123 may be used before RAI therapy for the detection of residual tissue. Teoh et al applied pre-ablative whole body RAI scanning, which was positive in 94.9% of patients (2). Routine pre-ablative RAI scan is offered after near total thyroidectomy and if there is remaining thyroid tissue, it should be destroyed with RAI (16).

Tc-99m pertechnetate scintigraphy is a low-cost and widely available method for the patients that require postoperative scanning for residual tissue (17). Nadig et al found that Tc-99m pertechnetate SPECT can estimate residual thyroid tissue while performing patient specific dosimetry with the advantage of simple technique (18). Pre-ablative Tc-99m pertechnetate scintigraphy not only provides information about the residual tissue, but can also predict the ablation success, hospitalization time and thyroiditis due to treatment. Pre-ablative Tc-99m pertechnetate scintigraphy is used to predict the outcome of the ablative treatment. A Tc-99m pertechnetate uptake value >1.4% has been reported to predict unsuccessful ablation, longer hospitalization and a higher risk of radioiodine-induced thyroiditis (19). In contrast, Thientunyakit et al stated that Tc-99m pertechnetate scintigraphy and 24 hour I-131 uptake in the thyroid remnant cannot predict the outcome of RAI therapy, although the ablative serum TG level may be a reasonable predictor for success of ablation. In that study, the I-131 whole body scan was negative in 92.9% of patients with negative Tc-99m pertechnetate scintigraphy (20).

The synthesis and release of TG from normal thyroid tissue is controlled by TSH, and thyroid tissue size and serum TSH levels are correlated to serum TG levels. The serum TG level after total thyroidectomy should be undetectable or within the normal range in patients without residual or metastatic thyroid tissue (21). Charles et al reported that serum TG levels are more sensitive than RAI scan during follow up and TG analyses may replace or become an important adjunct to RAI scan (22).

Residual thyroid tissue volume should be determined correctly when assessing for the completion thyroidectomy. Erbil et al., recommended that USG, radioactive iodine uptake and serum TSH level should be assessed to estimate the postoperative thyroid remnant volume for completion thyroidectomy in the patients with incidental thyroid carcinoma detected after the surgery (23). Zhao et al recommended serial stimulated serum TG measurement in a short period, such as 8 days. Serial measurements may be more informative

after thyroidectomy before ablative treatment than a single stimulated TG measurement (24).

In cases with negative serum TG and anti-TG levels with positive I-131 scan, this may be related to limitations in the immunoassays. Both stimulated serum TG and anti-TG levels with I-131 scan are recommended in the follow up of patients with high-risk thyroid cancer (25). In the current study, patients with measurable anti-TG levels were excluded because the anti-TG level may have interfered with the TG levels and TG levels may not have been measurable despite the high level of TG.

Filesi et al. recommended whole body I-131 scan and TG measurements for all patients after total thyroidectomy of differentiated thyroid carcinoma. In the presence of residual tissue, analysis of both scan and TG levels can provide reliable and early detection of metastases (26). Khammash et al compared Tc-99m and I-131 scans for the detection of residual and metastatic thyroid tissue in the follow up of patients, and Tc-99m pertechnetate was reported to have sensitivity, specificity and accuracy of 87%, 97% and 92.5%, respectively. Negative Tc-99m images cannot exclude residual or metastatic functioning thyroid tissue because of the false negative rate of 15.6% (27). In the current study, the sensitivity, specificity and accuracy values were not as high as in the study by Khammash et al, but the results were similar to those of the Ozdemir et al study, in which the residual tissue was evaluated with Tc-99m pertechnetate scintigraphy and therapeutic I-131 whole body scan. The post-operative Tc-99m pertechnetate scan was positive in 69.6% and negative in 30.4% of patients whereas therapeutic I-131 scan was positive in 93.9% and negative in 6.1% of patients. The sensitivity, specificity, accuracy, PPV and NPV of Tc-99m pertechnetate scan were 72.2%, 70.5%, 72%, 97.4% and 14.2%, respectively when the I-131 scan was accepted as the standard test (10). In the current study, despite the relatively high sensitivity, specificity, and accuracy and the excellent PPV, the NPV was very low, so the kappa value was 0.182 (p=0.022), indicating slight agreement between Tc-99m thyroid scintigraphy and I-131 scan. In the current study, measurable TG levels were more concordant with the I-131 scan with better sensitivity, accuracy and NPV than thyroid scintigraphy. The kappa was 0.411, showing moderate agreement between measurable TG levels and the I-131 scan. Kueh et al compared Tc-99m pertechnetate and I-131 scan for the detection of remnant tissue after thyroidectomy. Tc-99m pertechnetate was seen to have moderately high sensitivity (90%) and a very high PPV (100%). A positive scan is reliable for the presence of residual tissue, but in case of a negative scan additional scanning might be needed (17). In a study by Chantadisai et al, they compared Tc-99m pertechnetate whole body scan, neck and chest SPECT/CT with post ablative I-131 whole body scan and SPECT/CT for the presence of remnant or metastatic tissue. The percentage of concordance between the two scans was 96.4% per patient analysis with a good correlation of the unweighted kappa value of 0.7358. Better diagnostic parameters were determined with SPECT/CT. In the current study, only static images were acquired (5).

Conclusion

In conclusion, the sensitivity, specificity and accuracy of thyroid scintigraphy is relatively high and positive predictive value is excellent. However, because of the very low negative predictive value and kappa value, negative

thyroid scintigraphy should not be given too much attention. A measurable TG level seems to be more accurate and useful for detection of residual tissue.

Ethical Statement

As a nature of being a retrospective study, there is no need for consent of patient for the present study.

Conflicts of Interest

The authors declared no conflict of interest.

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CASE REPORT OPEN ACCESS

Melanonychia Striata: A Case Report

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Subungual melanoma has higher mortality than other skin melanomas caused by a late initial diagnosis of this disease, leading to a poor prognosis. Two-thirds of subungual melanoma symptoms begin with melanonychia striata, appearing as brown or black-pigmented lines of the nail plate. In this case report, we presented a case of melanonychia striata in a 30-year-old male. Longitudinal excision or partial avulsion was performed, followed by histopathology examination to exclude malignancy and determine further management for this case.

Keywords: Melanonychia striata, subungual melanoma

Introduction

The case of melanonychia striata (longitudinal melanonychia) is a condition in which the nail plate forms one or several brown or black-pigmented lines. This condition is caused by increased melanin production in the nail matrix, which is then stored in the nail plate. Proliferation and hyperplasia of melanocyte in the nail matrix can cause increased melanin production, besides bleeding or trauma (1). In Caucasian, the prevalence of melanonychia striata is 1.4%, most frequently occurred in the thumb, toes, and index fingers. While in Asian, the prevalence was found to be higher, reported as much as 20%-23% and 11.4% in the year 1933 and 1958, respectively (2).

Histopathology examination is needed since it is crucial to rule out the possibility of malignancy or melanoma in the case of melanonychia striata. In this case report, we presented a case of melanonychia striata in a 30-year-old male.

Case Presentation

A 30-year-old man was referred to the Surgical Oncology Clinic of Prima Medika Hospital with initial suspicion of subungual melanoma. The patient had discoloration of the first toenail of the left foot since six months ago (Figure 1). His nail was turning brownish-black, being darker over time, but painless. The patient was in good health and not taking any medication.

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There was no history of trauma and no similar complaints in his family. The patient also said that there was no family history of melanonychia striata, melanoma (or other diseases of the nail), other skin diseases such as psoriasis, atopic dermatitis, and others.

Figure 1. *Melanonychia striata* on the first left toenail

Figure 2. After partial avulsion procedure of the nail

We found a longitudinal brownish-black discoloration on first left toenail, 1 mm width, on physical examination of this patient. The nail was neither fragile nor split. His other nails were normal. There was no skin discoloration around the nail. Diagnosis of melanonychia striata (longitudinal melanonychia) was made based on the patient's age, physical examination, and histopathology results. The specimen was obtained from longitudinal excision (partial nail avulsion) of the nail plate and matrix, stained with hematoxylin-eosin. Histopathology results showed that there was no proliferation of melanocytes or malignant melanoma. In this case, longitudinal excision (partial nail avulsion) of the nail with melanonychia striata was done for diagnostic procedures and therapeutic management (Figure 2).

Discussion

Melanonychia striata is a condition where the nail plate forms one or several brown or black-pigmented lines (1). Increased nail pigmentation is caused by the activation of nail matrix melanocytes, which causes an increase in pigment production. Mechanism of activation of nail melanocytes is not fully understood but is believed to be caused by excessive expression of the α-melanocyte-stimulating hormone, adrenocorticotropic hormone, and ultraviolet. Melanonychia usually shows benign lesions on the nail matrix related to melanocytic nevus, lentigo, or increased benign melanocyte activity. However, a melanonychia can also represent pathological conditions such as bacterial or fungal infection, melanoma, and other malignancies (3).

About two-thirds of subungual melanoma cases appear with melanonychia striata as an early symptom. Some approaches can be taken to exclude malignancy i.e., "wait and see" and

longitudinal excision (which is chosen) (4,5). In malignant case, other nail surgery such as amputation or wide excision usually is performed, with the aim of removing local tumors on the nail, treating nail infections, reducing pain due to trauma, making the diagnosis by biopsy, or aesthetic purpose (6).

Nail plate surgery (nail avulsion) can be done either totally or partially. In this case, we performed partial nail avulsion for our patients. Compared with total nail avulsion, partial nail avulsion is preferred to reduce complications (bleeding, infection, pain in changing wound dressing, or during activities). Then, the main concern is to rule out the possibility of malignancy. In this patient, the histopathologic examination of longitudinal excision did not show any melanocyte proliferation (Figure 3).

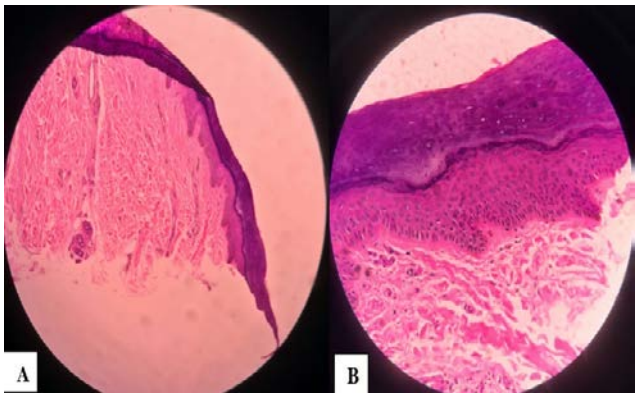

Figure 3. Microscopic examination of the histopathology of melanonychia striata
A: Mild increase in melanin pigment production in the basal layer (hematoxylin-eosin stain, 100x magnification).
B: No increase of melanocyte count (hematoxylin-eosin stain, 400x magnification)

Discoloration of the nail might have resulted from physiologically increased a melanocyte function rather than pathologically hyperplasia due to melanocytic nevus, or even malignant melanoma. In our case, no malignancy sign was found. There were no hyperpigmentation more than 6 mm and nail dystrophy (5). However, in some cases, a change from benign to the malignant lesion can still occur. Therefore, it is important to perform monitoring examinations annually (6).

Conclusion

Melanonychia striata is a change of nail pigment, recognized mostly as an early sign of a subungual melanoma. Histopathological examination after excision must be done to exclude the possibility of malignancy.

Ethical Statement

The Ethical Committee and Institutional Review Board where the present study was conducted, approved the study design. The patient has been consented that this case report will be submitted for publication.

Conflicts of Interest

The authors declared no conflict of interest

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SHORT COMMUNICATION OPEN ACCESS

COVID-19: Maternal and Child Health Care

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In the sunset of 2019, the world encountered the beginning of a pandemic due to corona viral infection disease (COVID-19). The rapid spread via respiratory route transmission, absence of vaccine and specific anti virals is the main reason for making the situation worse. Like every aspect COVID-19 was found to be of great concerns in maternal and child health care. The objective of this short communication was to found the effects of COVID-19 in maternal and child health care. It was identified that the clinical manifestations of COVID in pregnant and non-pregnant patients have same manifestations. The mode of delivery even has no significant association with specific infection. The evidence to support inutero peripartum or postpartum transmission is also deficient. Only positive finding observed was the presence of fetal distress. So it was clinched that after birth neonates must be kept in isolation for careful evaluation of any sign of infection and hence it's management. It was concluded that serial follow up investigations like cardiactocography, Doppler's and amniocentesis should be done to assess fetal wellbeing in the intrauterine period. However, in post partum period both mother and baby should remain in isolation for careful monitoring of any signs of infection and hence timely management.

Keywords: COVID-19, pregnancy, maternal outcome, neonatal outcome, diagnostic modalities

Introduction

Severe Acute Respiratory Syndrome - Corona Viral Infection (SARS-CoV-II)

Virus outbreaks have been occurring in the world for many decades. In December 2019, Severe Acute Respiratory Syndrome Corona viral infection (SARS-CoV-II) epidemic started from Wuhan China. Afterwards it encompassed two dozen countries with death toll to around millions across Globe. In 2020 the disease caused by this new SARS-CoV-II, had taken a shape of a pandemic, which is rapidly spreading and taking many lives daily. Few years back the member of same corona vial group i.e Middle east respiratory syndrome Corona viral infection (MERS-CoV) began in Saudi Arabia and took thousands of lives. Until that time till to date, the scientist are working to discover the vaccines and anti virals for CoV, but satisfactory results are deficient (1).

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Routes of Transmission

In the absence of vaccines and anti virals, the respiratory mode of spread is adding up to the worsening of situation. The first case of the CoVID-19 disease was through direct exposure to the Huanan seafood wholesale market of Wuhan, the animal-to-human transmission was thought to be the cause. The new virus seemed to be highly contagious, harboring a property for transmission amongst humans. The people who have symptoms are the most frequent source of COVID-19 spread (2). However, in subclinical or asymptomatic period of 3-4 days (5.2 days approx.) is even more dangerous. Unknowingly person can be a source for infection transmission. But still a debate is there for infection transmission in asymptomatic phase (3, 4). The Global statistical in current pandemic scenario, concluded that each positive patient can transmit the infection to an additional 2.2 individuals. This is how the regional epidemic doubles every seven days. Cumulative score of various regions around the Globe thus, doubles every week (2).

Predisposition & Clinical Presentations

The published data strongly supports that immunosuppressed, elderly, or patients with comorbidities are at high risk for acquiring infection. The most common symptoms in incubation period includes fever which is non responsive to antipyretics, and a state of malaise. Later on there is development of dry cough in the acute phase. After 5-7 days, high risk patients, begin to experience shortness of breath and increased respiratory rate. However, in more fragile elderly patients, dyspnea may already appear at the onset of symptoms (5). The frequency estimation of clinical presentations revealed that the highest percentage was seen for fever in 87.9%. This with passage of time was followed by dry cough (67.7%), fatigue(38.1%), and sputum production (33.4%). With deterioration of infection, next in sequence were shortness of breath (18.6%), myalgia/arthralgia (14.8%), headache (13.6%) sore throat (13.9%), and chills (11.4%). Less common symptoms were congestion (0.8%), nasal congestion (4.8%), nausea/vomiting (5%), diarrhea (3.7%), and hemoptysis (0.9%)(6).

Preventive Measure

Published data suggests that the use of isolation is the best way to contain this epidemic and pandemic. Close contact with patients spreads the infection at a faster rate. While practicing good hygienic measures like frequent hand washing, maintaining cleanliness are the keys to combat the spread of this infection. Besides this, for hospital settings, wearing of personal protective equipments(PPEs), frequent use of hand sanitizers, use of surface good disinfectants, can help reducing the spread of infection (2, 5).

In the current scenario of COVID-19 pandemic, a rapidly spreading pattern was observed across the Globe. In the absence of vaccine and specific anti viral, we are left with only adoption of preventive measures to combat this infection. Besides ones preventive measures mentioned above, positive pregnant females must be dealt as high risk pregnancies (7, 8).

COVID-19 & Pregnancy

Recklessly of the COVID-19, the presence of pneumonia in pregnancy exhibit high morbidity and mortality rates. It is considered one of the serious non-obstetric infection (9). About 25% of such cases requires mechanical ventilation and intensive care treatment. In comparison with bacterial pneumonia, viral pneumonia is concomitant with higher morbidity and

mortality rates. From such infection, common complications can be premature rupture of the membranes (PROM), intrauterine growth restriction(IUGR), intrauterine fetal death (IUFD), preterm labor, and neonatal death (6).

Maternal Outcomes Following COVID-19

Upon comparison with SARS-CoV-II (COVID-19) and MERS-CoV, low mortality rate, and less severe maternal and fetal outcomes were seen in COVID-19, pregnant ladies. So far Global statistics revealed only 32 (n) positive cases of COVID-19 in pregnant ladies. Amongst those 32 cases, none was in first trimester of pregnancy. The mortality rate amongst all these were zero. In maximum cases (n=27), mode of delivery was caesarean section, while remaining five cases had normal vaginal delivery. The marked symptoms of fetal distress was the main reason for specific mode of pre term delivery (10). In a published report by Zhu *et al*, it was concluded that only three women became symptomatic in the post-partum period. All after intensive care management completely recovered (11).

One more study revealed the presence of identical symptoms via comparative analysis of COVID-19 in pregnant and non-pregnant females. In both groups the predisposing factors were same and were labelled as high risk groups. Presence of typical infiltrates in lungs suggestive of severe pneumonia were confirmed by computed tomography. While supportive lab studies showed decreased total leucocyte counts, lymphopenia, mild thrombo cytopenia and deranged liver function tests (6).

Transmission from Mother to Child

The good supportive evidence is deficient for to support the vertical transmission route of COVID-19. A published study in Lancet, describes the transmission routes for SARS-CoV-II. Various samples were collected i.e amniotic fluid, umbilical cord blood and throat swabs of the neonates instantly after delivery. Besides that milk samples were also taken in postpartum period. All the samples revealed negative results (10). Moreover, placentas of positive cases were also examined. The histo pathological evaluation was negative to support the presence of infection. Concluding the published statistics, there is no evidence of intrauterine transmission of SARS-COV-2 onto the fetus (12).

Neonatal Outcomes

Nevertheless, cautiousness is obligatory to save the lives of babies born to a mother having COVID. This is direly required because the evidence for transmission inutero or peri-partum phase is extremely deficient. The neonatologists recommended keeping those babies in isolation and to have their close monitoring, so that any sign of infection can be timely diagnosed. It was observed that the Apgar score after one and five minutes was found unremarkable in babies of positive mothers. The elevated cardiac enzymes were seen in one baby, on first post partum day which later proved to be non significant for clinical relevance (10).

Amongst neonatal outcome, so far only one neonate turned to be positive, there was only one case of still birth and one mortality. Multi-organ failure along with disseminated intravascular coagulopathy on ninth day of life became the reason for mortality. While few neonates developed respiratory distress syndrome. Which was followed by gastro intestinal symptoms, fever, tachycardia and vomiting (13).

Breastfeeding in Cases of Suspected Infection or Confirmed SARS-Cov-2 Infection

In literature review regarding transmission of infection via breast feeding is deficient either for suspected or confirmed cases. But, still to be on safer side European institute of breast feeding and lactation recommends that the milk should be pumped off and feeding should be provided by healthy assistant (14,15).

Maternal & Neonatal Samples for COVID-19 Diagnosis by RT-PCR

To ensure maternal and child health, preferred samples can be umbilical cord blood, amniotic fluid, neonatal gastric samples, neonatal throat swab and breast milk samples. However, so far, there is no evidence supporting the vertical transmission of COVID-19 (10).

Management of Infected Pregnant Patients & Monitoring of Fetal Well Being

The right of treatment and management of pregnants is equal to that of non-pregnant patient, provided clear contraindications there. Though the evidence for using remdesivir and hydroxychloroquine in pregnancy is yet deficient. But the benefit and potential risks should carefully be weighed and explained to the mother, for opting the management. This is the same decision as in case for opting any management in pregnancy. However, isolation and quarantine should be the first modality to go for, just like in any positive or suspected case. Mechanic ventilation and oxygen support should be arranged to manage for the signs of respiratory failure. Superimposed bacterial and other co infections should be managed along with specific COVID. Prior the start of empirical antibiotics, recommended protocols for blood cultures should be followed for accurate management. Moreover, all recommendations and guidelines for the adoption of specific mode of delivery are deficient (16,17).

In concerns for fetal monitoring, regular cardiotocography (CTG), Doppler and amniotic fluid analyses should be done to eliminate placental failure and hence the development of intrauterine growth retardation (IUGR) (17).

Conclusion

It was concluded that serial follow up investigations like cardiactocography, Doppler's and amniocentesis should be done to assess fetal wellbeing in intrauterine period. However, in post partum period both mother and baby should remain in isolation for careful monitoring of any signs of infection and hence timely management.

Recommendations

1. Serial sampling of mother and baby during the pregnancy and after birth are necessary for safe maternal & child health care.
2. The preferred samples can be umbilical cord blood, neonatal throat swab, amniotic fluid, neonatal gastric and breast milk samples.
3. For the monitoring of fetal well-being, amniotic fluid analyses, Doppler and regular cardiotocography (CTG) should be done to eliminate placental failure and hence the development of IUGR.
4. The presence of fetal distress should be monitored carefully and can become an indication of cesarean section.
5. Neonatal isolation protocols should be strictly followed along with monitoring for the signs of infection, and blood complete picture.
6. European institute of breast feeding and lactation recommends that for positive or suspected cases, breast milk should be pumped off and feeding should be provided by healthy assistant.

Conflicts of Interest

The authors declared no conflict of interest.

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LETTER TO THE EDITOR OPEN ACCESS

Daptomycin or Vancomycin Plus Ceftaroline for Methicillin-Resistant Staphylococcus Aureus Bloodstream Infections

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To the Editor

Recently, one randomized clinical trial (RCT) by Tong et al showed that addition of an anti-staphylococcal β-lactam to daptomycin or vancomycin alone was not associated with improve outcome of patients with MRSA bacteremia (1). Moreover, more acute kidney injury occurred in combination group than monotherapy group in this RCT (1). However, another recent retrospective study by Jorgensen et al which investigated the effect of addition of a β-lactam to daptomycin in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection and found that the combination of a β-lactam and daptomycin was associated with a better outcome than daptomycin monotherapy (2). In addition to different study design between these two studies (1, 2), the choice of β-lactam in each of them was significant different. In Jorgensen et al's study (2), 87.5% (63/72) of combination therapy used cephalosporin, but most of the patents treated with combining flucloxacillin or cloxacillin (1). Therefore, we wonder whether cephalosporin, especially the ceftaroline, which exhibits potent *in vitro* anti-MRSA activity can be the better choice of daptomycin-based combination therapy to improve the outcome of patients with MRSA bloodstream infections. To clarify this issue, we conducted this meta-analysis to compare the effect of adding ceftaroline to vancomycin or daptomycin and monotherapy in the treatment of MRSA bacteremia.

Four studies (3-6) which compared the effect of combining ceftaroline and vancomycin/daptomycin and standard therapy were identified from the literature search. Table 1 summarized the characteristics of these studies. One study

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Table 1. Characteristics of Included Studies

Author, year	Study Design	Study Site	Study Period	No of patients		Regimen	
				Combi-nation	Mono-therapy	Combination	Monotherapy
Cortes-Penfield et al, 2018[3]	Retrospective study	Single center, in US	2012-2015	4	5	Ceftaroline + Daptomycin	Daptomycin
Geriak et al, 2019[4]	Prospective randomized study	3 centers in US	2017-2015	17	23	Ceftaroline + Daptomycin	Vancomycin or Daptomycin
McCreary et al, 2019[5]	Retrospective, matched cohort study	4 centers in US	2013-2017	58	113	Ceftaroline + Daptomycin	Vancomycin or Daptomycin
Ahmad et al, 2019[6]	Retrospective study	Single center, in US	2015-2017	15	15	Ceftaroline + Daptomycin	Vancomycin or Daptomycin

was RCT (4) and other three were retrospective studies (3,5,6). Each two studies were single(3,6) and multicenter studies (4,5). Primary outcomes as 28-day mortality was recorded for analysis. Secondary outcome including 90-day mortality, microbiological relapse and the risk of acute kidney injury were extracted from the enrolled studies.

Overall, 94 and 156 patients received combination therapy with daptomycin plus ceftaroline and monotherapy - vancomycin or daptomycin, respectively. Although 28-day mortality rate of combination therapy group was numerically than monotherapy group (7.4% [7/94] vs 14.7% [23/156]), this difference did not reach statistical significance (risk difference, -0.07; 95% confidence interval [CI], -0.21 ~ 0.08). The similarity between combination therapy and monotherapy was also observed regarding the 90-day mortality (risk difference, 0.08; 95%CI, -0.77 ~ 0.94). In addition, combination therapy was similar to monotherapy (risk difference, -0.06; 95%CI, -0.22 ~ 0.1) in terms of micro biological relapse. Finally, the risk of acute kidney injury was similar between combination therapy and monotherapy (risk difference,-0.21; 95% CI,-0.62 ~ 0.2).

Based on the above findings, the clinical outcome of patients with MRSA bacteremia treated by the combination of ceftaroline and vancomycin or daptomycin was similar to those by monotherapy of vancomycin or daptomycin. However, the case and study number are limited in this analysis, further large-scale study is warrant to confirm these findings.

Conflicts of Interest

The author declared no conflict of interest.

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