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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Characterization of Patients with Guillain-Barré Syndrome in the General Hospital of Mexicali

Fátima María Martínez-González,[1] Jeremy Hernández-Ríos,[1] Arely Gutiérrez,[1] Andrés Beltrán,[2] René González,[3] Hiram Jaramillo-Ramírez.[4]

Abstract

Background: Guillain-Barré Syndrome is a progressive autoimmune polyradiculoneuropathy characterized by symmetrical flaccid paralysis accompanied by areflexia, hyporeflexia or hyperreflexia on rare occasions. Worldwide, it remains the first cause of flaccid paralysis. It is usually associated with infectious disease history; however, there are various clinical variants, each with a different outcome. Prognosis is usually good, although 20% of patients could suffer a severe clinical variant of Guillain-Barré Syndrome and 5% will die despite treatment. **Methods:** This is a cross-sectional study, including the records of hospitalized patients with Guillain- Barré Syndrome at Mexicali's General Hospital within a five-year period. **Results:** In a five-year span there were 64 patients with Guillain-Barré Syndrome, most of the patients were men (70.3%), with age ranging 1 to 76 years. A total of 8 (12.5%) patients died, from which 7 (87.5%) required mechanical ventilation during hospitalization. Immunoglobulin therapy was provided to 56 (87.5%) patients, and 6 (10.7%) of them perished due to acute kidney injury. **Conclusion:** Guillain-Barré Syndrome is a common disease among male population, with no dominating onset age, however, leaning for the young and elder. Most of the patients that were hospitalized at the General Hospital of Mexicali had a history of previous infection (gastrointestinal, respiratory, or other infectious diseases). The need for mechanical ventilation represents a higher severity index, nonetheless, this does not mean that assisted ventilation is directly associated with mortality. As for treatment, immunoglobulin is the most common choice for therapy, though some of the patients died from acute kidney injury.

Key Words: Guillain-Barré Syndrome; Polyradiculoneuropathies; Immunoglobulin therapy; Mechanical ventilation; Acute kidney injury; Plasmapheresis (Source: MeSH-NLM).

Introduction

Landry-Guillain-Barré Strohl Syndrome is a progressive autoimmune polyradiculoneuropathy,[1] characterized by symmetrical flaccid paralysis with areflexia, hyporeflexia or hyperreflexia on very rare occasions.[2] Worldwide, it remains the first cause of flaccid paralysis. It is usually associated with a previous infectious disease; however, this is not always the case. There are various clinical variants, each with a different prognosis and mortality. Prognosis is usually good, although 20% of patients could suffer a severe clinical variant of Guillain-Barré Syndrome (GBS) and 5% will die despite treatment.[3-4]

Nowadays, in the post-polio era, Guillain-Barré Syndrome is the most common cause of acute flaccid paralysis of healthy individuals. It has a worldwide incidence of 1-2 adults per 100,000 per year, mainly affecting male population. There is no dominant age group, however, the incidence increases 20% every 10 years from the first decade of life.[5,6] While in México, Domínguez-Moreno reported an incidence of 0.89-1.89/100,000 people per year,[7] from our knowledge, there are not studies regarding Guillain-Barré Syndrome's epidemiology in the city of Mexicali, México, being the main reason for this study to be conducted.

There is not a specific etiology for the disease; however, it may occur in association with multiple viral or bacterial infections, many agents have been linked as a precipitating factor, for example, *Campylobacter jejuni,*[8] *Escherichia coli, Mycoplasma pneumoniae*, and viruses like *cytomegalovirus, Epstein-Barr, human immunodeficiency virus, herpes zoster*, and *hepatitis*. A study carry out in a city of México documented eleven cases of GBS from January to March 2017, 23% were associated with *Zika* virus, 7% *non-polio enteroviruses* and 38% *Campylobacter*.[9] A previous infection may trigger immune response that leads to acute polyneuropathy, approximately two-thirds of the patients refer a previous gastrointestinal or respiratory infection. In other studies, a small percentage of patients who have a history of vaccination, surgery, trauma or bone marrow transplant have also developed the disease.[6]

Clinical symptoms are broad and therefore misleading during diagnosis. Typically, it appears as a rapidly progressive symmetrical muscle weakness with absent, decreased or augmented deep tendon reflexes.[1] Weakness may range from mild motor impairment to complete paralysis of facial, respiratory or bulbar muscles, and limbs. Some unusual features include papilledema, myokymia, decreased auditory acuity, meningeal signs, vocal cord paralysis, and impaired alertness.[5,10]

In a prospective, observational, international study that included a thousand patients from Europe, America, Asia and Bangladesh with Guillain-Barré Syndrome, they identified numerous clinical variants (***Table 1***) and their frequency according to geographical region, concluding that in North America the most common subtype is sensorimotor (69)%.[11]

Electrophysiological studies have a crucial role in confirming the diagnosis and classifying the main variants as demyelinating or axonal. It's hard to distinguish subtypes on clinical features alone. Findings can be normal early in the course but appear to be altered two weeks after the onset of symptoms.[12]

[1] Medical Student (7th year), Faculty of Medicine, Autonomous University of Baja California, Baja California, México.
[2] Medical Student (6th year), Centre of University Studies of Xochicalco, Mexicali, B.C., México.
[3] MD, Internal Medicine, Neurology and Neurophisiology, General Hospital of Mexicali, Mexicali, B.C., México.
[4] MD, Internal Medicine, General Hospital of Mexicali, Mexicali, B.C., México.

About the Author: *Fátima Martínez-González is currently a 7th year medical student of the Faculty of Medicine, Mexicali Campus, México, of a seven-year program. She is also part of a student fellowship program dedicated to community scientific research at the General Hospital of Mexicali.*

Correspondence:
Fátima M. Martínez-González
Address: Dr. Humberto Torres Sanginés S/N, Centro Cívico, 21000 Mexicali, B.C., México
Email: fatima.martinez@uabc.edu.mx

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The aim of this study was to describe the clinical features of patients with GBS who were hospitalized at the General Hospital of Mexicali in a period (2014-2019), and their relationship with mortality.

Table 1. Guillain-Barré Syndrome clinical variants.[11]

Acute inflammatory demyelinating polyneuropathy
Acute motor axonal neuropathy (AMAN)
Acute motor and sensory axonal neuropathy (AMSAN)
Miller Fisher syndrome
Bickerstaff encephalitis
Pharyngeal-cervical-brachial weakness
Paraparesis
Acute pandysautonomia
Pure sensory GBS
Facial diplegia and distal limb paresthesia
Acute bulbar palsy with areflexia

Methods

This is a cross-sectional study, including the records of hospitalized patients with Guillain- Barré Syndrome at Mexicali's General Hospital within a five-year period. Sensitive information, such as name, remained in anonymity. The patients involved were assessed by medical staff who evaluated the presence of the Asbury and Cornblath criteria for diagnosis.[13]

The General Hospital of Mexicali is a public institution owned by the government with the objective to grant financial protection for patients who lack of social security, ensuring their access to health services. This is one of the many public hospitals that allows medical students to learn by enrolling on their academic programs. It is empirically known that the incidence of the disease has been on the rise over the past few years, suggesting that the study of the disease may be relevant to the community.

The following variables were analyzed: age, gender, time of onset, prodromal infections (gastrointestinal, respiratory or other), mechanical ventilation use, acute kidney injury, cranial nerve affection and choice of treatment. We studied cerebral spine fluid cell count, glucose and protein level, to consider albumin-cytological dissociation (protein levels were higher than 40 mg/dL and a cell count lower than 10 cells/mm$^{3)}$.[3]

Nerve conduction studies were only performed in patients whose diagnosis was uncertain, however, the reliability for neurophysiological criteria for diagnosis early in the course of GBS has yet to be determined.[14]

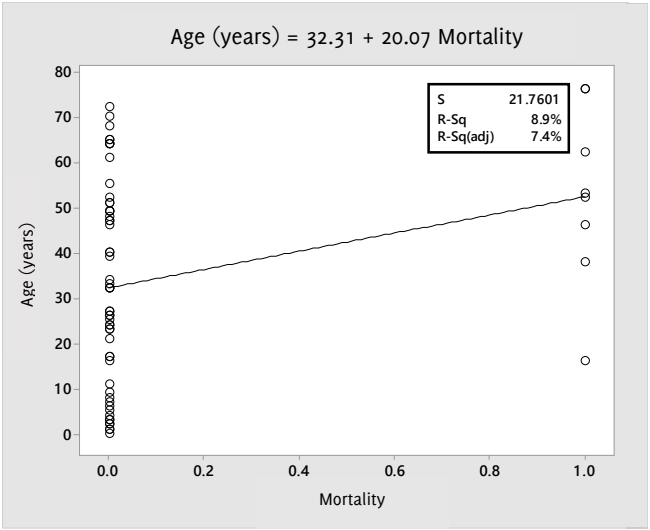
Results were considered significant if p-value < 0.05. Tables of categorical variables were analyzed for heterogeneity by the x^2 test, using Yates' continuity correction for two-by-two tables, or Fisher's exact test if expected frequencies were less than 5. Student's *t*-test was conducted to compare continuous variables between two groups. Data were analyzed by the Epi-Info statistical package version 7.2.2.16 and with Microsoft Office Excel (2018).

This study has been approved by the Institutional Review Board of the General Hospital of Mexicali.

Results

This study included 64 patients diagnosed with Guillain-Barré Syndrome within 5 years (2014-2019), 45 (70.3%) male patients and 19 (29.7%) female patients. Age ranged from 1 through 76 years, with an average age of onset of 35 years old. The most affected age ranges were 1-12 years and 41-59 years (21.88% both), however, the mortality rate increased with age (***Figure 1***). We estimated an incidence of 4 patients per 100,000 per year, meaning it has a high epidemiological impact.

Figure 1. Mortality and patients' age at diagnosis



Some patients presented with neurological symptoms 4 days before seeking medical attention (54%) and others suffered from respiratory or gastrointestinal infection before the start of neurological symptoms (55%), 20% and 59.3% respectively, while 14.6% patients refused to have respiratory or digestive infection, but presented other infections such as urinary tract infection, *HIV,* and *hepatitis C virus*.

The global mortality rate was 12.7%. From the 70.3% males included in this study, 9% passed away, compared to the 30.16% female patients, from which 21.05% of them died. (OR=0.37 95%CI 0.8-1.6).

As for mechanical ventilation, 28% required it during the course of the disease, with an outcome of 87.5% deaths (p-value <0.01). 6.3% developed acute kidney injury during hospitalization, all of them received immunoglobulin therapy, yet the sample size of the unexposed was too small to establish a statistical significance. Of the 55 patients who received immunoglobulin, 4 (7.3%) developed acute kidney injury and 6 (10.9%) of them perished. There were 8 (12.5%) patients who did not receive any type of treatment (immunoglobulin or plasmapheresis), and 2 (25%) of them died. One of the patients who received immunoglobulin had previously received immunoglobulin therapy 15 years ago due to an earlier episode of Guillain-Barré Syndrome and had to interrupt treatment because he developed anaphylactic shock and acute kidney injury during administration. This patient did not live, despite receiving hemodialysis and plasmapheresis (***Table 2***).

Table 2. Study results

Variable	Freq. (%)	Death (%)	OR (95% CI)
Total	64 (100)	8 (12.7)	
Men	45 (70.3)	4 (9)	1
Women	19 (30.16)	4 (21.05)	0.37 (0.8-1.6)
Previous infection	55 (86)	7 (12.7)	1.16 (0.12-10.8)
Gastrointestinal	38 (59.3)	6 (15.7)	2.2 (0.4-12.1)
Respiratory	13 (20)	2 (25)	1.3 (0.2-7.7)
Other	9 (14)	1 (12.5)	0.8 (0.09-7.9)
Mechanical ventilation	18 (28.5)	7 (87.5)	28 (3.11-251)
Acute kidney injury	4 (6.3)	1 (25)	2.5 (0.22-27.2)
Cranial nerve affection	20 (31.25)	1 (5)	0.2 (0.0.3-2.4)

Discussion

This study reviewed 64 cases of patients with GBS from 2014 through 2019, 70.3% were male and 30.16% were female with an obvious incline for males just like Carrillo-Pérez et al stated.[15] The average age of onset was 35 years, unlike Medina-Benites et al who reported an average of 43.85 years;[3] no predominant age range was observed for the onset of the disease, however, there is an increased incidence in young and elderly patients. While analyzing the data, an association between age and mortality was observed, demonstrating that age is directly proportional to mortality ($p < 0.0001$).

From the total of patients, 86% reported having had a previous infection from which 59.3% were gastrointestinal and 20% respiratory, unlike other studies where only 77% presented a previous infectious disease.[16] During characterization no patients were found with a history of trauma, surgery or vaccination, however, different studies reported there is an increased incidence after vaccination or surgery.[17]

Mechanical ventilation is associated to a poor outcome, and it is not a predictor for prognosis, yet, it is an indicator of a severity of the disease. It is well elucidated that the need for mechanical ventilation for acute respiratory failure translates severity. In this study 7 (10.9%) patients perished while on mechanical ventilation. In other studies the need for mechanical ventilation was compared to the history of previous infections, 52% presented a respiratory infection from which 28% required mechanical ventilation.[16] Furthermore, another study mentioned that only 13% of the study population (total of 8,364 patients) needed mechanical ventilation, although they had a larger number of patients. [17]

Regarding treatment, immunoglobulin was administered to 56 (87.5%) patients, 6 expired as they developed acute kidney injury, unfortunately, the sample size does was not enough to establish a relationship between acute kidney injury and the use of immunoglobulin, moreover, only one patient was treated with plasmapheresis ending in death since he had severe clinical disease and similarly developed acute kidney injury. In other studies treatment is divided into supportive measures, immunoglobulin and plasmapheresis (19%, 57%, 23% respectively) with a total of 21 without relating to mortality,[3] whereas in another study with 25 patients where most received plasmapheresis (52%) no significant change was found in disease progression.[14] The decision to administer immunoglobulin may be affected by the fact that ours is a public hospital, sometimes with limited resources, therefore, the availability of supplies may be affected.

This is a retrospective study, with obvious weaknesses involved. For example, the lack of information on some patients' records. Similarly, the score of Erasmus for outcome in Guillain-Barré Syndrome or the modified disability scale for GBS was not applied in this study.[3]

The incidence rate for GBS in our city is 4 per 100, 000 individuals per year, being twice as much as a previous study conducted in our country. We noted a higher prevalence among male sex, just like the rest of the studies regarding GBS, this without being a risk factor for mortality. Also, there is no prevailing onset age. The need for mechanical ventilation represents a higher severity index, nonetheless, this does not mean that assisted ventilation is directly associated with mortality. As for therapy, the use of immunoglobulin as first-choice treatment was associated with acute kidney injury, without an increment in mortality, though results were not statistically significant due to the size of our sample.

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Original Article

Dyslipidemia and hyperglycemia in psoriatic inpatients

Bojan Popchanovski,[1] Margareta Balabanova-Stefanova.[2]

Abstract

Background: Psoriasis is a chronic cutaneous T-cell mediated disease, which has been associated with many comorbidities, such as metabolic disorders. Specific abnormalities include dyslipidemia, insulin resistance, obesity, and metabolic syndrome, many of which are themselves risk factors for other diseases. The goal of this study was to evaluate the presence of dyslipidemia and hyperglycemia in patients with psoriasis. **Methods:** We compared 48 inpatients with plaque psoriasis aged 29-79, hospitalized between March 2018 and February 2019, to 48 age- and gender-matched controls. We evaluated dyslipidemia and hyperglycemia using enzymatic methods as part of a standard blood test, or medication history indicative of ongoing treatment of dyslipidemia and/or hyperglycemia. Hypertension was evaluated by registering blood pressure greater than 140/90 mmHg or ongoing antihypertensive treatment. Smoking habits were also noted. **Results:** There were statistically significant differences between psoriasis patients and controls for elevated total cholesterol (p=0,028), elevated LDL (p=0,015), hypertriglyceridemia (p=0,006), and hyperglycemia (p=0,021). The two groups had statistically insignificant differences for lowered HDL (p=0,084), hypertension (p=1), and smoking (p=0,836). **Conclusion:** Hypertriglyceridemia, hyperglycemia, and elevated LDL cholesterol were found to be more prevalent in the group containing psoriatic patients compared to the control group. This indicates that further investigation of metabolic abnormalities should be conducted in psoriatic patients which could greatly benefit from early treatment of the aforementioned underlying conditions.

Key Words: Psoriasis; Inpatients; Metabolic syndrome; Dyslipidemias; Hyperglycemia (Source: MeSH-NLM).

Introduction

Psoriasis is a chronic immune-mediated skin disorder, with a prevalence of 2%.[1] TNF-α, IFN-α, IL-23 and Th-17 cells play an important role in the pathogenesis of psoriasis.[2] Recent evidence suggests that metabolic abnormalities are present in the milieu of chronic inflammation, as in the case of rheumatological diseases.[3] Chronic inflammation is thought to cause cytokine-induced changes in glucose and lipoprotein metabolism,[4] alluding to a similar situation which happens in the case of insulin resistance caused by cytokines secreted by adipose tissue.[5]

The amount of data on the effect of psoriasis on metabolism is increasing, but various results have been reported. For triglyceride levels, there are studies that found increased levels[6-10] as well as statistically insignificant changes.[6, 11, 12] There are studies that associated psoriasis with higher,[12, 13] and others with normal LDL cholesterol levels.[6, 8, 11, 14-16] As for HDL cholesterol, there are studies that associated psoriasis with lower[6, 13, 15, 16] HDL levels, and studies that did not make that association.[8, 11, 12, 14, 17, 18] Correlation was reported between psoriasis and diabetes mellitus in some studies[9-11, 19, 20] and in other studies no such correlation was made.[6, 7, 14, 17] Results on hypertension and psoriasis were also conflicting, as there are studies that established a link[9, 10, 19, 20] and studies that did not.[7, 15]

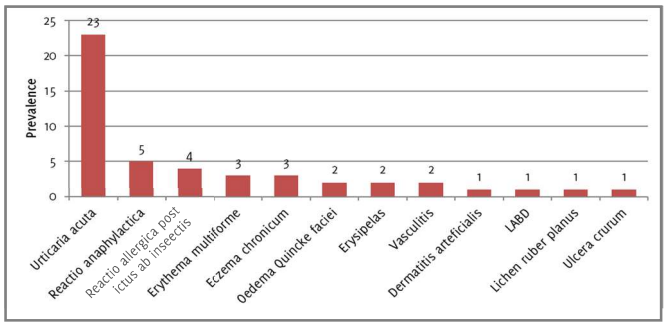
Quantitative and qualitative changes in lipoprotein metabolism, caused by chronic inflammation, may be of potential clinical significance in patients with a high risk of cardiovascular comorbidity. This study was conducted to examine the correlation between psoriasis and abnormal glucose and lipid metabolism.

Methods

This retrospective study included 48 inpatients (27 males, 21 females) with psoriasis vulgaris (plaque and nummularis type) aged 29-79, hospitalized in the University Clinic of Dermatology at the Medical Faculty in Skopje, between March 2018 and February 2019. Data was derived from the clinic's inpatient medical records. Psoriatic inpatients that had pustular psoriasis, psoriatic arthritis, erythrodermia, prior systemic treatment for psoriasis, concomitant tumors, chronic lung, heart, kidney and rheumatological diseases were excluded from the study. These 48 inpatients were paired with another 48 inpatients, matched for age (±1 year) and gender, hospitalized within the same timeframe, and on the same clinic. The exclusion criteria were the same for this group. The diagnoses of the control group inpatients were the following (***Figure 1***): Urticaria acuta (23), Reactio anaphylactica (5), Reactio allergica post ictus ab insectis (4), Erythema multiforme (3), Eczema chronicum (3), Oedema Quincke faciei (2), Erysipelas (2), Vasculitis (2), Dermatitis arteficialis (1), LABD (1), Lichen ruber planus (1), and Ulcera crurum (1).

The variables of interest were triglyceridemia, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glycemia, blood pressure, and smoking habits. Lipid parameters and blood pressure were evaluated according to cutoff values recommended by

Figure 1. Control group diagnoses.



[1] Medical Student, Medical Faculty, University Ss. Cyril and Methodius, Skopje, North Macedonia.
[2] MD, PhD, University Clinic of Dermatology, Medical Faculty, University Ss. Cyril and Methodius, Skopje, North Macedonia.

Correspondence:
Bojan Popchanovski
Address: Skopje 1000, North Macedonia.
Email: bpopcan@msn.com

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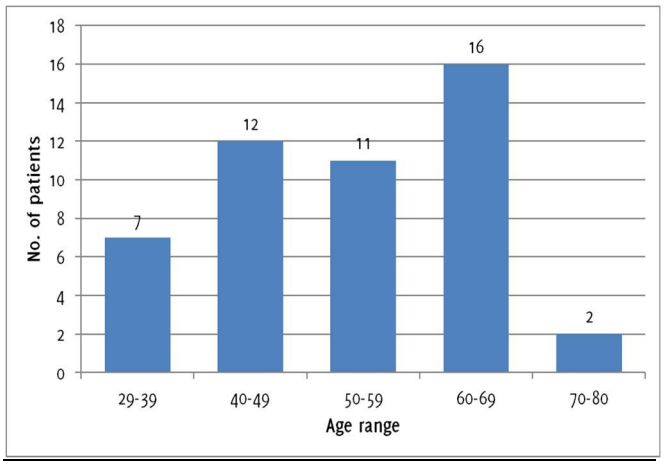
the National Cholesterol Education Program's Adult Treatment Panel III (ATP III), or ongoing antilipidemic and/or antihypertensive treatment according to the patient's medical history. These cutoff values were: 1.7 mmol/L for triglycerides, 3.3 mmol/L for LDL cholesterol, 1.0 mmol/L for HDL cholesterol, 140/90 mmHg for blood pressure. Glycemia was evaluated using the cutoff value of 6.1 mmol/L, recommended by the World Health Organization[21], or ongoing antidiabetic treatment. Smoking habits were evaluated using two categories: patients who are non-smokers, and patients who are currently smoking or have smoked in the past. Glycemia and lipid parameters were measured using enzymatic methods. Blood pressure was measured with a standard mercury sphygmomanometer. RStudio was used to perform a Student's t-test and to calculate the odds ratio with 95% confidence interval.

Figure 2. Age of participants.



Results

Among the 48 psoriatic patients, 7 were aged between 29-39, 12 were aged between 40-49, 11 were aged between 50-59, 16 were aged between 60-69, and 2 were aged between 70-80, as showed in ***Figure 2***. Identical distributions were present in the control group. In the psoriasis group, 14 patients (29,17%) had hyperglycemia, compared to 5 (10,42%) in the control group (p=0,021, OR 3.54, 95%CI 1.16-10.81). Hypertriglyceridemia was noted in 16 psoriatic patients (33,33%), and in 5 patients (10,42%) in the control group (p=0,006, OR 4.30, 95%CI 1.43-12.96). LDL cholesterol was increased in 16 psoriatic patients (33,33%), compared to 6 (12,5%) control patients, (p=0,015, OR 2.14, 95%CI 0.50-9.12). The differences between the psoriasis group and the control group were statistically insignificant for the remaining parameters. Ten (20,83%) psoriatic inpatients had lowered HDL cholesterol, compared to 4 (8,33%) control patients (p=0,084, OR 2.89, 95%CI 0.84-9.98). In the psoriasis group, 19 patients (39,58%) reported to have smoked or were current smokers, compared to 16 (33,33%) in the control group (p=0,836, OR 1.31, 95%CI 0.57-3.02). Finally, 16 patients in each group were found to have hypertension (p=1, OR 1.00, 95%CI 0.43-2.34). A summary of the results is given in ***Table 1*** and ***Figure 3***.

Discussion

Despite the conflicting findings of the current body of research on this topic, there is a complex pathophysiological explanation for the quantitative and qualitative changes in the case of rheumatological diseases, which may also be true for psoriasis. Proinflammatory cytokines released during the course of these diseases change many aspects of lipid metabolism, such as increased VLDL and triglyceride levels via increased hepatic fatty acid synthesis, decreased hepatic fatty acid oxidation and increased adipose tissue lipolysis. This ultimately contributes to the increase of triglyceride content in LDL and HDL particles, which subsequently leads to the formation of small dense LDL (sdLDL) particles. These particles are more atherogenic as a result of their high susceptibility to oxidation, high affinity for intra-arterial proteoglycans, and decreased clearance due to decreased affinity for LDL receptors. Additionally, lipoprotein lipase (LPL) activity is reduced, which further reduces the clearance of LDL particles.[3]

Table 1. Associated factors with psoriasis.

Parameter	Psoriasis	Controls	p-value	OR (95% CI)
Mean age	52,92	52,73	-	-
Sex (male/female)	27/21	27/21	-	-
Smokers	19	16	0,836	1.31(0.57-3.02)
↑gly	14	5	0,021	3.54 (1.16-10.81)
↑TAG	16	5	0,006	4.30 (1.43-12.96)
↓HDL	10	4	0,084	2.89 (0.84-9.98)
↑LDL	16	6	0,015	2.14 (0.50-9.12)
↑BP	15	16	1	1.00(0.43-2.34)

Legend: OR - odds ratio, CI - confidence interval, ↑gly - hyperglycemia, ↑TAG - elevated triglycerides, ↓HDL - elevated HDL cholesterol, ↑LDL - elevated LDL cholesterol, ↑BP – hypertension.

HDL particles are also subject to change in an inflammatory milieu, which equates to reverse cholesterol transport being severely impacted as a result. Apo A-1 clearance is increased due to decreased synthesis and increased breakdown in the kidneys, which both lead to lower affinity of Apo A-1 for HDL particles. Serum amyloid A (SAA), an acute phase protein generated during inflammation, binds to HDL particles, which lowers the affinity of Apo A-1 for its receptor, and increases the clearance of HDL particles. Cholesterol ester transfer protein (CETP) and lecithin-cholesterol acyltransferase (LCAT) levels are decreased, which lead to decreased cholesterol transport from HDL particles and decreased cholesterol ester formation, respectively. Certain phospholipid and cholesterol membrane transport proteins, such as ABCA1, ABCG1, and SR-B1, have reduced activity, which contributes to decreased hepatocyte uptake and decreased efflux from macrophages. Finally, lipoprotein (a) is generated, which has a high atherogenic potential.[3] This evidence of qualitative changes in lipoproteins suggests that perceived normal lipid levels may not be enough to exclude abnormalities in lipid metabolism.

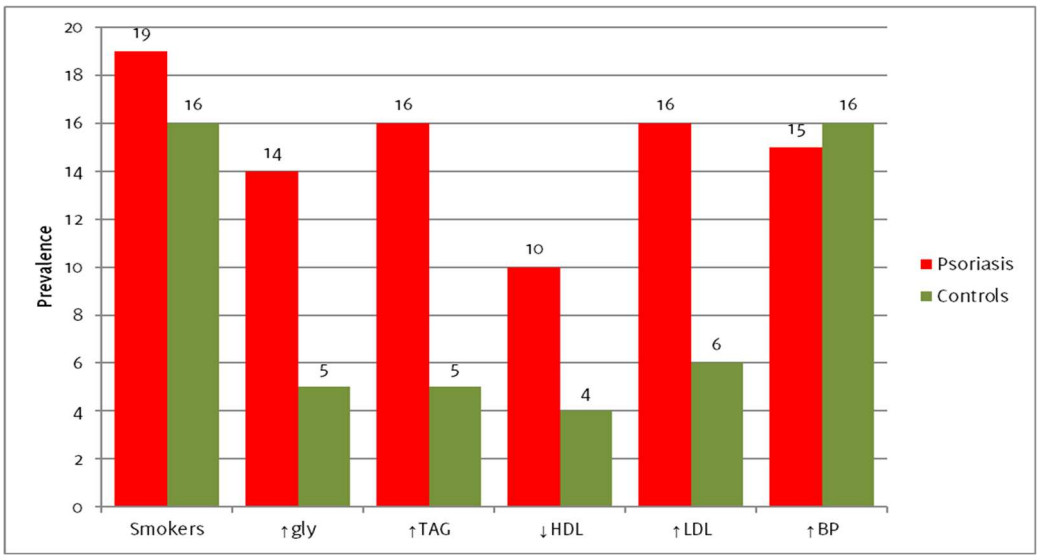
The inflammatory pathogenesis of psoriasis suggests that, skin and joint lesions aside, many more less visible metabolic effects may be present. Psoriasis causes slight but clinically actionable alterations in certain metabolic parameters, which are relevant in terms of cardiovascular comorbidity.

This study could be improved by increasing the sample size to increase the accuracy of the data and to narrow down the confidence intervals. An important drawback represents its retrospective design. The data gathered were only the parameters that are measured during routine examination in our clinic. Ethnicity is also one of these parameters not registered routinely, which may influence the prevalence, age of onset, disease course, and further changes to metabolic parameters. Additional useful parameters such as Psoriasis Area and Severity Index (PASI) and hsCRP, to determine the extensiveness of the psoriatic lesions and the cardiovascular risk, respectively, could be measured and tested more appropriately in a case-control scenario.

Another aspect not covered in this study is disease progress. Our results are only indicative of one point in time, and the history of disease progress and treatment for each individual patient is unknown. Five of the previously mentioned studies stated that their objective was to determine the prevalence specifically of metabolic syndrome in psoriatic patients[7, 9, 10, 14, 17, 22]. Four of them associated psoriasis with metabolic syndrome,[7, 9, 10, 17] and one found no such link[14]. One of these previously mentioned studies established a dose-response relationship

between the severity of psoriasis and the prevalence of metabolic syndrome[10], while another disproved that[22]. One meta-analysis, taking 12 studies into account, also established a dose-response relationship[4]. These diverse findings pertaining to the metabolic syndrome, combined with the diverse aforementioned results on individual metabolic parameters, indicate that many other factors, such as age of onset, duration, disease severity, and treatment, may play a role in terms of the order in which metabolic changes appear, and in the way they evolve over time. Consequently, we think that the next step in psoriasis research could be the effect of the dynamics of the PASI score and BMI over time and their ability to predict inapparent but forthcoming metabolic changes.

Figure 3. Summary of results.



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Review

Breast Cancer and Lymphedema: A Narrative Review

Athena Michaelides,[1] Constantina Constantinou.[2]

Abstract

Breast cancer is the second most common cancer diagnosed worldwide, and the leading cause of cancer death in women. The understanding of disease presentation by patients and health care providers is crucial for a correct diagnosis and management. Preventive measures emphasize risk-reducing behaviors such as a healthy diet, reduced alcohol consumption, increased physical activity, and breastfeeding children. Screening techniques such as mammography, ultrasound, and MRI aid in early detection. Following the screening, a breast biopsy is performed, and a histopathological assessment is carried out to confirm a breast cancer diagnosis. In addition to surgery, radiotherapy, and lifestyle modifications, treatment regimens include a range of medications such as anti-hormonal drugs and chemotherapy. Lymphedema is a severe and major long-term consequence of breast cancer treatment. The major contributors to the diminished lymph drainage are a lumpectomy/mastectomy procedure that involves the surgical removal of lymph nodes, and radiotherapy. The fluid accumulation of lymphedema poses physical limitations to the patient and impacts the overall quality of life. A sentinel lymph node biopsy is an essential method of identifying the first draining lymph nodes affected by metastasis. This procedure allows surgeons to later remove only affected lymph nodes, sparing those that are unaffected and hence reduce the risk and magnitude of lymphedema development. Patients who receive education about lymphedema demonstrate higher compliance with treatment and self-care management practices. The purpose of this review is to provide information about breast cancer, the development of lymphedema, and how to recognize and manage both.

Key Words: Breast cancer; Lymphedema; Breast tumor; Review; Review literature (Source: MeSH-NLM).

Introduction

Cancer is a disease process characterized by abnormal cell growth that can affect any part of the body. Benign tumors are confined to one part of the body, whilst malignant tumors spread via the blood or lymphatics to other parts of the body.[1] Amongst all cancer types, the most common is breast cancer (24.2%), followed by colorectal (9.5%), and lung cancer (8.4%). Of a total 4.2 million cancer deaths, breast cancer is the leading cause of cancer deaths in women (15%), followed by lung cancer (13.8%) and then colorectal cancer (9.5%).[2]

The mechanism of cancer development varies according to cancer type and origin, and the characteristics of the affected individual. Breast cancer development is mostly influenced by the presence of estrogen and progesterone hormones in the circulation giving rise to hormone receptor-positive breast cancer.[3] Less commonly, hormone receptor-negative cancer may arise. Other mechanisms include mutations in tumor suppressor genes, some of which are hereditary such as BRCA1 and BRCA2.[4]

Its widespread burden emphasizes the importance of screening, correct diagnosis, and treatment. The history and physical examination of the patient are important in the initial identification of suspected pathologies.[4] Imaging techniques such as mammography, ultrasound, MRI and CT have a role in further investigation of any abnormal findings.[5] The pathological findings detected through imaging are taken a final step further with a breast tissue biopsy providing the final diagnosis.[6]

Breast cancer is categorized according to 3 major classification systems: the histopathology of biopsied specimens, grade, or stage.[7] Each system establishes a final level of cancer spread and severity that determines the treatment regimen and predicted prognosis. Further to classification, presenting symptoms are organized into clusters, with clusters of increased symptom number and severity foreshadowing a worse prognosis.[8] According to the incidence rates of organs typically affected, the metastasis of breast cancer affects lymph nodes (64%), lungs (57%), red bone marrow (55%), liver (51%), bone (49%), adrenals (34%), and the brain (10%).[9] Over 90% of women who develop breast cancer, have what is referred to as 'early breast cancer' in which cancer is confined to the breast and axillary lymph nodes.[10] Since the lymph nodes are the primary site of cancer spread, the impact of lymph node removal is an appropriate point of further discussion.

As part of the treatment process, affected lymph nodes (and sometimes unaffected lymph nodes) are removed during lumpectomy/mastectomy surgeries.[11] Due to the reduced capacity of the remaining lymph nodes to remove excess interstitial fluid, lymphedema develops as a consequence and affects between 12-28% of women treated for breast cancer.[12] Lymphedema may also occur after radiotherapy due to the formation of scar tissue impeding lymph flow. Lymphedema presents as swelling of the affected arm that involves pain, heaviness and a disrupted functioning of everyday tasks.[11] It may progress to a more severe fibrotic process and soft tissue destruction that manifest as warts, tissue bulges and open wounds.[13]

The management of lymphedema includes a range of compression therapies and physical therapy.[14] Because a large portion of treatment involves self-care practices, it is crucial that the patient is adherent, and has access to information regarding the therapeutic process and progress.[15]

Since breast cancer is a significant contributor to the overall burden of cancer, and its treatment is a recognized contributor to lymphedema, the link between breast cancer treatment and lymphedema is proven to be a valuable topic for research. The purpose of this literature review is to provide a basic understanding of the principles of breast cancer and lymphedema to patients, medical professionals, and the general public.

[1] BSc, Medical student, University of Nicosia Medical School, Cyprus.
[2] BA, MSc, Ph.D., Associate Professor of Molecular Biology, Director of Research, University of Nicosia Medical School, Cyprus.

About the Author: *Athena Michaelides is in her final year of a 6-year MD (doctor of medicine) program at the University of Nicosia, Cyprus*

Correspondence:
Athena Michaelides
Address: 93 Ayiou Nikolaou Street, Engomi, University of Nicosia Medical School, Cyprus
Email: athena1.michaelides@gmail.com

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Papers were extracted from the PubMed database using varying combinations of the search terms breast cancer or breast carcinoma; presentation; diagnosis; classification; pathogenesis; management; and prevention. A second search that focused on the development of lymphedema included combinations of the search terms lymphedema; consequence; breast cancer; surgery; radiotherapy; diagnosis; classification; pathogenesis; management; and prevention. Papers were limited to human subjects, and the English language. Small-scale studies that were inconclusive or had results of no statistical significance were excluded. The literature was screened for the information considered to be most up-to-date and relevant to medical professionals and the wider public. The information was then extracted and summarized to be used for this review.

Presentation

With the development of screening techniques such as mammography and other imaging modalities, breast cancer is usually detected prior to the development of obvious signs and symptoms. However, the signs and symptoms that may become apparent to the patient still pose as an important area of discussion. A first sign of breast cancer that is usually noticed by the patient is a lump in the breast that feels different to the surrounding tissue.[16] A change in shape, size and general breast appearance may be noted.[1] Further skin changes reveal skin erythema, peeling, scaling, and a characteristic dimpling resembling that of an orange peel known as *peau d'orange*.[1]

Nipple changes are often unilateral and include distortion, inversion, retraction or elevation, and eczematous skin changes from the nipple and surrounding areola that is unresponsive to topical treatment.[1] The nipple may also secrete a serous or bloody discharge.[17] If the cancer has spread to the lymph nodes, pain and swelling around the clavicles and axilla may be present.[1]

Symptoms often present concurrently in breast cancer patients.[8] The total burden of symptoms shows a negative correlation with the quality of life, with every additional symptom relating to a further decline.[8] Symptoms include physiological disturbances as well as psychological effects. The physiological aspect includes pain, numbness, disturbed sleep, decreased sex drive, weight changes, peripheral neuropathy, gastrointestinal disturbance, and spontaneous menopause.[8-9] The psychological symptoms include fatigue, anxiety, depression, perceived cognitive impairment, mood changes, and a lowered self-esteem.[9]

Diagnosis

Patient history and physical examination

The patient's history and physical examination establish the link between risk factors and symptomatology. Clinical history assesses the risk of cancer and includes questions regarding the age of menarche, pregnancies to date, menopausal status, and medications such as oral contraceptive and hormone replacement therapy. A family history of breast and ovarian cancer in first degree relatives should also be established.[18]

As part of the physical examination, the patient is first positioned sitting upright with the upper body exposed so that a thorough inspection can be carried out to identify breast asymmetry, nipple changes and discharge, and visible masses. Specific skin changes to look out for include skin erythema, dimpling, and *peau d'orange*. Palpation of the breast parenchyma then proceeds with the patient in the supine position and ipsilateral arm placed over the head. Cervical, supraclavicular and axillary lymph nodes are also palpated for signs of lymphadenopathy.[18]

Imaging techniques

To further investigate suspicions of breast cancer, a range of imaging techniques are utilized. The American Cancer Society (ACS) recommends mammography as the primary mass screening technique for females between the ages of 40 and 74. However, the ionizing radiation poses a limitation to its widespread use especially in pregnant females in which mammography is contraindicated. False-positive and false-negative results also limit mammography as a diagnostic tool in patients.[5] Mammography has a false-negative result of about 13%. The chance of having a false-positive result ranges from 7-12%, with younger women and women with dense breasts being more likely to have a false-positive result.[5]

Breast ultrasound (US) is used as a supplement to mammography to improve sensitivity. In using acoustic waves to reflect breast structures, cysts and solid masses can be identified.[19] However, healthy and cancerous tissue may present similar acoustic properties that ultrasound may fail to differentiate between.[5]

Magnetic resonance imaging (MRI) is non-invasive and non-ionizing, making it ideal for high risk patients who cannot undergo other screening and diagnostic procedures. Magnetic fields with radio frequency signals are applied to create cross-sectional images for the identification of tumor masses.[17] High costs, lack of availability, time consumption, and its high false-positive rate limit the widespread use of MRI.[5] It is also difficult to detect some types of cancers such as invasive ductal and lobular carcinoma using MRI, but it has a role in the identification of distant metastasis.

Computer tomography (CT) uses radioactive waves to provide cross-sectional images from different angles of the body. It provides images of soft tissue, bone, and blood vessels, making it is useful for determining distant metastasis. However, CT has a low sensitivity and poses a radiation risk.[5] Position emission tomography (PET) involves the administration of a radioactive isotype and the detection of photons produced during the process of radioactive decay that interact with surrounding tissue.[20] PET is used for imaging distant metastasis and response to therapy. The use of ionizing radiation as well as a radioactive tracer limit its widespread use.[5]

Breast biopsy and fine needle aspiration

After relevant imaging of the patient's breast, the final diagnosis is made based on the results of a biopsy. This involves removing cells from the breast tissue to be examined in a laboratory in order to identify abnormalities.[6] The literature describes surgical biopsy as the gold standard for breast diagnosis before the 1990's.[6] This subjected the patient to a cumbersome process and an invasive surgery which proved to be unnecessary in some cases.

As an advancement, percutaneous needle biopsy (PNB) emerged as the preferred method of breast diagnosis. Fine needle aspiration biopsy (FNAB) was the first to emerge in this category.[6] Following FNAB, the introduction of the image directed core needle biopsy revolutionized the field with its ability to obtain histological samples that provide diagnostic information not achieved by FNAB. It can distinguish invasive from non-invasive cancer, determine tumor grade, and expression of hormone receptors.[6]

The full extent of the disease can be assessed before surgery by sampling areas susceptible to cancer spread. The surgeon may request that a sentinel lymph node biopsy (SLNB) be performed to investigate the extent of metastasis to nearby lymph nodes.[6] A radioactive substance or a dye are injected near the tumor. The first few lymph nodes that drain the breast tissue will absorb the radioactive substance and be detected by a probe. These lymph nodes can then be removed and checked for cancerous cells.[21] Further to this, a decision can be made regarding the extent of lymph node removal based on whether cancerous cells are present or not.

Classification

Tumors are mostly classified according to the histopathological features of biopsied specimens that are viewed under light microscopy.[7] Looking at the growth patterns and cytological features, two main categories of

breast cancer have been described: carcinoma in situ; and invasive (infiltrating) carcinoma. Breast carcinoma in situ is further classified as either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).[22] DCIS is the more common subtype and is sub-classified even further into five distinct types based on architectural features: comedo; cribriform; micropapillary; papillary; and solid. Invasive (infiltrating) carcinoma is further classified as: tubular; ductal lobular; invasive lobular; infiltrating ductal; mucinous (colloid); medullary; and infiltrating ductal.[22]

Another system classifies cancer according to grade and focuses on the appearance of cancer cells compared to normal tissue. The Scarff-Bloom-Richardson grading system allocates scores to features of breast tissue that include tubule formation, nuclear polymorphism, and mitotic count. The overall score classifies the tumor as grade 1 (well-differentiated, good prognosis), grade 2 (moderately differentiated, medium prognosis), or grade 3 (poorly differentiated, worse prognosis).[23]

The third system classifies cancer according to the stage, and follows the TNM (tumor, lymph node involvement, and metastasis) system. This system describes the severity of cancer and assists with the selection of appropriate treatment in conjunction with other factors such as the presence of estrogen and progesterone receptors.[24]

The Breast Imaging Report and Data System (BI-RADS) is a communication tool described by the American College of Radiology (ACR) to reduce variability when creating mammography, ultrasound, and MRI reports. It uses a standardized approach to define the features of a breast mass by detailing the density, location, micro/macrocalcifications, architectural distortions, and associated findings.[25] By doing this, BI-RADS aids in the reproducibility and comparison of radiological descriptions of breast cancer findings. ***Table 1*** describes the BI-RADS classification in more detail.

Table 1. BI-RADS Classification.[25]

Category	Explanation	Chance of malignancy	Action
0	Incomplete evaluation	N/A	Further imaging required
1	Negative examination. No masses, suspicious calcifications, or areas of architectural distortion	0%	Normal interval follow-up
2	Benign. Secretory calcifications, simple cysts, fat containing lesions, calcified fibroadenomas, implants, and intramammary lymph nodes	0%	Normal interval follow-up
3	Probably benign. Non-palpable circumscribed mass on baseline mammogram, a focal asymmetry, or a solitary group of punctate calcifications	<2%	Shortened interval follow-up
4	Suspicious findings	A – 2-10% B – 10-50% C – 50-95%	Biopsy considered
5	Highly suggestive of malignancy	>95%	Biopsy or surgery
6	Proven malignancy	N/A	Imaging for cancer staging or evaluation after chemotherapy

Legend: Derived from 'BIRADS classification in mammography' *European Journal of Radiology* 61(2007) pp. 192-194.[25]

Pathogenesis

The pathogenesis of breast cancer is variable across populations as it depends on an interaction between environment, lifestyle, and genetic susceptibility.[18] Several mechanisms contribute to the unchecked proliferation of breast tissue.

Hormone receptor-positive breast cancer (ER+ and PR+)

Estrogen and progesterone are central in regulating the growth and differentiation of mammary glands.[3] The effects of estrogen are mediated through its binding to estrogen receptors ER-a and ER-b, and those of progesterone to the progesterone receptor (PR).[3] Although the exact mechanism is not understood, the binding of estrogen and progesterone to their respective receptors on cancerous cells, leads to altered gene activity and uncontrolled ER- or PR-mediated breast tissue proliferation.[26] Approximately 80% of all cancers are ER-positive, and 65% of these are also PR-positive. The age-specific statistics suggest that there is an increased incidence rate of breast cancer before menopause (ages 40-50) that tends to slow down after this probably due to the decreased levels of circulating estrogens produced by the ovaries.[27] However, sources of these hormones are also exogenous in the form of the oral contraceptive pill (in pre-menopausal women) or hormone replacement therapy (in post-menopausal women).[26] An increased risk of breast cancer has been established in women who take these medications.[26-28]

HER-2 overexpression

HER-2 (human epidermal growth factor 2), otherwise known as ERBB2 (Erb-B2 receptor tyrosine kinase 2) is a receptor tyrosine protein kinase found on breast cells that accounts for 25-30% of breast cancers when overexpressed.[29] Under normal conditions, this receptor is found on breast cells to stimulate breast development.[29]

Tumor suppressor gene mutations

The PI3K/AKT pathway is important in regulating the cell cycle by initiating downstream survival signals that protect the cell from premature death.[30] This pathway is regulated by the tumor suppressor protein, PTEN, that turns off the PI3K/AKT by initiating apoptosis when conditions are appropriate.[31] Mutations in PTEN lead to a constantly activated PI3K/AKT pathway that in effect causes inappropriate proliferation.[31]

Five percent of breast cancer cases are attributed to genetic mutations in the tumor suppressor genes BRCA1 and BRCA2.[18-32] Of the hundreds of mutations identified, some have no impact, while others are involved in the development of hereditary breast-ovarian cancer syndrome that is responsible for breast and ovarian cancer in genetically related families.[33]

Management

The management and treatment of breast cancer vary according to disease type and severity, age, the overall health of the patient, and personal treatment preference.[34] In the early stages, local therapy such as surgery and radiotherapy are effective, whereas in advanced and metastatic cases, systemic therapy is preferred.[35] Compared to age-matched women without the disease, the 5-year survival of women with breast cancer has increased from 80% in the 1950's to 89% today.[11]

Surgery & Radiation Therapy

The initial management of breast cancer is surgery.[34] A more conservative lumpectomy (solitary lump removal), is the preferred surgical therapy when the tumor is smaller than 4cm in size.[36] A mastectomy (complete breast resection) is the treatment of choice when the patient presents with tumors in different breast areas, tumors that are large in relation to the breast, instances where radiotherapy in inaccessible to the patient, or when the patient requests to avoid systemic therapy.[36]

During the mastectomy surgery, axillary lymph nodes may also be removed to determine the extent of metastasis. These changes affect the lymph drainage of the ipsilateral arm, leading to lymphedema.[11]

Radiation therapy serves as an adjunct to lumpectomy and mastectomy surgeries, as a means of reducing local cancer recurrence.[35] Radiation therapy uses high energy X-rays or gamma rays to eradicate cancerous cells that either recur after tumor removal, or remain after surgery.[37] External beam radiation is the most common type of radiotherapy that utilizes energy from a machine exterior to the body.[37]

Due to the high intensity of the radiation, normal tissue surrounding cancerous tissue is also damaged. However, healthy tissue has a repair response that cancer cells lack, so radiation therapy is given over an extended period of 5-7 weeks to allow for recovery of the normal tissue.[35] Patients may experience fatigue, muscle stiffness, swelling, or tenderness during the treatment period as well as a change in skin color resembling that of a sunburn.[37] Similar to mammography, due to the high energy radiation, this therapy is contraindicated in pregnant patients.[35]

Development of Lymphedema

Under normal conditions, the role of the lymphatic system is to maintain fluid balance in tissues, fight infection and remove cellular debris from extracellular spaces. The venules reabsorb 90% of fluids that are filtered from the capillaries into the *interstitium* - the remaining 10% of fluid and proteins are removed by the lymphatic vessels to be returned to the bloodstream.[11] The lymphatic system thus balances the inward and outward flow, creating a stable overall interstitial pressure. A disruption of this balance results in lymphedema - an abnormal accumulation of interstitial fluid that leads to chronic inflammation and possible fibrosis.[38]

Lymphedema in the context of breast cancer is secondary to therapeutic interventions such as the resection of axillary lymph nodes or radiation therapy.[38] Lymph node removal compromises the overall drainage capacity of the lymphatic system. Superficial scarring following surgery or scarring post-radiotherapy may impede the lymphatic flow across the scar tissue leading to fluid accumulation proximal to the scar.[11] Localized post-surgery infection also leads to an increased volume of fluid and cellular components that may exceed the transport capacity of the impaired lymphatic system.[10]

Areas commonly affected by the diminished lymph flow are those that generally drain to the axilla such as the ipsilateral breast, chest, upper trunk, arm, and hand.[11] Increased age (>60 years), obesity (BMI >25), and a more extensive axillary lymph node dissection are associated with an increased risk of post-operative lymphedema.[38]

Hayes et al., conducted a study in which 33% of women developed lymphedema 6-18 months after breast cancer surgery.[39] A greater odds were associated with older age, treatment complications, and more extensive surgery (axillary node dissection, mastectomy, greater number of lymph nodes removed).[39] The risk of developing lymphedema post-radiotherapy is directly related to the radiation dose. The combination of surgery and radiotherapy poses an even higher risk.[38] Having a partner and partaking in regular activity was associated with a lower odds of lymphedema development.[39]

The typical presentation of lymphedema after breast cancer is local swelling in one or both arms.[13] Typical symptoms accompanying this include pain, heaviness, limited range of motion, and disruption of daily function - in particular, tasks involving gross and fine motor skills.[13] Early signs include swelling that pits with applied pressure. As the disease progresses, patients may present with fibrosis and fat accumulation in the affected area. Warts, skin folds and papules may present at later stages.[40] The patient may complain of impaired mobility and notice physical changes such as clothing or jewelry being too tight, difficulty writing, arm/hand puffiness, indentations, firm or leathery skin, and swelling after exercise.[39]

Unlike breast cancer diagnosis, there is uncertainty around lymphedema diagnosis amongst physicians. However, diagnosis is commonly made upon a measurable 2cm (or more) difference in arm circumference or 200mL difference in limb volume between affected and non-affected limbs.[11] A range of diagnostic evaluations have been identified to confirm lymphedema. Soft tissue imaging such as MRI, computed tomography (CT), and ultrasound assist in the detection of excess interstitial fluid. Lymphoscintigraphy, a nuclear medicine technique that images lymph vessels and nodes, detects slow or absent lymph flow. Bio-impedance spectroscopy (BIS) measures water content in tissues and has been especially useful in diagnosing breast cancer related lymphedema.[41]

Lymphedema progression can be established by examining tissue changes that are categorized into three stages: Stage I is characterized by pitting upon application of pressure that subsides with limb elevation. Stage II is characterized by increased fibrosis and fat accumulation that no longer pits with applied pressure and does not subside with limb elevation. Stage III represents fibrotic progression that encompasses a range of soft tissue manifestations such as warts, skin folds and papules that lead to impaired mobility and infection susceptibility.[40]

Two principal methods for managing breast cancer-related lymphedema are described: complex decongestive therapy (CDT); and exercise.[14] CDT is divided into two parts: an intensive phase which consists of four components, and a maintenance phase in which the patient practices self-care with occasional manual lymph drainage (MLD) by a therapist.

The four parts of the intensive phase include MLD, arm and shoulder exercises, compression therapy, and deep-breathing practices that promote venous and lymphatic flow.[14] Exercise for patients with lymphedema follows supervised programs with goals to restore range of motion (ROM) and upper limb function, increase muscle strength, and to control swelling.[14] Reduction in weight also helps lessen lymphedema.[42]

Educating patients about secondary lymphedema, and subsequent management should not be underestimated. Many patients report not having received sufficient information about lymphedema as a complication of breast cancer.[43] The use of lymph drainage massage services and compression garments was found to be utilized more amongst women who had received lymphedema education.[15] A positive correlation between patient education and adherence to lymphedema therapy is demonstrated, emphasizing the importance of patient education.[14]

Lymphedema prevention can be divided into pre-surgery and post-surgery techniques. Already mentioned as part of diagnostic techniques, a sentinel lymph node biopsy is the most important method of identifying lymph node metastasis.[44-45] Through identifying the axillary lymph nodes most likely to be affected by tumor metastases, it is possible to avoid unnecessary nodal dissection and hence lymphedema as a consequence.[45] This benefit is proven in a meta-analysis showing the rate of lymphedema as a complication following axillary dissection is four times higher than following sentinel

node biopsy.[46] Further to this, chemotherapy shows a protective effect against lymphedema development: 20-40% of node-positive patients tested node-negative after chemotherapy, so a sentinel node biopsy performed after chemotherapy could reduce unnecessary axillary dissection.[46]

Due to the difficulty in predicting populations at risk for developing lymphedema after undergoing breast cancer surgery, clinicians recommend risk-reducing behavior as the primary preventative measure in all patients undergoing axilla surgery.[47] The most widely recognized of these is the avoidance of venipuncture, injections, or taking blood pressure on the side of the affected arm, as well as the use of compression sleeves for air travel.[47] Women who receive lymphedema education prior to treatment, exercise regularly, and implement preventative self-care activities demonstrate a lower incidence of lymphedema following breast cancer surgery.[14, 48]

Systemic therapy

Systemic therapy treats cancer cells throughout the body using a range of medications and is subdivided into chemotherapy, endocrine (hormone) therapy, and targeted therapy.[34-35] The National Institute for Health Care Excellence (NICE) guidelines describe the populations in which chemotherapy is indicated. Adjuvant anthracycline-taxane combination chemotherapy is recommended in patients with invasive breast cancer who are at risk of disease recurrence. Neoadjuvant chemotherapy is offered to reduce the tumor size in patients with ER- invasive breast cancer and is considered in patients with ER+ invasive breast cancer. Neoadjuvant chemotherapy is given in combination with trastuzumab in patients with HER2+ invasive cancer.[34]

NICE recommend that docetaxel is given as single-agent first-line therapy; vinorelbine or capecitabine as single-agent second-line treatment; vinorelbine or capecitabine (whichever was not used as second-line treatment) as single-agent third line treatment.[34] Alternative options for second-line treatments are Everolimus and Fulvestrant, and a third line alternative is Eribulin.[34] Chemotherapy side effects include nausea and vomiting, hair loss, fatigue, mouth ulcers, dry and cracked skin, depression, weight changes, and an unpleasant taste in the mouth.

Endocrine therapy is indicated for patients with ER+ tumors, and is administered after surgery, radiotherapy, and chemotherapy with the purpose of preventing relapse.[48] Tamoxifen, which acts by inhibiting estrogen receptors, is the medication of choice for pre-menopausal women.[34, 48] Aromatase inhibitors (either steroidal or non-steroidal) that act by lowering the amount of circulating estrogen are indicated for post-menopausal women.[34] Patients who experience hot flushes as an adverse effect of hormone therapy, can reduce this by avoiding triggers such as caffeine, alcohol, and smoking. In cases where symptoms persist, serotonin-norepinephrine receptor inhibitors (SNRIs) such as venlafaxine may be administered.[49]

Trastuzumab (otherwise known as Herceptin) in combination with paclitaxel is the medication of choice for tumors that are hormone receptor-negative and HER2-positive.[34] Trastuzumab in a monoclonal antibody that blocks HER2 protein activity in breast cancer cells and hence halts tumor growth.[29].

Prevention

Since the leading risk factor for developing breast cancer stems from prolonged exposure to endogenous hormones, it is not easily modifiable.[51] Primary prevention of breast cancer is achieved by partaking in physical activity, maintaining a healthy weight, following a healthy diet, minimizing alcohol consumption, breastfeeding children, and minimizing the use of oral contraceptive pills and hormone replacement therapy.[51] Testing for BRCA1 and BRCA2 mutations is recommended in women with affected family members.[52] A bilateral mastectomy may be performed as prophylaxis for women who test positive for the mutations which are associated with increased risk of breast cancer.[52]

Estrogen receptor antagonists such as tamoxifen reduce the risk of breast cancer, but at the expense of an increased risk of endometrial cancer and thromboembolic events.[53] Because of this, they are reserved for treatment, and prevention only in high risk women.[53]

Conclusion

It is evident from the literature that breast cancer is a prevalent disease that affects women on a worldwide scale. It is also thoroughly described that breast cancer presents itself through a range of physical symptoms and clinical findings. This emphasizes the importance of screening techniques that aid in the early detection of the disease, and preventive measures. The limitations posed by each imaging technique (mammography, ultrasound, and MRI) suggest that each patient needs to be considered on an individual basis to select the most suitable method per patient. Treating breast cancer follows a similar individualized method, considering the mechanism of cancer pathogenesis through assessing hormonal exposure and gene overexpression.

Because breast cancer is in most cases confined to the breast and axillary lymph nodes, the adverse effects that arise through lymph node resection are just as crucial as the adverse effects that arise through breast resection. Functional impairment, psychological distress, and disturbed daily routine are some of the significant effects of lymphedema that require management. The literature provides evidence that effective lymphedema management relies on the patient's will to comply with self-care practices. For this reason, patient education is crucial.

Continuous research and development are underway to develop highly specific treatment regimens that target breast cancer on a molecular genetic level. The advancement of the sentinel lymph node biopsy also has positive implications for reducing lymphedema as a complication of breast cancer metastasis and treatment. This suggests a promising overall prognosis for the general female population moving forward.

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Review

Outcomes of Patients Referred for Arteriovenous Fistula Construction: A Systematic Review

Andrew Stanton Kucey,[1] Anish Engineer,[2] Shawn Stefan Albers.[1]

Abstract

Chronic Kidney Disease (CKD) affects 10-16% of the US population and its incidence is rising due to increasing prevalence of associated risk factors. Renal replacement therapy is required to treat late stage CKD and hemodialysis is the preferred modality for many patients. Vascular access is required for hemodialysis and arteriovenous fistulas (AVF) are currently the gold standard. This review intended to collate current knowledge on AVF outcomes regarding both the patient and fistula. Scopus and Medline were utilized to identify relevant literature. Inclusion and exclusion criteria were applied to narrow search results. Among CKD patients, 33.5-77.4% require a central venous catheter (CVC) before dialysis through a fistula. Many patients (33-51%) use a CVC regardless of AVF creation due to fistula immaturity or failure. There are large variations in AVF creation policies internationally; 16% of American hemodialysis patients use a fistula compared to 72% of German patients. Primary patency and primary AVFs' failure ranges from 60-70% and 20-26%, respectively. AVFs reduce morbidity and mortality in CKD. At present, too many patients are receiving hemodialysis through a CVC. Inadequate referral times for AVF creation can lead to fistula immaturity or failure in the intervention. Many countries are lagging behind recommended AVF creation rates published by the Kidney Disease Outcomes Quality Initiative. There is a paucity of literature concerning when a patient should be referred for AVF creation. It is paramount to have better predictive outcome measures and more clarity as to when patients will benefit from an AVF.

Key Words: Arteriovenous Fistula; Vascular Access Devices; Hemodialysis; Vascular Surgical Procedures; Chronic Renal Insufficiency (Source: MeSH-NLM).

Introduction

Chronic Kidney Disease (CKD) is a pathologic condition resulting in a progressive decline of kidney function. It currently affects 7-12% of individuals globally, while its incidence is rapidly rising.[1-4] The disease involves structural pathology such as nephron loss and fibrosis, which result in decreased glomerular filtration.[5] These insults to the kidney contribute to systemic complications of CKD, including fluid and electrolyte abnormalities, anaemia, mineral-bone disorder, metabolic acidosis, hyperuricaemia, hypertension, dyslipidemia, cardiovascular disease and endocrine dysfunction.[5] Severity of the disease can be divided into five stages depending on estimated glomerular filtration rate (eGFR), with substantial loss of kidney function and end-stage renal disease (ESRD) comprising stages IV and V, respectively.[6-8] Renal replacement therapy is necessary once a patient has progressed to ESRD. Kidney transplants are ideal for renal replacement; however, they are not widely accessible. Consequently, hemodialysis (HD) is often the modality of choice for patients in ESRD.[9]

The process of HD clears the blood of uremic toxins using a series of pumps, membranes and dialysates. Patients undergoing this long-term therapy require permanent vascular access placement, as suggested by the Kidney Disease Outcomes Quality Initiative (KDOQI).[1,8,10] The three main types of vascular access include arteriovenous fistulae (AVF), arteriovenous grafts (AVG) and central venous catheters (CVC).[8] The current gold-standard for HD access is the formation of an AVF, as it is clinically reported to have better patient outcomes with reduced morbidity and improved survival.[8,10-13] AVFs are established in the forearm through surgical anastomosis of a relatively small, peripheral artery with a larger subcutaneous vein.[14] According to the KDOQI, the optimal timing for AVF creation is 6 months before cannulation, however this maturation can be affected by factors, such as age and gender.[8,11] In the case where a patient's vascular integrity does not support a fistula, an AVG can be implemented. Studies indicate that AVGs have more drawbacks compared to AVFs. These include higher infection susceptibility potentially resulting in sepsis, reduced patency, and greater risk of complications ultimately leading to repeated interventions and diminished survival.[15] CVCs, on the other hand, are generally employed prior to AVF or AVG maturation, when immediate initiation of HD is required. Infection and thrombosis among other life threatening complications, are persisting impediments.[16] For instance, Lee *et al*. noted that catheter-related bacteremia was present in half of all HD patients studied 6 months after CVC implantation.[17] Furthermore, HD patients with CVCs have a 3.43-fold increase in relative mortality risk compared to patients with an AVF.[17-19]

Therefore, AVFs are the gold standard method to attain vascular access in patients undergoing HD, as they result in fewer complications when compared to CVCs and AVGs.[8,10-13] However, to better maintain access sites and retain the integrity of the vasculature, radiocephalic AVFs (RCAVF) are the recommended option by the KDOQI, and are associated with improved patient survival.[12,20] In cases where the creation of a RCAVF is not feasible due to poor vasculature brachiocephalic, brachiobasilic, and brachiobrachial AVFs can be created.[21] In spite of the clear benefits provided by AVFs for HD patients, they do carry some drawbacks and can potentially pose a risk for serious complications requiring hospitalization.[22] The reported complications surrounding fistulas include aneurysm development, stenosis of the vein, dialysis-associated steal syndrome (due to ischemia), thrombosis, and infection.[22] Additionally, the primary failure rates of AVF formation and maturation are approximated at 23% and 20-60%, respectively.[1,23-25] Indeed, AVFs are a source of patient morbidity, however, they still remain the principal type of vascular access for HD compared to AVGs or CVCs.[8,21] To ensure its success, the timing of AVF creation relative to

[1] BSc, MSc, Medical student, School of Medicine University College Cork, Ireland.
[2] BMSc, PhD, School of Medicine, Royal College of Surgeons Ireland, Ireland.

About the Author: *Andrew is currently a final year medical student at University College Cork, Ireland (4/4 years). He has attained an academic standard of first-class honors throughout his studies.*

Correspondence:
Andrew Stanton Kucey
Address: [Institution of affiliation address]
Email: 116100312@umail.ucc.ie

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HD must be considered. As there exists a long lag time between AVF formation and usage, fistulas can be created in a pre-emptive manner to circumvent potential CVC access, if HD is required. Even so, if the AVF is not needed or not used for access by the patient, the surgical procedure to create the fistula can result in unwarranted patient distress.[1] Moreover, the average maturation time for an AVF falls between 148 to 285 days, with a 75% successful cannulation rate at 16 weeks (112 days) post-surgery.[1,25,26]

Taking the aforementioned factors into account, the temporally sensitive nature of this complex therapeutic intervention must be considered at the time of consultation. The time-course for formation of the fistula needs to be appropriately managed from initial patient referral to when the mature AVF will be needed. As the incidence of CKD rises, more patients will require renal replacement therapy and the creation of an AVF for HD. Therefore, it is imperative that we analyze and examine current practices to determine the best course of action.

Objectives

This review will analyze the literature on arteriovenous fistulas used for vascular access to determine the current paradigms on:

1) Outcomes regarding the patient after AVF creation
   i. The proportion of patients who end up on dialysis
   ii. The number of patients who require a central line due to AVF immaturity or failure
   iii. Whether the patient receives a transplant and avoids dialysis or dies before dialysis commencement
   iv. Estimated prognosis between AVF and non-AVF patients
2) Outcomes regarding the fistula itself
   i. Primary AVF patency, secondary AVF patency
   ii. Primary and secondary AVF failure
   iii. Fistula maturation times
3) Predictive factors for AVF outcomes
   i. Sex, morbidity, lifestyle, site of fistula
   ii. Vein diameter, arterial flow rate.

Methods

Search Strategy

An electronic search was conducted using the databases of Medline (PubMed) and Scopus. The search identified publications pertaining to the objectives and research question of the current study.

Medline (PubMed):
("arteriovenous fistula"[MeSH Terms]) OR ("arteriovenous"[All Fields] AND "fistula"[All Fields]) OR ("arteriovenous fistula"[All Fields] AND "creation"[All Fields] AND "blood vessels"[MeSH Terms]) OR ("blood"[All Fields] AND "vessels"[All Fields]) OR ("blood vessels"[All Fields]) OR ("vascular"[All Fields]) AND "access"[All Fields] AND "outcomes"[All Fields])

This search returned 171 results. The results were narrowed down to 61 publications after filtering for free, full-text, and again to 49 results after specifying for human studies. The inclusion and exclusion criteria were applied to the abstracts of the remaining 49 papers. This narrowed the search to 6 papers. The abstracts were screened by all three authors and conflicts regarding inclusion and exclusion were resolved through group meetings.

Scopus:
(arteriovenous AND fistula AND creation AND for AND vascular AND access AND outcomes)

This search returned 383 results. After filtering for open access publications, 65 papers remained. Filtering for human studies, English availability, articles, and reviews narrowed the results to 58. The remaining articles had their abstract subject to the inclusion and exclusion criteria. Nine publications were identified based on this, 5 of the papers overlapped with the Medline results.

In total, 10 articles were identified between the two database searches (***Figure 1***).

Study Eligibility:

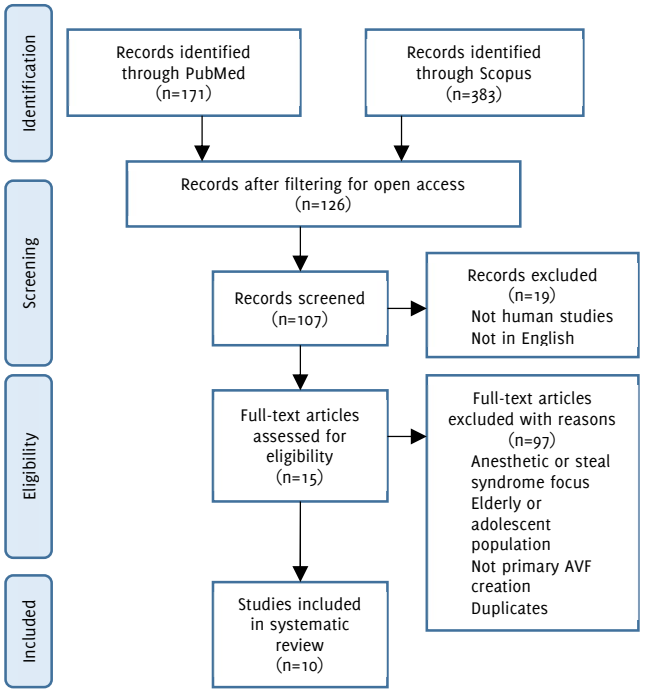
The inclusion and exclusion criteria were generated *a priori*. Studies were included if they addressed populations who underwent AVF creation for HD access, if primary patency or AVF maturation were mentioned in the abstract and if the authors reviewed the outcomes of their subjects after AVF creation. The selected manuscripts all present new data published in its first report and are not review papers.

Exclusion criteria specified studies carried out on non-human species, articles not available in English, and articles that were not available as Open Access. Additionally, papers addressing exclusively elderly or adolescent populations were removed. Finally, articles were excluded if the study evaluated endovascular fistula creation, focused primarily on anaesthetic technique or on steal syndrome, or if the study addressed AVF interventions and revisions rather than primary creation, it was excluded.

Definitions:

- Primary Patency – Time from AVF creation until thrombosis or until an intervention was required to maintain flow
- Secondary (cumulative) Patency – Time from AVF creation until abandonment
- Primary Assisted 1-year Patency – Measures whether the AVF was able to survive 1 year after cannulation with or without interventions
- Time to Maturation – Time from fistula creation until it is successfully cannulated
- Primary Failure – AVF was never suitable for dialysis cannulation
- Functional Primary Patency – Time from fistula cannulation until AVF failure or until the first intervention is required.

Figure 1. Flow diagram of study methodology with application of inclusion and exclusion criteria



Results

All of the papers identified by the search methods were assessed for their quality and validity using the Evidence-based librarianship (EBL) critical appraisal tool.[27,28] The abbreviated results are displayed in ***Table 1*** and the extended appraisal can be viewed in ***Appendix A***. All of the selected articles were deemed valid when applying the EBL criteria. [27] The methodology of all the papers identified to be eligible for review were adequate and minimized bias that the individual study may be susceptible to.

Patient Outcomes

A retrospective study looking at HD patients in Canada showed that 27% patients had at least one AV access created in a study population of 17,183 (***Table 2***).[29] Of the patients who had an AVF created, 65% were able to cannulate it for HD, while 33% had to resort to a CVC.[29] Of the patients who were referred late to a nephrologist, 8% had an AV access created as opposed to 39% who were referred early.[29] Prior to AVF creation, CVC use occurred in 35.7-77.4% of patients.[13,21,26,30,31] A study investigating the natural history of AVFs noted that 66% of vascular access procedures were to create an AVF, with 33% of these being RCAVFs.[26] Four studies reported that 48-75% of AVFs were being used for HD at the time of follow-up, while 37-51% of them were abandoned.[1,25,26,30,32] A study on pre-emptive AVF creation showed 49% of patients ended up on HD during their 10 month follow-up with 65% of these patients being dialyzed through their AVF.[1] This paper also reported that 23% of the patients never used their viable AVF for HD.[1]

A paper which assessed vascular access use since the dialysis outcomes and practice patterns study, found that 27% of Canadian and16% American HD patients were being dialyzed through an AVF.[13] This is in contrast to 72% of German and 69% of Japanese HD patients who utilized an AVF.[13] The proportion of HD patients using an AVG was highest in America at 15%, followed by Sweden at 9%.[13]

Table 1. Results of the EBL Critical Appraisal of selected articles for review.

Article	Population Validity Score (%)	Data Collection Validity Score (%)	Design Validity Score (%)	Results Validity Score (%)	Overall Score (%)
Al-Jaishi *et al* (2015)[29]	100	80	100	100	95
Biuckians *et al* (2008)[26]	75	80	100	100	90
Dageforde *et al* (2015)[30]	75	80	100	100	90
Ethier *et al* (2008)[13]	66	80	100	100	86
Kimball *et al* (2011)[1]	75	80	100	100	90
Korepta *et al* (2016)[21]	66	80	100	100	86
Lee *et al* (2012)[33]	66	80	100	100	86
Masengu *et al* (2016)[32]	75	80	100	100	90
Schinstock *et al* (2001)[31]	100	80	100	100	95
Wilmink *et al* (2016)[25]	100	80	100	100	95

AVF Outcomes

Four studies reported an average AVF maturation time of 148-285 days with a cumulative functional 1-year patency of 60-70%.[1,21,26,32] Primary failure was recorded in 3 studies and occurred in 20-26% of cases.[25,26,31] In one study, AVFs failed to mature 20% of the time.[30] Primary assisted 1-year patency was only measured in one study, and it was found to be 93-100%.[21] Complications occurred in 21.2% of AVFs and 54% of interventions occurred before maturation was achieved.[31] RCAVF were shown to have a higher primary failure rate but better overall survival than brachiocephalic and brachiobasilic fistulas.[25] When the AVFs were allowed to mature for 10 and 16 weeks, they had a 50% and 75% survival respectively upon cannulation.[25]

Pre-Operative Vasculature Status & AVF Outcomes

Dageforde *et al.* showed that minimum vein diameter is associated with lower risk for AVF failure.[30] Veins < 2.7 mm in diameter had > 33% failure to mature at 6 months.[30] A patent upper arm cephalic vein was shown to improve primary patency, secondary patency and maturation in patients undergoing RCAVF creation.[33] RCAVFs with arterial flow rates < 50 mL/min were shown to have a 7 fold increase in failure rate.[32] The flow rate was also shown to be a more sensitive marker than vein diameter when assessing failure to mature.[32]

Multivariate Analysis on AVF Outcome Predictors

Cox regression analysis associated female gender, being on dialysis at the time of AVF creation, and diabetes with worse AVF survival.[25] Dageforde *et al.* also showed that preoperative dialysis was associated with higher risk of AVF failure.[30] The study by Wilmink *et al.* also demonstrated that females were associated with higher primary failure and longer maturation times.[25] One study found that an age ≥ 65 years was an independent predictor of secondary AVF patency.[33] Those less likely to have an AVF created were females, as well as patients with a high number of comorbidities.[29] Gender was shown to be unassociated with primary or secondary patency by Schinstock *et al.*, however, body mass index (BMI), diabetes, AVF site, previous CVC use, and the diameter of the artery, were all associated with primary patency.[31] While diabetes did not have an association with secondary patency, increased age and thromboembolic disease status were related to secondary patency in addition to the aforementioned factors.[31] Kimball *et al.* found no relation between sex, BMI, smoking, age, race, fistula location and rate of AVF abandonment.[1] Another study failed to identify individual predictors of AVF failure from factors including smoking, age, sex, BMI, diabetes, hypertension and hyperlipidemia.[21] Finally, in a study looking at minimum vein diameter for AVF outcome prediction, coronary artery disease was associated with a lower risk of AVF failure overall.[30]

Discussion

This systematic review intends to combine recent investigations on outcomes of patients who are referred for AVF creation. The outcomes were subdivided into those that pertained to patient prognosis and those that measured the success of the AVF itself. The findings of this review suggest that patients are not being referred at an adequate time for AVF creation based on current KDOQI guidelines as 33.5-77.4% of patients are requiring a CVC use before they are using their AVF for HD.[8] Even once an AVF was made, 33-51% of the patients still ended up on a CVC for HD due to AVF immaturity or failure.[1,25,26,29,30,32]

There were vast differences between countries in regards to the uptake of the KDOQI recommendations for AVF implementation. These guidelines suggest that 65% of HD patients should be using a fistula for their HD sessions.[8,29] Only 27% and 16% of HD patients from Canada and USA, respectively, were being dialyzed through an AVF.[13] In contrast, 72% of German and 69% of Japanese HD patients were using an AVF.[13] These stark contrasts between nations may reflect local policies regarding healthcare or surgical preference, as 15% of American HD patients were using AVGs, while the next highest country was Sweden with 9%.[13] The level of access to vascular surgeons may also impact results across regions. This is especially applicable to the Canadian and American healthcare systems which have some of the longest wait times between AVF consultation and AVF creation.[13,34] Encouragingly, the use of AVFs is on the rise in most countries while the use of AVGs is on the decline[13] Between 1996 and 2007, the largest changes occurred in the US where the use of AVFs jumped from 24% to 47%, while AVG usage dropped from 58% to 29% in HD patients.[13] Despite the numerous drawbacks of an AVF procedure, it is still the best option of the available AV access modalities, and the literature supports its utility in terms of patient prognosis over AVGs and CVC.[8,35]

Table 2. Summary of reviewed publications, arranged alphabetically.

Authors and Location	Title	Objectives	Study Design	Sample Size	Population	Key Findings
Ahmed A. Al-Jaishi, Charmaine E. Lok, Amit X. Garg, Joyce C. Zhang, Louise M. Moist (2015). London, Canada.[29]	Vascular access creation before hemodialysis initiation and use: a population-based cohort study	To assess how many patients had AV access before HD To elucidate secular trends in AV access To estimate the effect of referral time on AV access creation	Retrospective population-based cohort study	n = 17,183	The study population consisted of adults who used HD as their first modality for renal replacement therapy between January 1, 2001 and December 31, 2010	27% of patients had at least one AV access created with a median time of 184 days between the procedure and HD commencement 65% of patients with an AV access were able to use it for dialysis, while 33% still had to use a CVC From 2001-2010 there was a decline in AV access creation before HD commencement; 32% to 22% ($P < 0.001$) 8% of patients with a late referral to nephrology had an AVG or AVF created, compared to 39% with an early referral
Andre Biuckians, Eric C. Scott, George H. Meier, Jean M. Panneton, Marc H. Glickman (2008). Norfolk, USA.[26]	The natural history of autologous fistulas as first-time dialysis access in the KDOQI era	To determine the natural history of AVFs in first time vascular access patients	Retrospective chart review	n = 80	The study population consisted of all patients undergoing their first AVF creation from January 1, 2005 until June 30, 2005 in a single vascular practice	75% of AV access candidates had prior CVC HD use 67% of first-time access patients had an AVF created, 33% had an AVG 33% received an RCAVF, 67% had a BCAVF. Time to first cannulation was significantly shorter in BCAVF than RCAVF (P=0.03) 48% of AVF were being used for HD at follow up (mean time of 278 days), and 11% matured without intervention Average maturation time was 148 days, cumulative functional patency at 1 year was 63% 48% of AVFs were being used for HD 37% of the AVFs were abandoned, 20% being from primary failure
Leigh Anne Dageforde, Kelly A. Harms, Irene D. Feurer, David Shaffer (2015). Nashville, USA.[30]	Increased minimum vein diameter on preoperative mapping with duplex ultrasound is associated with arteriovenous fistula maturation and secondary patency	To determine whether vein diameter measured by preoperative duplex ultrasound is associated with fistula maturation and secondary patency	Retrospective chart review	n = 158	The study population consisted of patients who had an AVF created from February 2009 until June 2011	Larger minimum vein diameter was associated with lower risk for AVF failure Greater than 33% of veins < 2.7mm failed to mature at 6 months Multivariate analysis showed that for every 1mm increase in minimum vein diameter, the risk of failure to mature was reduced by 45% and there was a 36% reduction in risk of fistula failure (HR, 0.555; P=0.005 & HR, 0.639; P=0.001 respectively) 20% of fistulas failed to mature 53% of fistulas were used for HD within the study period 49% of patients had prior tunnelled catheter use for HD
Jean Ethier, David C. Mendelssohn, Stacey J. Elder, Takeshi Hasegawa, Tadao Akizawa, Takashi Akiba, Bernard J. Canaud, Ronald L. Pisoni (2008). Ann Arbor, USA.[13]	Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study	To describe changes in vascular access trends since the dialysis outcomes and practice patterns study (DOPPS)	Retrospective review of a prospective database	DOPPS I n = 16402 DOPPS II n = 12839 DOPPS III n = 7921 n = 37,162	The study population was HD patients at participating centres from: France, Germany, Italy, Japan, Spain, the USA and the UK in DOPPS I. Centres in Australia, Belgium, Canada, Sweden and New Zealand were added for DOPPS II and III.	In the interval between DOPPS I and DOPPS III, the use of AVFs in the USA increased from 24% to 47%. AVF use also increased in the UK, Australia, and New Zealand Spain, Italy and Germany saw their AVF use decline AVG use declined in all countries, the largest fall was 58% to 29% in the USA CVC use increased in Europe, Canada and the USA from DOPPS I to III; 50% of patients from DOPPS II initiated HD with a CVC 35.7% of patients used a CVC if they had seen a nephrologist ≥ 4 months prior to HD start, as opposed to 77.4% who were seen < 1 month prior to HD Patients with longer wait times for surgical referral and evaluation had lower odds of initiating HD with an AVF (AOR 0.89 per 5 days longer; P<0.0001)

Authors and Location	Title	Objectives	Study Design	Sample Size	Population	Key Findings
Traci A. Kimball, Ken Barz, Kelly R. Dimond, James M. Edwards, and Mark R. Nehler (2011). Denver, Colorado and Portland, Oregon, USA.[1]	Efficiency of the kidney disease outcomes quality initiative guidelines for preemptive vascular access in an academic setting	To determine the efficiency of prophylactic AVF for HD To determine the incidence of HD within late stage CKD patients To determine AVF functional patency and morbidity within study population	Retrospective chart review	n = 150	The study population was comprised of late stage CKD patients who underwent pre-emptive AVF creation across 2 academic centers.	Median time from surgical consultation to AVF creation was 31 days (min, max; 1, 400) At 10-month follow-up, 49% of patients were on HD and 65% of them were using their AVF 35% of patients on HD who were not using their AVF did not have AVF failure 23% never initiated HD but had a viable AVF, 28% never went on HD and also abandoned their AVF Mean maturation time for AVFs being used for HD was 285 days Incidence of AVF abandonment was 51%
Lindsey M. Korepta, Jennifer J. Watson, Erin A. Elder, Alan T. Davis, M. Ashraf Mansour, Christopher M. Chambers, Robert F. Cuff, Peter Y. Wong (2016). Grand Rapids, USA.[21]	Outcomes for forearm and upper arm arteriovenous fistula creation with the transposition technique	To examine the rates of complication, failure, maturation, and patency in forearm cephalic vein (FACVT), upperarm cephalic vein (UACVT), and upper arm basilic vein transpositions (UABVT) for AVF creation	Retrospective chart review	n = 165	All patients undergoing AVF creation via FACVT, UACVT, or UABVT from January 1, 2006 until December 31, 2012.	57% of patients were using a tunneled CVC for HD before AVF creation Average vein diameter was 3.2mm to 3.9mm No significant differences between groups in terms of time to maturation, primary 1-year patency (63-70%), or primary assisted 1-year patency (93-100%) 84% of FACVT, 88% of UACVT, and 86% of UABVT patients were able to use their AVF Average time to cannulation from when the AVF was created was 9.9±4.7 weeks
J.H. Lee, J.H. Won, C.K. Oh, H.A. Jung (2012). Suwon, Republic of Korea.[33]	Clinical significance of upper-arm cephalic vein patency in autogenous radio-cephalic wrist fistulas for hemodialysis	To determine the role of upper-arm cephalic veins in RCAVF clinical outcomes	Retrospective chart review	n = 183	The study population included consecutive patients having an RCAVF created from March 2003-February 2009. Patients were divided into two groups depending on their upper-arm cephalic vein; stenosed or occluded were group B, group A had a patent lumen.	Multivariate analysis showed upper arm cephalic vein status to be a predictor of primary and secondary patency in RCAVFs ($P<0.005$) Maturation failure within 8 weeks was significantly higher in group B (26.7% vs. 9.8% in group A; $P<0.009$) Group A had significantly longer mean primary patency ($P=0.011$), however secondary patency was not significantly different between groups A and B Overall primary patency and secondary patency were both significantly greater in group A than B ($P<0.0001$)
Agnes Masengu, James McDaid, Alexander P. Maxwell, Jennifer B. Hanko (2016). Belfast, UK.[32]	Preoperative radial artery volume flow is predictive of arteriovenous fistula outcomes	To determine whether pre-operative ultrasound analysis of vessels can predict AVF outcomes	Retrospective cohort study	n = 152	The study population consisted of all patients from a single center who underwent AVF creation after ultrasound mapping of their blood vessels (from August 2011-December 2014).	RCAVFs with arterial flow less than 50ml/min failed to mature 7 times more often than those with higher flow rates ($P<0.001$) Radial artery volume flow < 50ml/min is a more sensitive measure for fistula failure to mature than mean vessel diameter of < 2.7mm 69% of the AVFs were functionally patent, 60% of the AVFs achieved primary patency 45% of AVFs failed to mature and were abandoned Females were associated with higher AVF failure to mature
Carrie A. Schinstock, Robert C. Albright, Amy W. Williams, John J. Dillon, Eric J. Bergstralh,	Outcomes of arteriovenous fistula creation after the fistula first initiative	To determine the outcomes of AVFs created at a single clinic and factors that predict their patency	Retrospective cohort study	n = 293	The study population was comprised of patients over 18 years old who were undergoing their first AVF	50.5% of AVFs were created after HD commencement Kaplan-Meir survival at 3, 6, 12, and 18 months for primary patency was 67%, 50%, 41%, and 30%; secondary patency was 92%, 86%, 77%, and 73% respectively

Authors and Location	Title	Objectives	Study Design	Sample Size	Population	Key Findings
Bernice M. Jenson, James T. McCarthy, Karl A. Nath (2011). Rochester, USA.[31]					creation the Mayo Clinic.	Univariate analysis showed arterial diameter predicts the primary and secondary AVF patency (HR, 0.83; 95% CI, 0.73 to 0.94 and HR, 0.67; 95% CI, 0.55 to 0.82 respectively) Multivariate analysis showed that diabetes increased the risk for lower primary patency (HR, 1.45; 95% CI, 1.06 to 1.99) and arterial diameter significantly influenced secondary patency (HR, 0.69; 95% CI, 0.56 to 0.84) Primary failure occurred in 26% of AVF 21.2% of AVF incurred a complication, and 54% of interventions happened before it was viable for HD
T. Wilmink, L. Hollingworth, S. Powers, C. Allen, I. Dasgupta (2016). Birmingham, UK.[25]	Natural history of common autologous arteriovenous fistulae: consequences for planning of dialysis access	To determine primary failure, maturation times, and survival of common AVFs in order to aid future AVF planning	Retrospective longitudinal cohort study	n = 1,206 fistula operations	The study population consisted of patients undergoing AVF creation at a single centre from December 1, 2002-December 31, 2011.	Primary failure occurred in 23% of AVFs in the study; 75% were needled for dialysis and 74% were functional RCAVFs had better survival than other AVFs, leading to more cumulative dialysis time Pre-dialysis AVF creation resulted in better AVF survival 10 weeks of maturation should be allowed before commencing dialysis on an AVF for 50% survival, 16 weeks for 75% survival Irrespective of age, the best available option is RCAVF creation 4 months before estimated dialysis commencement date

Regarding the fistulas themselves, the results of this study are consistent with what was reported in a meta-analysis by Al-Jaishi *et al.*, in 2014.[24] They reported a primary patency of 60% at 1 year and 51% at 2 years. Secondary patency was 71% and 64% at one and two years, respectively.[24] The pooled primary failure from the same study was 23%.[24] The current study found primary patency to be 60-70% while primary failure ranged from 20-26%. Secondary patency was difficult to estimate due to variations in reporting between the different publications. However, the abandonment rate for the fistulas ranged from 37-51%, which leads to the conclusion that the secondary patency may be lower in this review.

The success of AVFs can be predicted by multiple factors but the most accurate methods reviewed in this study are preoperative arterial flow rate and minimum vein diameter measurements.[30,32] Both of these parameters had high predictive capability compared to factors such as sex, age, morbidity status, lifestyle factor and fistula site.[30,32] Other than arterial flow rate and vein diameter, there was discordance between the publications as to whether other factors correlated with AVF outcomes or not.

All publications included in this review were deemed valid using the EBL critical appraisal tool. Using this method, a threshold of ≥ 75% of the specified criteria was necessary for validity in each individual section and cumulatively, in the individual articles. The lowest overall score was 86%, which was calculated for 3 different studies.[13,21,33] The main area of methodological concern arose from population validity. Three studies were found to have assessed a poorly representative population, as all of them attained a score of 66%. Problematic areas for the population validity were: a small sample size, lack of clearly defined exclusion and inclusion criteria, and no randomization of subjects in comparative studies. For the rest of the validity calculation, all studies were found to be diligently designed other than the pervasive theme of ambiguity regarding whether the investigators played a role in delivering a service to the target population or not.

The articles included in this study were stringently examined using a standardized appraisal tool, reducing bias in calculating the validity of the selected publications. The limitations of this study are that there were only two databases used to identify publications to be included in the review. The database search was only carried out by one investigator which leaves the possibility for selection and reporting bias. This review is limited by an English availability filter used in the database search. The free-full text filter may have removed potentially relevant articles.

Future studies should be directed to the application of preoperative vasculature assessment for prediction of AVF outcomes. Further investigation into the reasons for late referrals to nephrology and vascular surgery in ESRD patients would also be beneficial. Finally, examining the rate of eGFR decline in patients to try and make standardized recommendations for when to refer them for AVF consultation based on their diminishing renal function could provide important and topical data.

Conclusions

The gold standard for vascular access is still the AVF. With the aging global population, there will be an increasing demand for dialysis, which necessitates better standardization regarding patient referral for AVF creation. There are large variations in vascular access use between countries, despite HD patients faring much better when being dialyzed through an AVF as opposed to AVGs or CVCs. A concerted effort is required to try and meet the KDOQI guidelines for timely vascular access creation, improved AVF function and enhanced patient survival.

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Appendix

Appendix A. Full EBL Critical Appraisal Checklist for all articles included in review.

EBL Critical Appraisal Checklist[27]		Al-Jaishi *et al* (2015)[29]	Biuckians *et al* (2008)[26]	Dageforde *et al* (2015)[30]	Ethier *et al* (2008)[13]	Kimball *et al* (2011)[1]	Korepta *et al* (2016)[21]	Lee *et al* (2012)[33]	Masengu *et al* (2016)[32]	Schinstock *et al* (2001)[31]	Wilmink *et al* (2016)[25]
Section A: Population	Is the study population representative of all users, actual and eligible, who might be included in the study?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	Are inclusion and exclusion criteria definitively outlined?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
	Is the sample size large enough for sufficiently precise estimates?	Y	N	Y	Y	N	N	N	N	Y	Y
	Is the response rate large enough for sufficiently precise estimates?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the choice of population bias-free?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If a comparative study: a) Were participants randomized into groups? b) Were the groups comparable at baseline? c) If groups were not comparable at baseline, was incomparability addressed by the authors in the analysis?	N/A	N/A	N/A	N Y N/A	N/A	N Y N/A	N Y N/A	N/A	N/A	N/A
	Was informed consent obtained?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Section A validity:	100%	75%	75%	66%	75%	66%	66%	75%	100%	100%
Section B: Data Collection	Are data collection methods clearly described?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
	If a face-to-face survey, were inter-observer and intra-observer bias reduced?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the data collection instrument validated?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	If based on regularly collected statistics, are the statistics free from subjectivity?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Does the study measure the outcome at a time appropriate for capturing the intervention's effect?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the instrument included in the publication?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Are questions posed clearly enough to be able to elicit precise answers?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Were those involved in data collection not involved in delivering a service to the target population?	U	U	U	Y	U	U	U	U	U	U
	Section B validity:	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%
Section C: Design	Is the study type / methodology utilized appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there face validity?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the research methodology clearly stated at a level of detail that would allow its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was ethics approval obtained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are the outcomes clearly stated and discussed in relation to the data collection?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Section C validity:	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Section D: Results	Are all the results clearly outlined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are confounding variables accounted for?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Do the conclusions accurately reflect the analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is subset analysis a minor, rather than a major, focus of the article?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are suggestions provided for further areas to research?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there external validity?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Section D validity:	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Overall Validity Score:		95%	90%	90%	86%	90%	86%	86%	90%	95%	95%

Legend: Y, N, U, N/A

Calculation for section validity: (Y+N+U=T): If Y/T <75% or if N+U/T > 25% then you can safely conclude that the section identifies significant omissions and that the study's validity is questionable. It is important to look at the overall validity as well as section validity.

Calculation for overall validity: (Y+N+U=T): If Y/T .75% or if N+U/T , 25% then you can safely conclude that the study is valid.

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Review

The Role of Intraindividual Carotid Artery Variation in the Development of Atherosclerotic Carotid Artery Disease: A Literature Review

Shawn Stefan Albers,[1] Andrew Stanton Kucey,[1] Anish Engineer.[2]

Abstract

Carotid artery disease (CAD) is associated with numerous risk factors, including hypertension, hyperlipidemia, hypercholesterolemia, diabetes mellitus, and smoking. In most patients, these systemic risk factors do not affect the carotid arteries equally, resulting in asymmetrical CAD. It is unclear if anatomic variations in the carotid arteries predispose an individual to formation of atherosclerotic CAD. Therefore, we wanted to assess (1) the inter-individual or intra-individual anatomical variations in the carotid arteries and (2) whether anatomical variations predispose the development of atherosclerotic CAD. We searched Medline and Scopus over the past 20 years as well as included article bibliographies. Two investigators independently screened abstracts and full-text articles; extracted data and assessed risk of bias. We included full-text primary articles that evaluated anatomical characteristics and the presence of CAD. A total of 8 articles were selected using the search parameters and an additional two articles were included after reviewing references of relevant papers. Evidence suggests that a low outflow/inflow ratio, elevated bifurcation height, and bifurcation angle are associated with increased risk for CAD. Additionally, tortuosity and kinking of the carotid arteries may affect the formation of CAD but coiling of the arteries which is a natural age-dependent process, does not affect CAD development. This review suggests there are anatomic variations in the carotid arteries that increase the risk of developing carotid artery disease. The most significant risk factors include a low outflow/inflow ratio, increased internal carotid artery tortuosity, elevated bifurcation height, and bifurcation angle.

Key Words: CT carotid angiogram; Carotid artery disease; Carotid bifurcation; Carotid artery anatomy; Carotid stenosis (Source: MeSH-NLM).

Introduction

Carotid artery disease (CAD) is a vascular disease characterized by progressive narrowing of the blood vessel lumen due to atherosclerotic plaque deposition within the subendothelial lining.[1] CAD is a leading cause of stroke, which is the third leading cause of mortality worldwide.[2] Systemic risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and smoking contribute to the formation of atherosclerotic plaques.[3] Local factors such as hemodynamics and shear stress also influence plaque formation, thus displaying the multi-faceted pathogenesis of CAD.[4] Atherosclerosis is regarded as a systemic disease, however, there is significant intraindividual variation in the extent to which the carotid arteries are affected.[5,6] This suggests that there may be intraindividual features that predispose a particular artery to develop CAD.[7]

Blood vessel anatomy and geometry have a marked effect on both the initial formation of atherosclerotic plaques and the development of CAD.[8] Atherosclerotic plaques preferentially deposit around the carotid bifurcation,[9] disrupting blood flow in all directions and thereby contributing to the pathogenesis of CAD.[10] A reduced outflow/inflow ratio, which compares the external carotid artery (ECA) and internal carotid artery (ICA) diameters to the common carotid artery (CCA), is an important indicator of plaque formation. A lower ratio can lead to reduced wall shear stress and an increased risk of endothelial damage, which would precipitate atherosclerotic CAD.[11] It has been previously shown that the optimal ratio is 1.15; deviation from this can increase the risk of endothelial damage leading to atherosclerotic plaque formation.[12]

Initial atherosclerotic lesions occur early in fetal life, but do not have significant effects during childhood.[13] Formation of these lesions depends on factors such as maternal hypercholesterolemia, susceptibility of the arteries, and numerous genetic factors.[13] Aging coincides with marked increases in stress and anatomical changes in the carotid arteries.[14] Increases in vessel diameter and tortuosity of the carotid arteries have been associated with normal aging and disease progression.[14] Age-related degradation and fragmentation of the stabilizing elastin protein plays a role in the structural alterations seen in the carotid arteies.[15] Interestingly, there is inter-ethnic variation of atherosclerotic plaque development at the carotid bifurcation, with blacks displaying a lower prevalence compared to Caucasians and Hispanics. This remains consistent in populations of blacks with an elevated vascular disease risk profile.

Although there are many known risk factors for the development of atherosclerotic CAD, both locally and systemically, many of these fail to address the presence of asymmetrical CAD within the same individual. This knowledge gap is important as it limits potential therapeutic interventions that would prevent CAD in certain populations. A comprehensive explanation for the presence of asymmetrical CAD is therefore needed to better understand the development and pathological progression of this disease. The aim of this review is to answer 2 key questions: Are there inter-individual or intra-individual anatomical variations in the carotid arteries? Do carotid artery anatomical variations predispose individuals to the development of atherosclerotic CAD?

[1] BSc, MSc, University College Cork, School of Medicine, Ireland.
[2] BMSc, PhD, Royal College of Surgeons in Ireland, School of Medicine, Dublin, Ireland.

Correspondence:
Shawn Stefan Albers
Address: Gaol Walk, University College, Cork, T12 YN60, Ireland.
Email: salbers@uwo.ca

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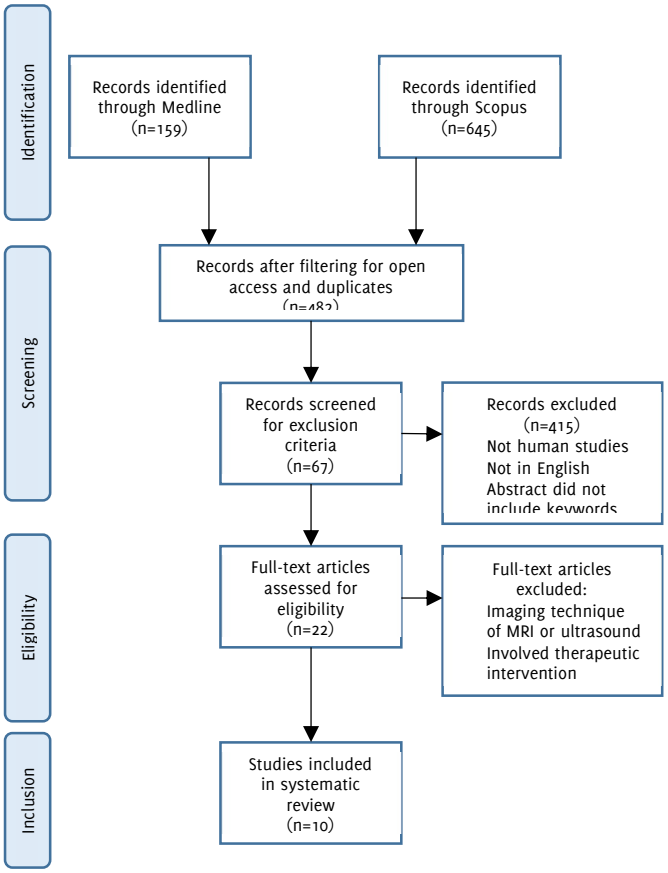
Patients and Methods

Literature Search Strategy

An electronic search was conducted on Scopus and Medline (PubMed) to identify relevant publications investigating anatomical factors that may contribute to CAD. The following search parameters were used: "(Carotid artery diseases) AND (diagnostic imaging OR cerebral angiography) AND (anatomy OR anatomic) AND bifurcation". Only studies involving humans, written in English and published in the past 20 years were considered for inclusion. The initial search resulted in 645 journal articles. By selecting articles published in the last 20 years, another 215 articles were excluded. Another 29 and 16 journals were eliminated by filtering out non-English and non-human studies, respectively. This yielded 385 articles for further screening (***Figure 1***).

Using identical parameters as mentioned previously, a second search was conducted on Medline which yielded 159 articles. Filtering for articles published over 20 years ago eliminated 22 results. Another 3 and 24 articles were removed by including only journals published in English and human studies respectively. The total number of articles collected on Medline was 110 (***Figure 1***).

Figure 1. Flow diagram of study methodology with application of inclusion and exclusion criteria.



The 385 Scopus and 110 Medline articles were combined on EndNote and 13 duplicates were removed. Using the exclusion criteria listed below, 482 articles were reduced to 67. These abstracts were independently reviewed by two investigators (SA, ASK) the titles and abstracts for imaging technique, therapeutic intervention, and diagnostic imaging. In total, 22 full articles were carefully reviewed by two investigators (SA, ASK) and 8 articles were included in the study from Scopus and Medline searches. Any discrepancies between the two investigators were resolved using a third investigator (AE). Additionally, the authors reviewed the bibliographies of the relevant articles included in this manuscript. An additional two articles were reviewed and selected for inclusion (***Figure 1***).

Eligibility criteria

Studies were excluded based on the following parameters: abstracts not containing the word "carotid"; abstracts not containing the words "anatomy or anatomical or geometry; articles using MRI or Ultrasound as their main imaging modality; articles that investigated a therapeutic intervention. Inclusion parameters included: articles studying the anatomy or geometry of the carotid bifurcation; articles studying the anatomy or geometry of the internal carotid artery, external carotid artery and/or common carotid artery; and articles using Computed Tomography (CT) scans.

Data Extraction

The following information was extracted from each article: Objectives; population demographic including mean age and range, and sex; sample size; methods and selection criteria; key findings; results; strengths and limitations.

Results

Anatomical risk factors for CAD

Five studies, summarized in ***Table 1***, focused on inter-individual and intra-individual anatomical variations at the carotid bifurcation in patients with CAD. The outflow/inflow ratio ranged from 0.38 to 1.28 between individuals, while 42% of patients with unilateral CAD had greater than 25% side-to-side difference in outflow/inflow ratio ($P<0.0001$).[17] There was a positive linear relationship between the ICA angle and degree of ICA stenosis (OR, 1.05 per degree increment).17 An ICA angle of greater than 31.50 correlated with greater ICA stenosis.[18] Another study showed a positive correlation between bifurcation angle and bifurcation height, with a 3.340 increase in the angle for each 1/3 vertebral body elevation of the origin of the carotid bifurcation ($P<0.01$).[19] Contradictory evidence from Kemenskiy et al., showed a bifurcation angle of 25.360 9.16 in CAD and 47.770 25.61 in non-CAD patients ($P=0.01$).[20]

25% of patients with atherosclerotic CAD had a positive correlation between kinking of the ICA and high bifurcation height, whereas only 3.2% of patients showed ICA kinking with medium and low bifurcation height ($P<0.01$).19 ICA kinking and coiling was present in 20% of patients with CAD, with 80% presenting bilaterally and 20% unilaterally. Kinking was associated with aging, and patients greater than 55 years old have been shown to be at an elevated risk of this anatomical variation.[21]

Demographic variation in carotid anatomy and CAD

Four studies summarized in ***Table 2*** investigated the demographic differences in carotid anatomy in both healthy and CAD patients. ICA stenosis was independently associated with age (OR, 1.05 per year increment), male sex (OR, 1.72) and current or past smoking history (OR, 1.85).18 Males were more likely to have a point of maximal stenosis in the ICA (OR, 2.29, $P=0.001$), however, women were more likely to have ECA stenosis (OR, 1.54, $P<0.0001$) and a higher outflow/inflow ratio (0.77 F, 0.71 M, $P<0.001$).[22]

Neonates did not have marked differences in outflow/inflow ratios or carotid artery diameter when comparing males and females.[23] For every decade of life increase there were concurrent increases in: carotid bulb diameter (0.64mm), ICA tortuosity (0.04), CCA tortuosity (0.03) and bifurcation angle of 100 ($p<0.05$).20 These geometrical changes correlated with degradation and fragmentation of intramural elastin.20 Tortuosity was most accurately measured using 3D reconstructed CT angiograms, using a computer generated curved length (CL) with a multi-planar measured and calculated straight-length diameter (SLD).[24] African Americans had a lower ICA/CCA ratio ($P<0.01$) compared to Caucasians and Hispanics, however there was no significant difference in outflow/inflow ratio between the three race-ethnic groups ($P>0.05$).[25]

Carotid bifurcation anatomy and CAD pathogenesis

The final study, summarized in ***Table 3***, investigated the association between carotid bifurcation and pathogenesis of CAD. There was no significant difference between the outflow/inflow ratio between the asymptomatic (0.72) and symptomatic (0.71) sides ($p=0.95$).

Furthermore, there was no association between bifurcation anatomy and plaque ulceration, with an outflow/inflow ratio of 0.69 in ulcerated plaques and 0.72 in non-ulcerated plaques (p=0.06).[26]

Each of the 10 selected journal articles were critically appraised using the EBL criteria, with the results summarized in ***Table 4***. The studies had overall validity scores that ranged from 78.2 to 88.0% (***Appendix 1***). The numerical and statistical values of each study are summarized in ***Appendix 2.***

Table 1. Anatomic risk factors for the development of CAD.

Author, Date, Location, Title	Objectives	Type of study, Sample size	Mean Age (Range)	Sex, %	Methods, Selection criteria	Key findings	Strengths/Limitations
Schulz U.G.R. and Rothwell P.M. (2001) UK[17] Major Variation in Carotid Bifurcation Anatomy A Possible Risk Factor for Plaque Development	Assess the extent of variation of the carotid bifurcation between and within individuals	Retrospective Cohort Study Sample size = 3018	Unknown	Unknown	Measured arterial diameters of the ICA, ECA, CCA and bulb and calculated ratios from CT angiograms **Inclusion criteria:** <30% ICA or CCA stenosis **Exclusion criteria:** >30% ICA or CCA stenosis	Large variation between individuals: ECA range between 0.5 to 1.3x size of ICA. Outflow area range from 62% less to 28% more than Inflow area Intra-individual variation: 42% of people had >25% asymmetry in outflow/inflow between left and right carotids.	**Strengths:** Large population from multiple centers around Europe Clear inclusion exclusion criteria Use of ratios allowed for consistent analysis of different CT angiograms **Limitations:** Biased population of predominately elderly with established vascular disease. Single observer with a Jeweler's eyepiece, not computerized. Different CT angiogram quality and technique within database
Phan T.G., et al (2012) Australia[18] Carotid Artery Anatomy and Geometry as Risk Factors for Carotid Atherosclerotic Disease	Assess the relationship between carotid artery anatomy and geometry and ICA stenosis	Case-control Study Sample size = 178	68.4 (unknown)	M, 65%	Bifurcation and vessel angles and vessel radii were measured from 3D reconstructed segmented CT angiograms. **Inclusion criteria:** Patients with established carotid artery disease. **Exclusion criteria:** Unknown	Positive linear relationship between ICA angle and degree of ICA stenosis. Increase in angle showed increased ICA stenosis. ICA angle >31.3° correlated with ICA stenosis. ICA radius was an independent predictor of ICA stenosis.	**Strengths:** Large sample size of patients with established carotid artery disease. Measurement protocol had multiple controls to limit variability. 3D reconstruction software used for consistency. **Limitations:** Selection bias of patients with high vascular risks.
Kamenskiy A.V., at al (2015) Nebraska[20] Age and disease-related geometric and structural remodeling of the carotid artery	Assess if age-related carotid artery geometry changes affect the development of atherosclerotic carotid artery disease	Prospective Cohort Study Sample size = 32	Healthy 43 (15-64) Unilateral CAD 68 (49-86)	Healthy M, 40% Unilateral CAD M, 70%	Carotid artery diameter, tortuosity and bifurcation angle were measured in 3D reconstructed CT angiograms. **Inclusion criteria:** Patients with unilateral carotid artery disease. **Exclusion criteria:** Patients with bilateral carotid artery disease	For every decade of life increases in bulb diameter (0.64mm), bifurcation angle (10°) and tortuosity of the ICA and CCA. Larger bulb diameter, smaller bifurcation angle, increased tortuosity of CCA, and reduced tortuosity of ICA are seen in CAD vs non-diseased. Geometrical changes correlated with degradation and fragmentation of intramural elastin.	**Strengths:** Correlated findings with histological elastin-staining to assess structural changes. 3D reconstruction and computerized measurements increased accuracy. **Limitations:** Type 1 error due to low sample size. Did not follow patients over time (longitudinal study to assess effect of aging).

Author, Date, Location, Title	Objectives	Type of study, Sample size	Mean Age (Range)	Sex, %	Methods, Selection criteria	Key findings	Strengths/Limitations
De Syo S., Franjic B.D., Lovricevic I., Vukelic M. and Palenkic H. (2004) Croatia[19] Carotid Bifurcation and Position and Branching Angle in Patients with Atherosclerotic Carotid Disease	Assess the correlation between carotid bifurcation height and angle in the neck in carotid artery disease patients	Cross-sectional Study Sample size = 154	Male 57.2 (24-76) Female 58.4 (27-79)	M, 75%	154 bi-plane orthogonal aortic arch arteriograms were obtained from symptomatic carotid artery disease patients and bifurcation height in relation to cervical spine and bifurcation angle were measured. **Inclusion criteria:** Symptomatic carotid artery disease patient. **Exclusion criteria:** fully Occluded bifurcation and poor imaging	Positive correlation between bifurcation height and branching angle. The bifurcation angle increases 3.34° for each 1/3 vertebral body elevation of bifurcation height	**Strengths:** Used a standardized and accepted method of measuring bifurcation height. Large range of patient ages (24-79). **Limitations** Statistical analysis was not included in methods. Outdated, non-computerized method of bifurcation angle measurement. Confounding variables such as degree of carotid artery disease on anatomy and geometry not taken into consideration.
Cappabianca S., Somma F., Negro A., Rotondo M., Scuotto A. and Rotondo A. (2016) Italy[21] Extracranial internal carotid artery: anatomical variations in asymptomatic patients	Assess anatomical variations in the ICA and estimate the prevalence within the sample population	Prospective Cohort Study Sample size = 316	64 (37-81)	M, 54%	ICA anatomy and deformities were assessed using CT angiography and MRI. **Inclusion criteria:** All patients with angiograms performed. **Exclusion criteria:** Patients with metal devices. Equivocal interpretation.	CT angiograms detected 100% of ICA abnormalities, MRI detected 89.9%. Kinking/coiling of ICA was present in 20.7% of patients. Kinking in patients › 55 years old. Coiling in patients ‹ 37 years old.	**Strengths:** All images independently evaluated by radiologist. Compared accuracy of MRI to CT angiogram. **Limitations:** Area of further research not stated Presence of carotid artery disease not reported Effect of age on anatomical variation not discussed

Table 2. Demographic variations in carotid artery anatomy in patients with and with CAD.

Author, Date, Location, Title	Objectives	Type of study, Sample size	Mean Age (Range)	Sex, %	Methods, Selection criteria	Key findings	Strengths/Limitations
Schulz U.G.R. and Rothwell P.M. (2001) UK[22] Sex Differences in Carotid Bifurcation Anatomy and the Distribution of Atherosclerotic Plaque	Assess any anatomical variation at the carotid bifurcation between sexes	Retrospective Cohort Study Sample size = 3018	Male 62.1 (unknown) Female 62.3 (unknown)	M, 72%	Vessel diameters at disease free areas were measured on CT angiograms and ICA/CCA, ECA/CCA, ICA/ECA, bulb/CCA and outflow/inflow ratios were calculated. **Inclusion criteria:** Angiograms with ‹50% stenosis. Contralateral vessels with no disease. **Exclusion criteria:** Angiograms with ›50% stenosis.	Average ICA/CCA, ICA/ECA and outflow/inflow were larger in women vs men. Lower average outflow/inflow ratio in men. Women showed more stenosis in ECA, men had more stenosis distal to carotid bulb.	**Strengths:** Large population from multiple centers around Europe. Ratios eliminate magnification difference in CT angiograms. Exclusion criteria eliminated much of the effect of atherosclerotic disease on anatomy. **Limitations:** Uneven populations (2168 male, 850 female). CT angiograms from different centers with different techniques and skills. Anatomical study should only involve non-atheromatous individuals. Single observer with Jeweler's eyepiece for measurement.
Sehiril U.S., Yalin A., Tulay C.M., Cakmak Y.O. and Gurdal E. (2005) Turkey[23] The diameters of common carotid	Assess the average diameters of the CCA, ICA, ECA and outflow/inflow ratio in newborns	Cross-sectional Study Sample size = 20	Newborns (Gestational week 34-40)	M, 55%	Fixed carotid arteries were dissected from newborn cadavers and vessel diameters were measured. **Inclusion criteria:** Available cadavers. **Exclusion criteria:**	CCA, ECA, ICA diameter larger in males. CCA, ECA, ICA diameter and outflow/inflow greater on the	**Strengths:** Rare population. Simple and accurate measurement. **Limitations:** Small sample size. No significant difference. No exclusion criteria.

Author, Date, Location, Title	Objectives	Type of study, Sample size	Mean Age (Range)	Sex, %	Methods, Selection criteria	Key findings	Strengths/Limitations
artery and its branches in newborns					Unknown.	right vs the left in both sexes. Outflow/inflow ratio larger in males.	Unknown ethical approval.
McNamara J.R., Fulton G.J. and Manning B.J. (2015) Ireland[24] Three-dimensional Computed Tomographic Reconstruction of the Carotid Artery: Identifying High Bifurcation	To define a reproducible method for identifying patients with high carotid bifurcations	Retrospective Cross-sectional Study Sample size = 86	68 (20-90)	M, 54%	3D reconstructed CT angiograms were used to assess the curved length and straight-line distance of the ICA. Bifurcation height was measured relative to 8 anatomical landmarks. **Inclusion criteria:** Patients with symptomatic or asymptomatic carotid artery disease. **Exclusion criteria:** Occlusion of the ICA and abnormal positioning of patient.	Measuring the distance of the bifurcation from the mastoid process gives the best indication of a high bifurcation. Bifurcations within a distance 5cm of mastoid process is likely to be in the highest quartile (82.9% sensitive, 80.1% specific). No straight line distance difference between left and right ICA.	**Strengths:** Population specific for those likely to receive a carotid endarterectomy. High level of accuracy using 3D reconstruction of thin slice CT angiography. Inter-observer accuracy of measurement 0.996. **Limitations:** Small population size. Current software cannot calculate straight line distance. No assessment of intra-operative clinical correlation for relevance of a high carotid bifurcation.
Koch S., Nelson D., Rundek T., Mandrekar J. and Rabinstein A. (2009) Florida[25] Race-ethnic Variation in Carotid Bifurcation Geometry	Assess structural differences in carotid bifurcation anatomy between Caucasians, African Americans, and Caribbean Hispanics	Retrospective Cohort Study Sample size = 153	59.8 (unknown)	M, 54.4%	CT angiograms from 3 different races were analyzed and the CCA, ICA, ECA and carotid bulb diameters were measured. **Inclusion criteria:** <50% vessel stenosis. **Exclusion criteria:** >50% vessel stenosis based on the NASCET criteria.	African Americans had lower ICA/CCA and ICA/ECA but an elevated ECA/CCA ratio compared to Caucasians and Hispanics. There were no differences between Caucasians and Hispanics. There were no differences in cross-sectional outflow/inflow ratio between the 3 groups.	**Strengths:** Observer was blinded to ethnic group. 2 observers used for measurements (high inter-observer accuracy 0.96). **Limitations:** Hospital-based patient cohort, not representative of global population. Variation in ratios is small but statistically significant (may not be physiologically significant). Age variation between groups which may contribute to anatomical variation.

Table 3. Carotid artery anatomy and the pathogenesis of CAD.

Author, Date, Location, Title	Objectives	Type of study, Sample size	Mean Age (Range)	Sex, %	Methods, Selection criteria	Key findings	Strengths/Limitations
Schulz U.G.R. and Rothwell P.M (2003) UK[26] Association between Arterial Bifurcation Anatomy and Angiographic Plaque Ulceration among 4,627 Carotid Stenoses	Assess the relationship between carotid artery vessel anatomy and plaque stability in a human model	Retrospective Cohort Study Sample size = 3018	Unknown	Unknown	CT Angiograms were studied for carotid artery anatomy and plaque ulceration in randomized patients from the European Carotid Surgery Trial. **Inclusion criteria:** Presence of symptomatic carotid artery disease. **Exclusion criteria:** Poor imaging, near full occlusion and contralateral carotid bifurcation with no atheromatous plaque evidence.	No association between bifurcation anatomy and plaque ulceration in affected artery. High ECA/CAA and outflow/inflow ratio show reduced plaque ulceration but not significant.	**Strengths**: Large population from multiple centers across Europe. Data was analyzed by two independent observers. **Limitations:** Measurements made by Jeweler's eyepiece, not computerized. Inter-observer agreement on measurement was 0.79. Biased cohort selected from the European Carotid Surgery Trial, not representative of the general population.

Discussion

This review summarizes inter-individual and intra-individual carotid artery bifurcation variations seen in patients with CAD. It also highlights anatomical and demographic factors that are associated with CAD pathogenesis. Finally, it provides a better understanding of why people develop unilateral CAD when both sides are equally exposed to systemic risk factors.

A reduced outflow/inflow ratio is a significant predictor of the development of atherosclerotic CAD. A lower ratio was found in patients with unilateral CAD,[17] in males[22] and in association with increased

Table 4. Critical appraisal and selection score of reviewed articles based on the EBL critical appraisal checklist.

Article	Population Validity Score (%)	Data Collection Validity Score (%)	Study Design Validity Score (%)	Results Validity Score (%)	Overall Validity Score (%)
McNamara et al (2015)	60.0	100	100	83.3	86.6
Schulz et al (2001)	60.0	100	100	83.3	86.9
De Syo et al (2005)	80.0	57.1	80	100	78.2
Koch et al (2009)	75.0	100	80.0	83.3	84.6
Schulz et al (2001)	60.0	85.7	100	83.3	82.6
Schulz et al (2003)	60.0	100	100	83.3	86.9
Phan et al (2012)	50.0	100	100	83.3	83.3
Kamenskiy et al (2015)	57.1	100	100	100	88.0
Sehirli et al (2005)	60.0	85.7	80.0	83.3	78.3
Cappabianca et al (2016)	100	85.7	100	66.7	88.0

plaque ulceration.[26] The stability of atherosclerotic plaques is directly influenced by local hemodynamic and mechanical forces.[26] Mechanical forces arise during the cardiac cycle, whereby pressure changes lead to alternating compression and tension on a plaque.[26] A reduction in the outflow/inflow ratio can change local hemodynamic forces, resulting in an impaired and reduced flow energy. This can increase local stress on the vasculature, and lead to endothelial damage and plaque formation.[11] Surprisingly, blacks showed no difference in outflow/inflow ratio despite significantly different ICA, ECA, and CCA dimensions compared to Caucasians and Hispanics.[25] Blacks are regarded to have a higher adverse vascular risk profile but a lower prevalence of atherosclerotic CAD. Carotid anatomy and geometry may still play a role in this disparity, however further investigations are required.

Carotid artery geometry and anatomy change with physiological aging. At birth, male and female carotid anatomies are very similar, with outflow/inflow ratios close to the predicted optimal value of 1.15.[23] This optimal outflow/inflow ratio has been well established for decades, and any deviation from this can lead to greater local stress and endothelial damage.[12] A reduced outflow diameter can cause an increased pulse wave pressure exerted on the surrounding endothelial lining of the blood vessel, which can lead to damage and plaque development.[23] Unsurprisingly, elderly patients with established CAD demonstrate significant deviation from the optimal outflow/inflow ratio, averaging as low as 0.67.[26] Increases in ICA kinking,[21] carotid bulb diameter, ICA and CCA tortuosity, and bifurcation angle are more prevalent as the population ages.[20] These alterations in the absence of disease are correlated with degradation and fragmentation of intramural elastin.20 Elastin provides the retractive force, which counteracts traction and pressure forces, thereby stabilizing the artery and maintaining its integrity and straight shape.[15] Secondly, there are marked differences in elastin orientation within the ICA and CCA. Elastin in the CCA is found in both the circumferential and longitudinal directions; in the ICA it is predominately found longitudinally within the muscular layer.[20] Degeneration of elastin in the longitudinal direction likely results in increased tortuosity in both the ICA and CCA.[20] There are differences in tortuosity between the CCA and ICA in patients with atherosclerotic CAD. Straighter ICAs and more tortuous CCAs are present in CAD, which appears to be linked to plaque deposition within the ICA.[20] Furthermore, ICA kinking may be a predisposing factor to the development of atherosclerotic plaques and can be unilateral or bilateral.[21] The threshold at which geometric and anatomic changes may precipitate or protect from the formation of atherosclerotic CAD is not currently known. The invasive nature of CT angiography makes it unethical to subject healthy individuals to this procedure. Therefore, these areas of study require further investigation.

There is controversy in the literature concerning the bifurcation angle and the presence of CAD. A significant association between elevated bifurcation angle of the ICA and the presence of CAD within the ICA was seen in a study by Phan et al (OR).[18] This finding was based on a large retrospective cohort study of 178 patients. Kamenskiy et al., on the other hand, found a more acute bifurcation angle to be associated with greater CAD.[20] These findings were based on a smaller sample size and examined drastically different populations, which included older patients with less severe CAD. Phan et al. focused their study on patients with advanced stenosis and larger ICA bulbs, which have been shown to laterally displace the arterial centerline causing an increase in bifurcation angle.[18] Simulation studies showed elevated bifurcation angles were associated with reduced wall shear stress, precipitation of the formation of fatty streaks, and creation of atherosclerotic plaques.18 These results were taken one step further to show an association between the bifurcation angle and bifurcation height in CAD patients by De Syo et al.[19] A positive correlation between bifurcation height and bifurcation angle was seen in patients with unilateral CAD.19 It is unknown whether bifurcation angle and height are independent or synergistic risk factors for the development of CAD.

This study summarizes 10 critically appraised journal articles that investigated the effect of carotid anatomy on the presence of CAD. These studies were conducted all around the world, most using large sample sizes, thereby giving a global perspective on anatomical variations in CAD. This study compiles results from studies investigating the link between carotid anatomy and CAD, an area where there is currently a paucity of data available.

The current study was limited to articles published in English, which exclude possible relevant manuscripts on this topic. Despite using similar imaging techniques, the articles reviewed had significantly different measurement techniques. This discrepancy may account for some inter-study variability. Many of the reviewed articles studied specific populations, leading to high selection bias. Finally, a literature review is designed to minimize researcher bias, however, this is not completely avoidable due to the requirement for individual judgment on which results to include in the study

Conclusion

This is a literature review which highlights the significant association between carotid artery anatomy and geometry in initiation and progression of CAD. Carotid artery anatomy is optimal and equal bilaterally at birth, but changes with age. These changes appear to predispose an individual to the development of atherosclerotic CAD and add to an already extensive list of risk factors. Despite the extensive literature available highlighting this, there is need for further research in order to understand the exact pathogenesis of CAD. A longitudinal study, following specific cohorts over time, will give the best indication on natural and pathogenic changes of carotid anatomy and the development of CAD.

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Appendix 1. EBL critical appraisal checklist.

EBL Critical Appraisal Checklist		Schulz et al (2003)	Schulz et al (2001)	Phan et al (2012)	Kamenskiy et al (2015)	Koch et al (2009)	De Syo et al (2004)	McNamara et al (2015)	Schulz et al (2001)	Sehirli et al (2005)	Cappabianca et al (2016)
Section A: Population	Is the study population representative of all users, actual and eligible, who might be included in the study?	N	N	N	Y	N	Y	N	N	Y	Y
	Are inclusion and exclusion criteria definitively outlined?	Y	Y	N	Y	Y	Y	Y	Y	N	Y
	Is the sample size large enough for sufficiently precise estimates?	Y	Y	Y	N	Y	Y	Y	Y	N	Y
	Is the response rate large enough for sufficiently precise estimates?	N/A	N/A	Y	N/A	Y	N/A	N/A	N/A	N/A	N/A
	Is the choice of population bias free?	N	N	N	N	Y	Y	N	N	Y	Y
	Were participants randomized into groups?	N/A	N/A	N/A	N	N	N/A	N/A	N/A	N/A	Y
	Were the groups comparable at baseline?	N/A	N/A	N/A	Y	Y	N/A	N/A	N/A	N/A	Y
	If groups were not comparable at baseline, was incomparability addressed by the authors in the analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Was informed consent obtained?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
	Section A Total	**60.00**	**60.00**	**50.00**	**57.10**	**75.00**	**80.00**	**60.00**	**60.00**	**60.00**	**100.00**
Section B: Data Collection	Are data collection methods clearly described?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
	If a face to face survey, were inter-observer and intra-observer bias reduced?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the data collection instrument validated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If based on regularly collected statistics, are the statistics free from subjectivity?	Y	Y	Y	Y	Y	U	Y	Y	Y	U
	Does the study measure the outcome at a time appropriate for capturing the intervention's effect?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
	Is the instrument included in the publication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are questions posed clearly enough to be able to elicit a precise answer?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Were those involved in data collection not involved in delivering a service to the target population?	Y	Y	Y	Y	Y	N	Y	Y	N	Y
	Section B Total	**100.00**	**85.70**	**100.00**	**100.00**	**100.00**	**57.10**	**100.00**	**100.00**	**85.70**	**85.70**
Section C: Study Design	Is the study type/ methodology utilized appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there face validity?	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
	Is the research methodology clearly stated at a level of detail that would allow its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was ethics approval obtained?	Y	Y	Y	Y	Y	U	Y	Y	U	Y
	Are the outcomes clearly stated and discussed in relation to the data collection?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Section C Total	**100.00**	**100.00**	**100.00**	**100.00**	**80.00**	**80.00**	**100.00**	**100.00**	**80.00**	**100.00**
Section D: Results	Are all the results clearly outlined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are confounding variables accounted for?	Y	Y	Y	Y	Y	Y	N	Y	N	Y
	Do the conclusions accurately reflect the analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is subset analysis a minor, rather than a major, focus of the article?	N	N	N	Y	Y	Y	Y	U	Y	Y
	Are suggestions provided for further areas to research?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
	Is there external validity?	Y	Y	Y	Y	U	Y	Y	Y	Y	U
	Section D Total	**83.30**	**83.30**	**83.30**	**100.00**	**83.30**	**100.00**	**83.30**	**83.30**	**83.30**	**66.70**
Overall Validity		**86.9**	**82.6**	**83.3**	**88.0**	**84.6**	**78.2**	**86.6**	**86.9**	**78.3**	**88.0**

Legend: *no (n), yes (y), unsure (u), doesn't apply (n/a)*

Appendix 2. Consolidation of numerical and statistical values from review articles.

Author, Date, Location	Values	Statistics	Results
Schulz U.G.R. and Rothwell P.M (2003) UK[26] Association between Arterial Bifurcation Anatomy and Angiographic Plaque Ulceration among 4,627 Carotid Stenoses	Outflow/inflow - 0.72 ± 0.25 asymptomatic side - 0.71 ± 0.23 symptomatic side Outflow/inflow on symptomatic side - 0.69 ulcerated plaque - 0.72 not ulcerated plaque	P = 0.95 P = 0.06	Outflow/inflow ratio did not vary much between symptomatic and asymptomatic sides Outflow/inflow ratio did not significantly affect plaque ulceration on symptomatic side
Schulz U.G.R. and Rothwell P.M. (2001) UK[17] Major Variation in Carotid Bifurcation Anatomy A Possible Risk Factor for Plaque Development	Outflow/inflow asymmetry of > 25% - 42% of patients with <30% stenosis Outflow/inflow ratio - 0.73 ± 0.24 in patients with <30% stenosis Outflow/inflow ratio - 0.76 ± 0.25 in patients with no disease	P < 0.05	Large variation between individuals: ECA range between 0.5 to 1.3x size of ICA Outflow area range from 62% less to 28% more than Inflow area Intra-individual variation: 42% of people had >25% asymmetry in outflow/inflow between left and right carotids
Phan T.G., et al (2012) Australia[18] Carotid Artery Anatomy and Geometry as Risk Factors for Carotid Atherosclerotic Disease	Symmetrical stenosis - 39% of patients Asymmetrical stenosis - 61% of patients ICA angle - 23.3° ± 14.01° with 0% ICA stenosis - 31.25° ± 21.60° with 10%-49% ICA stenosis - 35.47° ± 19.01° with 50%-79% ICA stenosis - 43.17° ± 24.69° with >80% ICA stenosis Association with ICA stenosis - ICA angle OR 1.05 per degree increment - Male sex OR 1.72 - Bifurcation angle OR 0.60	P < 0.05	Positive linear relationship between ICA angle and degree of ICA stenosis – increase in angle showed increased ICA stenosis ICA angle >31.3° correlated with ICA stenosis ICA radius was an independent predictor of ICA stenosis
Kamenskiy A.V., at al (2015) Nebraska[20] Age and disease-related geometric and structural remodeling of the carotid artery	Anatomical increases with each decade of life - Carotid bulb diameter increases by 0.64 mm - ICA tortuosity of 0.04 - CCA tortuosity of 0.03 - Bifurcation angle of 10° Angle of bifurcation in unilateral CAD - 25.36° ± 9.16 in diseased - 47.77° ± 25.61 in non-diseased	P < 0.05 P = 0.01	Bifurcation angle and tortuosity of the ICA and CCA increases each decade of life Smaller bifurcation angle, increased tortuosity of CCA and reduced tortuosity of ICA are seen in CAD vs non-diseased Geometrical changes correlate with degradation and fragmentation of intramural elastin
Koch S., Nelson D., Rundek T., Mandrekar J. and Rabinstein A. (2009) Florida[25] Race-ethnic Variation in Carotid Bifurcation Geometry	Outflow/inflow ratio - African Americans 0.80 ± 0.28 - Caucasian 0.79 ± 0.21 - Hispanic Caribbean 0.77 ± 0.21 ICA/CCA ratio - African Americans 0.59 ± 0.10 - Caucasian 0.65 ± 0.10 - Hispanic Caribbean 0.64 ± 0.10	P < 0.05	African Americans had lower ICA/CCA and ICA/ECA but an elevated ECA/CCA ratio compared to Caucasians and Hispanics There were no differences between Caucasians and Hispanics There were no differences in cross-sectional outflow/inflow ratio between the 3 groups
De Syo S., Franjic B.D., Lovricevic I., Vukelic M. and Palenkic H. (2004) Croatia[19] Carotid Bifurcation and Position and Branching Angle in Patients with Atherosclerotic Carotid Disease	Average bifurcation angle - 40.5° ± 17.14 Average bifurcation height - 9.01 ± 2.96 Kinking of ICA in patients with high bifurcation height - 25% Kinking of ICA in patients with medium and low bifurcation height - 3.2% Bifurcation angle increases for each 1/3 of vertebral body height increase in bifurcation height - 3.34° increase per height increase	P < 0.01	Positive correlation between bifurcation height and branching angle The bifurcation angle increases 3.34° for each 1/3 vertebral body elevation of bifurcation height

McNamara J.R., Fulton G.J. and Manning B.J. (2015) Ireland[24] Three-dimensional Computed Tomographic Reconstruction of the Carotid Artery: Identifying High Bifurcation	Curved Length ICA - 81.8 ± 11.4 mm Straight length distance - 72.1 ± 9.6 mm Tortuosity - 1.15 ± 0.13 Bifurcation from mastoid process - 57.8 mm Bifurcation at the middle third of C4 - 17.9%		Measuring the distance of the bifurcation from the mastoid process gives the best indication of a high bifurcation Bifurcations within a distance 5cm of mastoid process is likely to be in the highest quartile (82.9% sensitive, 80.1% specific) No straight line distance difference between left and right ICA
Schulz U.G.R. and Rothwell P.M. (2001) UK[22] Sex Differences in Carotid Bifurcation Anatomy and the Distribution of Atherosclerotic Plaque	ICA/CCA - 0.67 F - 0.62 M ECA/CCA - 0.55 F - 0.55 M ICA/ECA - 1.19 F - 1.12 M Outflow/inflow - 0.77 F - 0.71 M Maximum stenosis - OR 2.29 M to F ECA stenosis - OR 1.54 F to M	P < 0.0001 P = 0.44 P < 0.0001 P < 0.001 P = 0.001 P < 0.0001	Average ICA/CCA, ICA/ECA and outflow/inflow were larger in women vs men Lower average outflow/inflow ratio in men Women showed more stenosis in ECA, men had more stenosis distal to carotid bulb
Sehiril U.S., Yalin A., Tulay C.M., Cakmak Y.O. and Gurdal E. (2005) Turkey[23] The diameters of common carotid artery and its branches in newborns	CCA - 1.94 ± 0.33 mm M - 1.75 ± 0.30 mm F ECA - 1.54 ± 0.26 mm M - 1.31 ± 0.31 mm F ICA - 1.41 ± 0.28 mm M - 1.42 ± 0.41 mm F ECA/ICA - 0.80 ± 0.09 M - 0.75 ± 0.14 F ICA/CCA - 0.73 ± 0.09 M - 0.70 ± 0.16 F Outflow/inflow - 1.18 ± 0.22 M - 1.10 ± 0.33 F	P > 0.05	CCA, ECA, ICA diameter larger in males CCA, ECA, ICA diameter and outflow/inflow greater on the right vs the left in both sexes Outflow/inflow ratio larger in males
Cappabianca S., Somma F., Negro A., Rotondo M., Scuotto A. and Rotondo A. (2016) Italy[21] Extracranial internal carotid artery: anatomical variations in asymptomatic patients	Imaging vascular anomaly detection - CTA 100% - MRA 89.9% Carotid bifurcation - C4 level 59.9% - C3 level 19.3% - C5 level 11.3% - C2 level 9.5% Kinking and coiling - 20.7% of patients - bilateral 80% - unilateral 20%	P < 0.05	CT angiograms detected 100% of ICA abnormalities, MRI detected 89.9% Kinking/coiling of ICA was present in 20.7% of patients Kinking in patients > 55 years old Coiling in patients < 37 years old

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Experience

Predatory Journals: What You Need to Know About Them?

David Avelar-Rodriguez.[1]

The Experience

Recently, I have noticed that the number of emails I receive from possible predatory journals has increased dramatically, either in the form of junk (most of them) or regular email. I receive them every day, including weekends and holidays, and often awake to an email full of invitations to contribute to these "scientific" journals. Although most researchers are already aware of this scam, it is never too late to warn others, especially early career researchers. In addition, the number of predatory journals appears to be growing;[1] thus, it is important that we know who they are and what their intentions are.

What is a Predatory Journal?

Defining a predatory journal is difficult. Predatory journals do not follow international publishing standards[2] and their main motive is financial gain.[3] One of the main reasons why it is so difficult to reach consensus on its definition is, in part, because certain open access journals that seem to fit the definition are simply lacking editorial quality, but are not predatory *per se*; that is, they are legitimate journals with poor publishing standards.[4] In a recent paper by the World Association of Medical Editors (WAME),[2] the authors provide a succinct synthesis about predatory journals and thoroughly review different approaches to identify a possible predatory journal. In particular, they provide their own table of "warning signs" to watch for (***Table 1***) and a very useful algorithm, which I believe should be used when dealing with a possible predatory journal. It is important to note, however, that all the available criteria are arbitrary and have not been validated, and thus they should be used carefully. In summary, predatory journals are illegitimate open access publishers whose only mission is financial gain at the expense of publishing all types of literature (including poor, but possibly also good quality), as long as authors pay for the publication fees.

How do predatory journals operate?

Predatory journals operate by mass-emailing researchers in hopes of getting researchers to publish with them2–4; they acquire your email address from your already published work. In my experience, email invitations from predatory journals are generally low quality, contain poor English usage, and use persuasive language as well as exaggerated adjectives to refer to you and your work. This is confirmed when I compare my own experiences to the criteria listed by the WAME in Table 1. Lately, I have also noticed that they are using the "Request a Read Receipt" tool, so that they know whether you opened their email or not. Moreover, it is not uncommon to receive invitations from journals in which you lack expertise; for example, I am interested in general pediatrics, gastroenterology and global health, and my research has been focused on these disciplines accordingly. Why would an Ob & Gyn journal, or even a psychiatry journal, want me to publish my work with them? So also consider this aspect when you receive these emails.

Table 1. "Warning Sign" features that should increase suspicion that a journal is predatory

No information as to whether there are author fees in the Instructions for Authors.
Peer review is not mentioned in the Instructions for Authors.
Little or no information is provided regarding the editor or editorial board.
No location is listed for the journal offices, or location is very different than the location of the editors and editorial board.
The journal website is not easily accessible in an internet search (could be a problem in a legitimate journal in a low- or middle-income locale).
The journal publishes either an unusually small, unusually large, or markedly variable numbers of articles each year.
You or your colleagues have received formulaic e-mail solicitations for submissions that do not specify an interest in particular projects or areas that you are working on.
Promised routine turnaround times for review and publication are so rapid that they seem "too good to be true" and would be unlikely to encompass the time necessary for true peer review.
You do not receive a response to e-mail or telephone messages sent to the editor or journal office within a few days.
The name of the journal is very similar to the name of a well-known, established journal with a good reputation.
The publication fees are atypical for the scholarly publishing industry (much higher or much lower fees can both signal problems [with recognition that journals in low- or middle-income countries may have legitimately low fees]).
It is difficult to identify articles published in the journal when searching Google Scholar or other databases (with recognition that new journals or those in low- or middle-income countries may face lags in indexing).
Information about author affiliations and/or contact information is not present in published articles.
Someone you know listed on the editorial board or journal staff, when you query them about the journal, is unaware of their supposed affiliation with the journal.

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[1] National Institute of Pediatrics, Mexico City, Mexico

About the Author: *David Avelar Rodriguez is student editor of the IJMS and graduated from Universidad Autónoma de Guadalajara, School of Medicine. He is currently a clinical researcher at the National Institute of Pediatrics and is applying for medical residency in Canada this year.*

Correspondence:

David Avelar-Rodriguez

Address: Insurgentes Sur 3700 Letra C, Insurgentes Cuicuilco, 04530 Mexico City, CDMX, Mexico.

Email: davidavelar1@outlook.com

Editor: Francisco J. Bonilla-Escobar
Student Editors: Madeleine Jemima Cox
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Here are some common examples of email invitations from possible predatory journals:

> *"Dear Prof. (even though you are not a professor)/Dr. [your name],*
>
> *We are in shortfall of one article for successful release of volume # …. / We humbly request you to submit any of your articles including commentaries, opinions …. / I am delighted to inform you that [journal's name] is planning to release volume # Issue # and we need two articles to accomplish this issue…. / We are pleased to inform you that the journal is under process of accepting the articles from the experts like you / Based on your eminence and contribution towards the scientific community we request you to publish your work in [journal's name]*
>
> *Your article with the title [title of your manuscript] has left a deep impression on us / has impressed us deeply / has attracted widespread attention"*

What is the impact of predatory journals on today's scientific community?

Not only are predatory journals scamming researchers and making profit in a fraudulent manner, but are also jeopardizing the credibility of science itself, with the latter being the most critical and scary consequence in my opinion. Indeed, recent research demonstrated that a relatively large number of possible predatory journals in the fields of neurosciences[5] and rehabilitation[6] is indexed in PubMed – PubMed is amongst the most important databases we rely upon to conduct our research! (For review see [7,8]) Unquestionably, the predatory publishing issue is a global concern that needs to be addressed immediately.

In conclusion, it is paramount that we as researchers spread the word and are aware of the predatory publishing model. As you continue to publish more and more, and considering the rise in the number of predatory journals in recent years, you should expect to receive their invitation emails eventually, if not already received. It is important to keep in mind what their emails look like, and if you end up curiously surfing their website (which some of them look legitimate), be sure to apply the criteria and algorithm published by the WAME[2] and use your own –or your more experienced colleague's– judgment.

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ULS

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Sculpture for Surgeons

Natalia Katarzyna Bober.[1]

The Experience

''Sculpture for Surgeons'' was a three-day course hosted in London and led by Luke Shepherd, a professional sculptor. During that time, each of the participants created a bust of the human model from scratch (***Figure 1***). This course was mainly aimed at surgeons to improve their appreciation of facial anatomy and help in future operations. However, the event welcomed medical professionals at various stages of training. I met plastic trainees and consultants, as well as medical students and junior doctors. Each of us had a different experience with sculpting. Some of us, like me, never touched the clay before; others were sculpting regularly. We all started together and step by step Luke Shepard led us through the meticulous steps of capturing the complexity of facial topography.

It all started with the most difficult step: observation. We often consider ourselves good observers, able to spot details and nuances. However, how good are we though when it comes to three-dimensional observation? We tend to fixate on two-dimensional pictures, forgetting about the depth. For instance, we know that the ear is located behind the temporomandibular joint, but how high is it in relation to the eye? At what angle is it? Which part of the pinna is the most distal? These were only some of the questions I tried to answer, which I had never thought about before. Only later did I realize that observing and analyzing took me, in fact, more time than the actual sculpting. While it might be relatively easy to create a face, the real difficulty lies with the accurate recreation of the actual model.

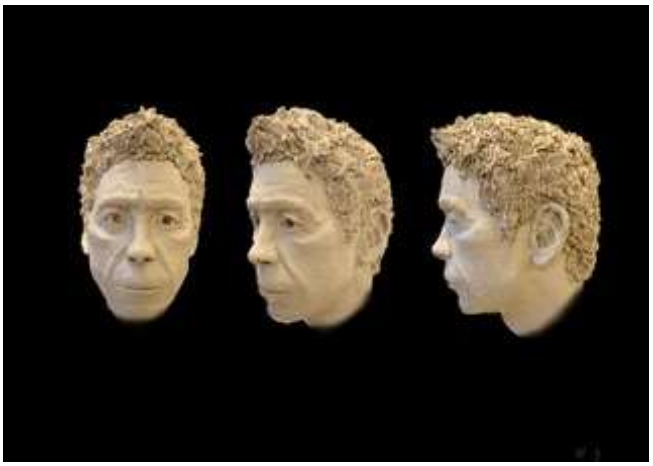
The next step involved translating observation into sculpture, which required unbelievable precision. We received countless advice on how to approach it and how to get the most precise measurements using only pencils and calipers, to maintain the realistic dimensions of the sculpture. Each day we were being taught more advanced steps. From creating the profile on day one, to tips on shaping the eyes on day three, Luke Shepard was an extremely supportive teacher. He allowed us to discover an artist and careful observant in each of us. After demonstrations of subsequent steps, he would always take a tour around the room to see up close how we were getting on. Whenever he came towards my sculpture, this gave me a chance to reflect on my work. I was grateful for all the tips, and it definitely helped me develop a more critical eye.

Nowadays, the practical workshops incorporated into medical education tend to be limited to absolutely necessary skills such as cannulations or suturing, with many students complaining about the lack of hands-on experience.[1] I personally believe there is a strong emphasis on knowledge of theory, with scarcity of manual development opportunities, let alone creative or artistic workshops. There is increasing interest and need for this type of activities to be incorporated into medical curriculum.

For example, Gelgoot et al. carried out a literature review on this topic and found some promising responses.[2] This included university courses using discussions over paintings as a way of reflecting on topics such as mental illness, doctor-patient relationship, suffering and death. Penn State, Harvard and UT Austin are among the universities incorporating humanities into medical education.[3] Many argue that it is essential for the development of communication and interpersonal skills, as well as critical thinking. In fact, studies are showing that exposure to visual arts leads to positive personal qualities such as empathy and can reduce burnout among the medical students.[4] Practical art courses including drawing and sculpting, such as the Art of Anatomy and Surgery SSC Course organized at King's College London, were shown to improve dexterity, personal expression and medical knowledge.

Incorporation of art into medicine has numerous benefits. Not only does it contribute to personal development and improvement of numerous skills such as observation or imagination, but it also allows for the valuable insight and understanding of the patients' experience. Opportunities for medical students are constantly expanding, yet not all medical programs offer a variety of humanities courses. That is why I am absolutely grateful for having the chance to attend the "Sculpture for Surgeons" event. I found the course to be an invaluable experience and a great self-development opportunity. It definitely improved my understanding of the complexity of facial anatomy and most importantly, it contributed to my observation skills, which are crucial for every doctor.

Figure 1. Three views of artist's bust rendition



Legend: Photograph provided by the "Sculpture for Surgeons".

[1] Medical student, King's College London GKT School of Medical Education, UK.

About the Author: *Natalia Katarzyna Bober is currently a fifth-year medical student at King's College London GKT School of Medical Education, UK.*

Correspondence:
Natalia Katarzyna Bober
Address: Strand, London WC2R 2LS, UK.
Email: natalia.bober@kcl.ac.uk

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Having Diabetes in a Middle-Income Country

Diego Carrion Alvarez,[1] Nallely Alejandra Obregon Perales.[1]

The Experience

In our university, we started clinical rotations in family medicine. For six months, we learned how to diagnose and treat patients from all socioeconomic classes. However, some cases had an impact on us. A lady in her late 60's came for her routine diabetes check-up. She had been diagnosed just three months ago; currently, she was taking metformin and trying to improve her lifestyle. Her lab tests results were still above the recommended values. Our doctor invited us to ask her about her habits and diet. She did not exercise; furthermore, the nutritionist recommended her a Mediterranean diet. We suggested the idea of starting insulin if her lab results persisted. Her answer shocked us: "Doctors, how am I supposed to change my diet? The plan provided by the nutritionist includes fish and olive oil. I barely have money to buy a few eggs, beans and tortillas, and eat chicken or meat only when possible. Even more, I doubt I could afford the syringes and the needles for the insulin injections." Our tutor recommended small diet changes and increased the metformin dose. The patient was discharged with a new appointment to review her glucose values. Upon this scenario, we learned what it is like to have a chronic disease as a low-income patient in a middle-income country.

Health and Economics

In Mexico, diabetes represents a significant health problem. The current lifestyle, dietary habits, and an alarming increase in obesity rates are just the tip of an underlying issue. In 2012, diabetes prevalence was around 8.9%. However, prospective studies expect it to grow to 22.6% by 2050, meaning that almost one in every three Mexicans will suffer from the disease.[1] The picture in Latin America is similar since the prevalence of diabetes has increased by 9% from 2014 to 2016.[2] In a country like Mexico, where according to the World Bank 3.2 million inhabitants live with less than 1.90 USD a day and 44.4 million struggle to survive with less than 5.50 USD, it can be difficult to change your lifestyle. Diabetes is a multifactorial disease, and even though poverty plays a significant role in its development, other factors such as governmental policies addressing unhealthy food and encouraging early lifestyle changes contribute to the big picture. These factors are mentioned in Figure 1 and need to be considered when outlining the correct public health approach to the problem.[3] Low-income populations tend to have worse outcomes and so they need to be targeted by health institutions.[4]

The Cost of Diabetes

Diabetes is one of the most prevalent diseases worldwide. It is a chronic disorder and requires strict control. In 2015, the economic burden of diabetes was estimated at 1.3 trillion USD globally and is estimated to increase up to 2.2 trillion USD by 2030; furthermore, even if countries meet international targets, that will not reduce the burden of the disease.[2] Latin American healthcare systems absorb part of the economic charge by providing medical appointments, lab tests and certain medications. However, due to the huge amount of patients and the lack of resources, they are unable to afford the newest medication available, relying on cheaper drug options. Polypharmacy is an important part of diabetes management, and since not all drugs are available, some patients may be unable to reach therapeutic goals, presenting complications or switching to insulin-based treatments.[5] Healthcare systems also cover the costs of complications such as neuropathy, retinopathy, nephropathy or limb amputation; these are all complications that impact negatively on the economy taking out of the workforce otherwise productive individuals. Even with these systems, diabetes still represents a cost for the patient; changing to a healthier lifestyle and buying syringes and needles is a patient's responsibility, as well as the acquisition of a glucometer, lancets and paper strips for proper self-management.

What can students do?

It is said that each individual is a world; the personalization of treatment in middle income countries needs to start. Mexican guidelines are outdated, and they stick to the recommendations of the American Diabetes Association (ADA) without considering the differences in our countries healthcare systems, social structure, and economic capabilities. An example of a more personalized adaptation can be found in the 2018 consensus between the ADA and the European Association for the Study of Diabetes (EASD) since in this guideline policymakers do contemplate medicine costs.[6] However, contexts are unique to each country and they even vary between regions; Mexican health authorities, such as the "Centro Nacional de Excelencia Tecnológica en Salud", need to change their approach and focus the attention of protocols also on treatment individualization based on economic status and even the patients' cooperation. As students, it is our duty to demand better healthcare options for our patients by pushing governmental institutions to shift to a more personalized care and ensure that preventive health policies may endure.

[1] Medical Student, University of Monterrey, Monterrey, Mexico.

About the Author: *Diego Carrion is currently a 5th year medical student of Universidad de Monterrey, Monterrey, México of a 7 year program. He is also a recipient of a Millenium Fellowship student fellowship.*

Correspondence:

Diego Carrion Alvarez

Address: Av. Ignacio Morones Prieto 4500 San Pedro Garza García Nuevo León, México.

Email: diego.carrion@udem.edu

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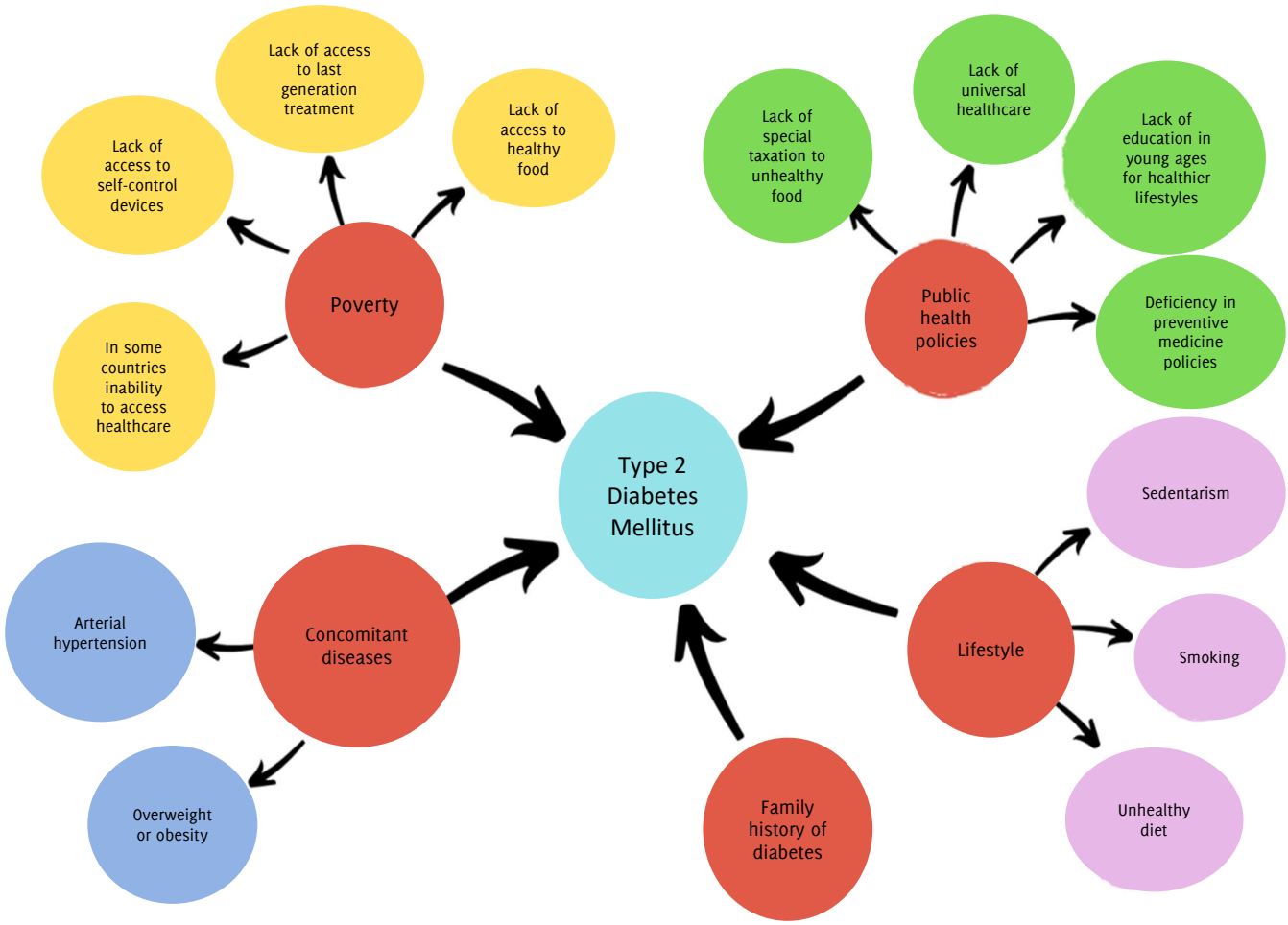
Figure 1. Risk Factors associated with the Development of Type II Diabetes Mellitus.



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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Medical Students Burning Out: Why and What We Can Do About It?

Abuzar Siraj.[1]

The Experience

Said plainly, burnout is when you just can't cope anymore. A state of complete physical and emotional exhaustion resulting in a drop in performance and aversion to all work-related activities. It is most often used in context of the medical profession because of the notoriously long working hours, mountainous workload and the near nonexistent margin for error that residents sign up for when they begin training. But it is now becoming evident that this mystical psychosocial condition that had long been ignored and swept under the carpet also affects medical students, as one study on US medical students shows that 50% of US medical students were burned out.[1] In Cameroon, a study showed that 30% had symptoms of major depressive syndrome.[2] Being a medical student from Pakistan, I was particularly curious about the extent of student burnout here, which one recent study shows to be approximately 20%.[3] It becomes apparent that burnout does not discriminate based on race, creed or nationality.

Hence it goes without saying that this is a major problem, one that must be addressed not only for the betterment of the affected individuals but also for the people near them; including parents, patients and peers. For instance, 11% of medical students in the US contemplated suicide.[1] While we must not be naive in assuming that burnout is the sole cause of this worrying figure, it is surely a contributory factor no doubt. Additionally, physician burnout has been associated with almost 2 times as much patient safety incidents and subpar professionalism with poor care delivery to patients, ultimately resulting in significantly reduced patient satisfaction.[4]

Medical students are subjected to an enormous amount of complex medical information and are expected to have it down cold, all in record short time. I have noticed students in my medical college become increasing reclusive as the academic year progresses and finals slowly approach. The short encounters that they do have with one another are always played out in a manner that would put professional actors to shame. Both parties exchange pleasantries, claiming studies are "going well" with a bright smile on their face. No one wants to appear weak in the cutthroat world we live in. But alas, this seemingly meaningless façade proves to do more harm than good as both parties develop feelings of inadequacy when they return to their abodes. Which prompts them to study for even longer hours, as a result get exceedingly burned out. And so, a vicious cycle ensues.

Case Western Reserve University developed Wellness Electives for students to avoid getting burnout.[5] The results of which proved to be promising. And while many students would like wellness electives introduced in 1st year and 2nd year curriculum at their medical schools, the results may not always be encouraging. I say this because other medical schools have dedicated wellness lectures for students which for the most part are designed to help medical students in need, but I argue that can do more harm than good for those already burned out. Waking up at 7 in the morning to attend a mandatory lecture that you feel doesn't help you in the slightest, when you'd rather be home studying for your upcoming exam. This adds undue anxiety to the already tiresome lives of medical students.

The stigma associated with burnout, and with any other mental health issue for that matter, is possibly the most damaging reason why it is becoming so prevalent. Students fear talking about it and seeking help will only jeopardize their image in the eyes of their colleagues and their future patients. Fearing their career will be over before it even begins as the notorious "Burned Out" label adheres to them and will invariably almost always be brought up in the future; be it during residency interviews or in fellowships.

Add to this the extended periods of time medical students spend away from family and loved ones, who in many cases are the main support system for them, it furthers hinders their ability to cope with the stresses of student life.

We are only beginning to uncover the myriad causes of student burnout. From high stake tests and clerkships, to prolonged study hours, to the toxic medical school and hospital environment, to being in countless dollars of debt and to be away from home are all contributory. Since the causes are many, it should not come as a surprise that the strategies to dealing with it are multiple too. There is no one-size-fits-all solution for it.

I believe support must be personalized for each individual. Simply reducing stress in the workplace will not decrease the incidence and prevalence of student burnout. Rather, a more holistic approach is required encompassing the social interactions and the coping capacity of each individual.[6] In fact, regular campaigns addressing student burn out should be carried out, encouraging individuals to come forward and speak out about the problems they or those close to them may be facing.[7] Such steps are necessary because many burned out students will never get help on their own, as one study showed only one-third of burned out individuals actually seek out help.[8] Unfortunately, since the stigma regarding mental health is still very much alive and thriving, it is imperative that when students come for help, the services provided to them be confidential.

Students of today will be physicians of tomorrow. How can we expect them to treat their patients, if they themselves are not well?

[1] MBBS (final year), Khyber Medical College, Peshawar, Pakistan.

About the Author: *Abuzar Siraj is a final year medical student at Khyber Medical College, Peshawar, Pakistan.*

Correspondence:
Abuzar Siraj
Address: University of Peshawar، Rd No. 2, Rahat Abad, Peshawar, Khyber Pakhtunkhwa 25120, Pakistan
Email: abuzar_siraj@yahoo.com

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Anas Saad – Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Andres Zorrilla-Vaca – Universidad del Valle, Cali, Colombia

Aswini Pujahari - Department of Surgery, Armed Forces Medical College, Pune 411040, India.

Bogdan Socea – Surgery Department, "Carol Davila" University of Medicine and Pharmacy & Surgery Department, St. Pantelimon Emergency Clinical Hospital, Bucharest, Romania.

Camelia Cristina Diaconu – Internal Medicine Department, "Carol Davila" University of Medicine and Pharmacy & Internal Medicine Clinic, Clinical University Hospital of Bucharest, Bucharest, Romania.

Christian Ortega-Loubon – Department of Cardiac Surgery, Clinic University Hospital of Valladolid, Valladolid, Spain.

Cristian Răsvan Băicuş – Internal Medicine Department, "Carol Davila" University of Medicine and Pharmacy & Internal Medicine Clinic, Colentina Clinical Hospital, Bucharest, Romania.

Daniel Coriu – Hematology Department, "Carol Davila" University of Medicine and Pharmacy & Department of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania.

Eugen Enesi – Service of Radiology, Neuroradiology Division, Faculty of Medicine, University of Tirana UHC "Mother Teresa", Tirana, Albania.

Gabriel Motoa – Universidad del Valle, Cali, Colombia

Hanna Mysliwiec – Department of Dermatology and Venereology, Medical University of Bialystok, Bialystok, Poland.

Hossam Elfeki – Mansoura Univ Hosp, Mansoura Fac Med, Colorectal Surg Unit, Dept Gen Surg, Elgomhuoria St, Mansoura, Egypt & Aarhus Univ Hosp, Dept Surg, Aarhus, Denmark.

Hugo Mendieta Zerón – Autonomous Univ State Mexico UAEMex, Med Res Ctr CICMED, Mol Biol Lab, Toluca, Mexico

Jacob Ross – School of Medicine, Flinders University & Joanna Briggs Institute, University of Adelaide, Australia.

Joyce Antonella Jimenez-Zambrano – Universidad Católica de Santiago de Guayaquil. Guayaquil, Ecuador.

Karim A. Rehman – Department of Internal Medicine, Cleveland Clinic, Cleveland, USA.

Laura Martínez-Garza – Department of Genetics, University Hospital 'Dr. José Eleuterio González', Monterrey, Nuevo León 64460, México.

Lukas Rasulić – School of Medicine, University of Belgrade & Dept. of Peripheral Nerve Surgery, Functional Neurosurgery and Pain Management Surgery, Clinic for Neurosurgery, Clinical Center of Serbia, Belgrade, Serbia.

Maria Elisabeta Baldassarre – Department of Biomedical Science and Human Oncology, School of Medicine, University "Aldo Moro" & Neonatology and Neonatal Intensive Care Unit, Policlinico Hospital, Bari, Italy.

Mariagiovanna Cantone – Neurology Department, "Sant'Elia" Hospital, Caltanissetta, Italy.

Michael Sticherling – Friedrich-Alexander-Universität of Erlangen-Nürnberg, Universitätsklinikum Erlangen, Department of Dermatology, Erlangen, Germany.

Muneer J. Al-Husseini – Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Najdat Bazarbashi – Department of Cardiology, Heart and Vascular Institute, Cleveland Clinic, Cleveland, USA.

Correspondence:

Executive Committee of the International Journal of Medical Students

Address: 1400 Locust Street, Suite 3103, Pittsburgh, PA 15219. USA. Tel.: 413-232-7884, Fax: 412-232-8966

Email: editor.in.chief@ijms.info

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Paul Marcel Morgan – University of Belize, Faculty of Science and Technology, Belmopan, Belize.

Pavan Kumar Tandra – University of Nebraska Medical Center, Department of Internal Medicine, Division of Hematology & Oncology, Omaha, NE 68198 USA.

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