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From the Editor

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This is the second issue this year of the journal that include research papers and a review from Saudi Arabia.

Alnefaie, Z et al looked at the prognosis, complications and quality of life after fibrinolysis versus PCI Post MI. The authors stressed that Management of acute MI is carried out through adopted a reperfusion strategy either pharmacological (intravenous fibrinolysis) or mechanical (primary percutaneous coronary intervention (PCI)) to re-open the occluded coronary artery. Many literature studies have compared the efficacy, the complications, and the long-term outcome of both the intravenous fibrinolysis and primary PCI. Despite the superiority and overgrowing popularity of primary PCI in management of acute MI, fibrinolysis is still widely utilized. Many factors play a role in choice of the reperfusion strategy to be adopted particularly the time from the symptom onset, the time required for preparing for PCI, and patient co-morbidities e.g. risk for bleeding. Primary PCI is generally more efficacious in achieving reperfusion. It is safer with lower mortality rates, and it is associated with lower risk to develop restenosis, re-infarction, heart failure, shock cerebrovascular stroke, or intracerebral haemorrhage. However, the less availability and the variable outcomes with operator experience are the main disadvantages that make PCI not feasible at many situations.

Helvaci, M. R et al stressed that Pulmonary hypertension (PHT) is common in sickle cell diseases (SCDs). All patients with SCDs were included. The study included 434 patients (212 females). Transfused units of red blood cell (RBC) (48.1 versus 28.5, p=0.000), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were also higher in males. There were 31 mortality cases (17 males) with similar mean ages in males and females (30.2 versus 33.3 years, respectively, p>0.05). Mean ages of COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), deep venous thrombosis and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and benign prostatic hyperplasia (41.5 years) were higher. The authors concluded that SCDs are severe inflammatory processes on vascular endothelium particularly at capillary level, since capillary system is the main distributor of hardened RBCs into tissues. Although various arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of PHT in SCDs.

Helvaci, M. R et al tried to understand whether or not there is a lower prevalence of systemic lupus erythematosus (SLE) due to an immunosuppression in the sickle cell diseases (SCDs). All patients with the SCDs and age and sex-matched controls were studied. The study included 428 patients with the SCDs (220 males) and 433 controls (223 males). Although SLE was diagnosed in 6.0% of the control cases (24 females and two males), this ratio was only 0.4% (one female and one male) in the SCDs patients (p<0.001). On the other hand, transfused units of red blood cells in their lives (47.6 versus 28.4, p=0.000), chronic obstructive pulmonary disease (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), coronary artery disease (18.1% versus 12.9%, p<0.05), chronic renal disease (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with SCDs. SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failures in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of lower prevalence of SLE in the SCDs.

Maurice Brygel, General Surgeon from Melbourne, Australia provides insights into Clinical Assessment and Risk Management strategies when operating in the Ano-rectal region. With adverse events increasing in hospitals worldwide Risk Management has become a major part of Quality Assurance.

What a low prevalence of systemic lupus erythematosus in sickle cell diseases

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ABSTRACT

Background: **We tried to understand whether or not there is a lower prevalence of systemic lupus erythematosus (SLE) due to an immunosuppression in the sickle cell diseases (SCDs).**

Methods: All patients with the SCDs and age and sex-matched controls were studied.

Results: **The study included 428 patients with the SCDs (220 males) and 433 controls (223 males). Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, p>0.05). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were higher in males with the SCDs (p<0.001 for both). Although SLE was diagnosed in 6.0% of the control cases (24 females and two males), this ratio was only 0.4% (one female and one male) in the SCDs patients (p<0.001). On the other hand, transfused units of red blood cells in their lives (47.6 versus 28.4, p=0.000), chronic obstructive pulmonary disease (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), coronary artery disease (18.1% versus 12.9%, p<0.05), chronic renal disease (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with SCDs.**

Conclusion: **SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failure in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of the lower prevalence of SLE in the SCDs.**

Key words: **Systemic lupus erythematosus, sickle cell diseases, chronic endothelial damage, immunosuppression**

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Introduction

Chronic endothelial damage may be the major cause of aging and associated morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause, and probably whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, excess weight, smoking, and alcohol for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature (1, 2). Similarly, sickle cell diseases (SCDs) are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failure in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem since sickling is rare in peripheric blood samples of the SCDs cases with associated thalassemia minor, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced severe and continuous vascular endothelial inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (3, 4). Capillary systems may mainly be involved in the process due to their distribution function for the hard bodies. We tried to understand whether or not there is a lower prevalence of systemic lupus erythematosus (SLE) due to an immunosuppression in the SCDs.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients with the SCDs and age and sex-matched controls were studied. The SCDs were diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of SCDs patients including smoking habit, regular alcohol consumption, painful crises per year, transfused units of RBCs in their lives, surgical operations, leg ulcers, and stroke were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Cases with acute painful crisis or another inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, hepatic function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest X-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Associated thalassemia minor was detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. SLE is classified with the criteria of American College of Rheumatology of 1997 (5). In differential diagnosis, patients with rheumatoid arthritis (RA) were classified with the criteria of early rheumatoid arthritis (ERA) (6). The ERA criteria includes a morning stiffness of 30 minutes or longer, arthritis of three or more joint areas, arthritis of hand joints, positivity of rheumatoid factor, and positivity of anti-cyclic citrullinated peptide antibody. RA is defined by the presence of three or more of the criteria. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). An X-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (8). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination, liver function tests, ultrasonographic evaluation, and tissue samples in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Avascular necrosis of bones is diagnosed by means of MRI (11). Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, prevalence of RA was detected both in the SCDs and control groups. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 428 patients with the SCDs (220 males) and 433 age and sex-matched control cases (223 males), totally. Mean ages of the SCDs patients were similar in males and females (30.6 versus 30.1 years, respectively, $p>0.05$). Mean ages of the control cases were 30.4 versus 30.3 years, respectively ($p>0.05$ for both). Prevalence of associated thalassemia minor was similar in males and females with the SCDs (72.2% versus 67.7%, respectively, $p>0.05$). Both smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were significantly higher in males with the SCDs ($p<0.001$ for both) (Table 1). Although SLE was diagnosed in 6.0% of the control cases (24 females and two males), this ratio was only 0.4% (one female and one male) in the SCDs group ($p<0.01$) (Table 2). In other words, 89.2% of all SLE patients were female. The mean ages of SLE

Table 1: Characteristic features of the sickle cell patients

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Prevalence	51.4% (220)	Ns†	48.5% (208)
Mean age (year)	30.6 ± 10.1 (5-58)	Ns	30.1 ± 9.9 (8-59)
Thalassemia minors	72.2% (159)	Ns	67.7% (141)
Smoking	***24.0% (53)***	***<0.001***	***6.2% (13)***
Alcoholism	***5.0% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases
†Nonsignificant (p>0.05)

Table 2: Comparison of the patient and control groups

Variables	Patients with SCDs*	*p*-value	Control cases
Number	428	Ns†	433
Female ratio	48.5% (208)	Ns	48.4% (210)
Mean age of males	30.6 ± 10.1 (5-58)	Ns	30.4 ± 11.1 (9-59)
Mean age of females	30.1 ± 9.9 (8-59)	Ns	30.3 ± 10.4 (9-58)
Prevalence of SLE‡	***0.4% (2)***	***<0.001***	***6.0% (26)***

*Sickle cell diseases
†Nonsignificant (p>0.05)
‡Systemic lupus erythematosus

Table 3: Associated pathologies of the sickle cell patients

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBCs‡	***47.6 ± 61.6 (0-434)***	***0.000***	***28.4 ± 35.8 (0-206)***
COPD§	***25.4% (56)***	***<0.001***	***7.2% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***7.2% (16)***	***<0.001***	***1.9% (4)***
Leg ulcers	***20.0% (44)***	***<0.001***	***7.2% (15)***
Digital clubbing	***14.0% (31)***	***<0.001***	***6.2% (13)***
CAD¶	***18.1% (40)***	***<0.05***	***12.9% (27)***
CRD*	***10.4% (23)***	***<0.05***	***6.2% (13)***
Stroke	***12.2% (27)***	***<0.05***	***7.6% (16)***
Pulmonary hypertension	12.7% (28)	Ns	12.5% (26)
Varices	8.6% (19)	Ns	5.7% (12)
Rheumatic heart disease	6.8% (15)	Ns	5.7% (12)
Avascular necrosis of bones	25.0% (55)	Ns	25.0% (52)
Sickle cell retinopathy	0.9% (2)	Ns	0.4% (1)
Mortality	7.2% (16)	Ns	6.7% (14)

*Sickle cell diseases
†Nonsignificant (p>0.05)
‡Red blood cells
§Chronic obstructive pulmonary diseases
¶Coronary artery disease
**Chronic renal disease

cases were 37.0 ± 13.6 (17-58) and 36.5 ± 3.5 (34-39) years in the control and SCDs groups, respectively. On the other hand, transfused RBCs in their lives (47.6 versus 28.4 units, p=0.000), COPD (25.4% versus 7.2%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (7.2% versus 1.9%, p<0.001), leg ulcers (20.0% versus 7.2%, p<0.001), digital clubbing (14.0% versus 6.2%, p<0.001), CAD (18.1% versus 12.9%, p<0.05), CRD (10.4% versus 6.2%, p<0.05), and stroke (12.2% versus 7.6%, p<0.05) were all higher in males with the SCDs, significantly. There were two cases with sickle cell retinopathy in males and one in females (p>0.05). There were 30 mortality cases (16 males) during the ten-year follow-up period. The mean ages of mortality were 30.8 ± 8.3 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 3). Beside these, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV was positive in 5.8% (25) of the study cases, HCV RNA was detected as positive just in three (0.7%) by PCR.

Discussion

Chronic endothelial damage may be the leading cause of early aging and related morbidity and mortalities in human beings. Physical inactivity, excess weight, smoking, alcohol, chronic inflammatory and infectious processes, and cancers may accelerate the process. Probably, it is the most common type of vasculitis all over the world. Whole afferent vasculature including capillaries may mainly be involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the continuous endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Although early withdrawal of the causative factors may retard the final consequences, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature (12).

SCDs are life-threatening hereditary disorders affecting around 100,000 individuals in the United States (13). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (14), because the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced severe and continuous endothelial damage, inflammation, edema, and fibrosis terminate with end-organ failure in early years of ages. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (15), whereas they were 33.3 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBCs support during medical and surgical emergencies in the Hatay region of Turkey. Actually, RBCs support must be given during all medical and surgical emergencies in which there is evidence of clinical deterioration in the SCDs (16, 17). RBCs supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling induced endothelial damage all over the body during such events. According to our 18-year experiences, simple RBCs transfusions are superior to the exchange. First of all, preparation of one or two units of RBCs suspensions at each time rather than preparation of six units or higher provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusion of one or two units of RBCs suspensions at each time decreases the severity of pain and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBCs suspensions at each time decreases transfusion-related complications in the future. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevents some deaths which have developed during transport to the tertiary centers for the exchange. Fifthly, transfusions of RBCs suspensions in the secondary health centers prevents some extra costs on the health system developed during the exchange in the tertiary centers. On the other hand, longer survival of females in the SCDs (15) and longer overall survival of females in the world (18) cannot be explained by the atherosclerotic effects of smoking and alcohol alone, instead it may be explained by higher physical efforts of male sex in life that may terminate with an exaggerated sickling and vascular endothelial damage in early years of life (19).

SLE is an autoimmune disease characterized by skin lesions on sun-exposed areas, oral lesions, nonerosive arthritis, fever, positive antibodies to double-stranded DNA, renal and central nervous system (CNS) involvement, and cytopenias (20). It is mostly seen in women with a younger mean age (20). Similarly, 89.2% of all SLE patients were female, and the mean age of SLE cases was 37.0 years in the present study. Like Hatay region of Turkey, the prevalence of SLE is higher than RA in some areas (6.0% versus 2.7%, p<0.001) (21), and higher prevalence of marriage with close relatives may be an underlying cause. The sera of most patients contain antinuclear antibodies (ANA), often including anti-double-stranded DNA antibodies (22). Articular symptoms are seen in 90% of patients, and they may exist for years before the diagnosis (23). For example, the average time from the onset of symptoms to diagnosis was 5 years in the above study (20). As a difference from RA, most lupus polyarthritis is non-destructive in nature. Cutaneous lesions include characteristic malar butterfly erythema, discoid lesions, and erythematous, firm, maculopapular lesions of face, sun-exposed areas of neck, upper chest, and elbows. Photosensitivity is seen in 40% of cases. Generalized lymphadenopathy is also common. CNS involvement may cause personality changes, stroke, epilepsy, and psychoses (24). Renal involvement may be silent or even fatal. The most common manifestation is proteinuria (25). There were increases in the incidence of renal involvement and neurological symptoms throughout the disease course (20). Diagnosis of SLE requires highly trained specialists who are able to differentiate early symptoms of SLE from other pathologies. For example, early-stage SLE can be difficult to differentiate from RA if arthritic symptoms predominate (26-28). Thus, although RA and SLE have similar agents in the treatment protocol, ANA and anti-double-stranded DNA antibodies should be studied in every patient with RA (29, 30). Clinicians in the Hematology Clinics should be aware of SLE due to the frequent thrombocytopenia in differential diagnosis, particularly with idiopathic thrombocytopenic purpura. Immunosuppression therapy has made it possible to control the disease with improved life expectancy and quality of life (25). According to our observations,

methotrexate may be the simplest, cheapest, orally used, and one of the most effective treatment regimens for both SLE and RA. It can suppress inflammation and reduce corticosteroid doses. Its benefit begins in 3 to 4 weeks. It can be given 2.5 to 20 mg in a single dose once weekly, starting with 7.5 mg/wk and gradually increased as needed.

SCDs are severe inflammatory processes terminating with major health problems in early years of life (31). For example, menarche is retarded in females with the SCDs (32). Additionally, the severe and continuous endothelial inflammation all over the body causes an overlapping chronic disease anemia. Furthermore, end-organ insufficiencies can even suppress the immune system of the patients. Acute sinusitis, tonsillitis, and urinary tract infections are the common causes of painful crises and hospitalization, and they can rapidly progress into the severe and life-threatening infections including pneumonia, meningitis, and sepsis due to the relative immunosuppression in such patients (33). For example, tonsillary hypertrophy is a frequent physical examination finding that may be the result of a prolonged infectious process due to the relative immunosuppression in such patients (34). Severe and prolonged endothelial inflammation induced prominent weight loss and cachexia are also common in them (4). Autosplenectomy, painful crises, hospitalizations, invasive procedures, RBCs supports, medications, prevented normal daily activities, and an eventually suppressed mood of the body can even suppress the immune system (35, 36). In another definition, SCDs may cause an immunosuppression with several mechanisms in the human body.

As a conclusion, SCDs are severe and continuous inflammatory processes on vascular endothelium, particularly at the capillary level, and terminate with end-organ failures in early years of life. Beside that, SCDs may cause moderate to severe immunosuppression by several mechanisms that may be the cause of significantly lower prevalence of SLE in the SCDs.

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Prognosis, Complications and Quality of Life After Fibrinolysis versus PCI Post MI

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ABSTRACT

Acute myocardial infarction (MI) is a major health problem that carries considerable morbidity and mortality. Management of acute MI is carried out through adopting a reperfusion strategy either pharmacological (intravenous fibrinolysis) or mechanical (primary percutaneous coronary intervention (PCI)) to re-open the occluded coronary artery. Many literature studies have compared the efficacy, the complications, and the long-term outcome of both the intravenous fibrinolysis and primary PCI. Despite the superiority and overgrowing popularity of primary PCI in management of acute MI, fibrinolysis is still widely utilized. Many factors play a role in choice of the reperfusion strategy to be adopted, particularly the time from the symptom onset, the time required for preparing for PCI, and patient co-morbidities e.g. risk for bleeding. Primary PCI is generally more efficacious in achieving reperfusion. It is safer with lower mortality rates, and it is associated with lower risk to develop restenosis, re-infarction, heart failure, shock cerebrovascular stroke, or intracerebral haemorrhage. However, the less availability and the variable outcomes with operator experience are the main disadvantages that make PCI not feasible in many situations. This review article aims to compare the efficacy and advantages of intravenous thrombolysis and PCI and their prognosis, complications, and long-term impact on quality of life.

Key words: **acute myocardial infarction, fibrinolysis, PCI**

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Introduction

Coronary heart disease is a major public health problem that carries a considerable morbidity and mortality worldwide. Reports from the heart and stroke statistics note that almost half of the patients suffering from coronary heart disease in 2017 had a history of acute myocardial infarction (MI).[1] Myocardial infarction constitutes 33% of the cases of acute coronary syndrome, and it may present with either non-ST segment elevation MI (NSTEMI) or ST segment-elevation MI (STEMI). STEMI represents an acute occlusion of one of the epicardial coronary arteries due to thrombosis. It is diagnosed via an electrocardiogram and requires a prompt reperfusion.[2]

Reperfusion therapy comprises the immediate restoration of blood flow through or around the occluded coronary artery. It aims not only at addressing and treating the primary cause of occlusion, but also at improving the outcome. [3,4] The main strategies of reperfusion are pharmacological and mechanical approaches. Pharmacological reperfusion includes the use of intravenous fibrinolytic agents to achieve thrombolysis, whilst mechanical reperfusion entails the use of primary percutaneous coronary intervention (primary PCI) or immediate coronary artery bypass grafting.[5,6] This review article aims to compare the efficacy and advantages of intravenous thrombolysis and PCI and their prognosis, complications, and long-term impact on quality of life.

Fibrinolytic Reperfusion Therapy

Fibrinolytic therapy has been known for many decades for reperfusion after acute coronary artery occlusion leading to STEMI. More than 90% of cases of STEMI occur due to thrombus formation and rupture of intra-arterial atherosclerotic plaques.[7] Fibrinolytic agents used for reperfusion act on various points of coagulation pathways to inhibit thrombus formation and enhance the outcome. The main agents currently available for intravenous fibrinolysis are streptokinase, alteplase, reteplase, and tenecteplase.[8]

Streptokinase is the most widely used fibrinolytic agent. It was derived from beta-hemolytic streptococci. It is composed of a single polypeptide chain that binds to plasminogen forming active plasminogen that activates plasmin.[9] The main adverse events of streptokinase are allergic reactions (such as shivering, fever, rash, or rarely hypotension and anaphylaxis), bleeding (often minor bleeding, major bleeding is rare). Alteplase or recombinant tissue plasminogen activator (rtPA) is another fibrinolytic agent that is fibrin-specific and enhances plasminogen activation.[10] It is preferred to streptokinase due to its lower allergic risk. Reteplase or recombinant plasminogen activator (rPA) is a mutant of rtPA that is less-fibrin selective and possesses a longer half-life.[11] Tenecteplase is the last developed fibrinolytic agent. It was genetically-engineered to be very fibrin specific and to have a long half-life.[12]

Primary Percutaneous Coronary Intervention

Primary percutaneous coronary intervention (PCI) was first performed in 1977, and has undergone multiple developmental stages for better outcome.[13] Currently, primary PCI is considered the strategy of choice for patients with acute STEMI if performed in a timely fashion[14]. It is also preferred for patients with posterior myocardial infarction or myocardial infarction with left bundle branch block.[15] The technique used for primary PCI comprises the introduction of a wire via femoral or radial arteries to the coronary artery. Intravascular sonography and optic coherence tomography are used during PCI procedure to measure the intracoronary artery pressure and to assess the size, burden, and characteristics of the atheromatous plaque occluding the coronary arteries. Thrombectomy devices are used to mechanically remove the atheroma, and intra-arterial stents are inserted to keep the lumen patent or balloon angioplasty is carried out to prevent re-occlusion. Anti-thrombotic agents, antiplatelet drugs, and glycoprotein-inhibitor therapy are co-utilized to inhibit thrombosis[16]. Primary PCI was reported to have high success rates with more than 90% of patients achieving a thrombolysis in myocardial infarction (TIMI) 3 flow.[4] Primary PCI has lower risk of bleeding and stroke in comparison to intravenous fibrinolysis.[17] Therefore, they have largely replaced the sole use of IV fibrinolysis except in certain situations as will be discussed in the next section.

Fibrinolysis Versus PCI

Many studies have been conducted to compare the safety, efficacy, and outcome of intravenous fibrinolysis and primary PCI. Randomized controlled trails have explored the superiority of primary PCI with stents versus fibrinolysis and primary PCI with balloon angioplasty versus fibrinolysis. Results from these studies clarified certain indications for each of these approaches.

Indications of PCI versus fibrinolysis

The choice of reperfusion approach in patients presenting with acute myocardial infarction depends on a number of factors. These factors include the time from the onset of MI symptoms, the time expected for transport to a well-equipped PCI la boratory, the risk of STEMI, and the bleeding risk.

Primary PCI is currently the approach of choice for most of the patients with acute myocardial infarction who present to the hospital within 90 minutes of their presentation. However, it requires the availability of a skilled PCI laboratory with experienced surgeons. The medical contact-to-balloon or door-to-balloon time must be less than 90 minutes or the door to needle time is more time is more than one hour.(14) Other indications for primary PCI include the presence of cardiogenic shock, increased risk of bleeding or intracranial hemorrhage (ICH), high risk for STEMI, or late presentation to the hospital after three hours from the onset of manifestations (Table 1).[18]

Advantages and disadvantages of PCI and fibrinolysis

The main advantages of fibrinolysis include the ease of its administration, its availability in the vast majority of emergency departments in different hospitals, and its high efficacy particularly when administered during the first 60 minutes of symptom onset.[14] On the other side, intravenous fibrinolysis is less effective than primary PCI when given during the first three hours. The rate of achievement of TIMI 3 flow is about 40-50% with fibrinolysis versus around 90% with primary

Table 1: Comparison between intravenous fibrinolysis and primary PCI

	Fibrinolysis	PCI
Indications	• Presentation <1 hr from symptom onset • Presentation ≤ 3 hrs from symptom onset and delay to PCI>90 min • Prolonged transport • Door-to-balloon time - door-to-needle time > 1 hr • Medical contact-to-balloon or door-to-balloon > 90 min	• Late presentation >3 hrs from symptom onset • Presentation 2-3 hrs from onset with available well-equipped PCI lab and surgical backup • Door-to-balloon time - door-to-needle time < 1 hr • Medical contact-to-balloon or door-to-balloon < 90 min • Doubt or High risk for STEMI • Cardiogenic shock
Advantages	• Easy administration • Wide availability in most EDs • High efficacy especially in the first hour	• Higher efficacy (90% TIMI 3 flow rates) • More safe • Less re-infarction/restenosis • Less cerebrovascular stroke • Less bleeding/intracranial haemorrhage • Effective up to 18 hours from symptom onset
Disadvantages	• Less efficacy than PCY (40-50% TIMI 3 flow rates) • Risk of bleeding and intracranial haemorrhage • Risk of cerebrovascular stroke • Not effective after 3-6 hours	• Not available in all hospitals • Variable outcomes (operator-dependent) • Not feasible in all conditions • Higher cost
Efficacy	Lower	Higher
Mortality rate	Higher	Lower
Risk of stroke	Higher	Lower
Risk of ICH	Higher	Lower
Restenosis	Higher	Lower
Heart failure	Higher	Lower
Cardiac arrest	Higher	Lower
Long-term outcome	Worse	Better

PCI.[15] Furthermore, intravenous fibrinolysis carries a high risk for bleeding and intracerebral hemorrhage, and it is significantly less effective than primary PCI if administered within 3 to 6 hours from symptom onset.[17]

Primary PCI, on the other hand, is the strategy of choice in patients with acute STEMI. It is highly superior to IV fibrinolysis (with more than 90% restoration of TIMI 3 flow rate) and markedly lower risk for bleeding or intracranial hemorrhage.[20] It is also superior as regards the long-term outcome with considerably low risk for restenosis or re-infarction.[21] Moreover, primary PCI is less affected by patient-related factors such as the time of symptom onset, and its efficacy is established over up to 18 hours from clinical presentation.[22] The main disadvantages, however, are being less available, not often feasible, and being operator-dependent. So the, the outcome would vary from one center and one interventionist to another.[23]

Prognosis, complications, and long-term outcome of PCI versus fibrinolysis

The long-term outcome after primary PCI is generally better than fibrinolysis. Various literature studies approved the superiority of PCI over intravenous fibrinolysis as regards the mortality rates, risk for restenosis or re-infarction, and risk for bleeding and intracranial hemorrhage. Despite the multiplicity of studies supporting the general superiority of primary PCI to fibrinolysis, data from other researchers are conflicting.

Primary PCI was proven to have lower 30-day mortality rates (4.4% versus 6.5% mortality rate in fibrinolysis). Higher rates were reported among the CAMI study.(17) The mortality rate was 15% and 7.7% among patients undergoing fibrinolysis and PCI, respectively ($P<0.05$). Despite the superiority of PCI in the vast majority of the studies, many trials (such as FAST-MI, STREAM, and WEST) reported no significant difference in mortality rates between PCI and fibrinolysis-treated

groups.[15,24,25] In disagreement with this, Westerhout et al. reported that the mortality rates are lower among patients who undergo fibrinolysis within two hours of symptom onset in comparison to primary PCI.[26]

One of the main contraindications for intravenous fibrinolysis is bleeding tendency and risk for intracranial hemorrhage.[15] Thus, primary PCI is considered the approach of choice in these conditions. However, researchers from the STREAM trial reported no statistically significant difference between fibrinolysis using tenecteplase as regards the hemorrhagic complications particularly intracranial hemorrhage.[5] Similarly, results from the CAMI study reported no significant difference between primary PCI and fibrinolysis as regards hemorrhagic stroke and major bleeding.[17] Hemorrhagic stroke occurred in 0.6% and 0.3% of patients who underwent fibrinolysis and primary PCI, respectively ($p>0.05$). Major bleeding occurred in 5% of the fibrinolysis-treated cases and 3% of PCI-treated patients ($p>0.05$).

After reperfusion, the risk for cerebrovascular stroke is 0.7% among patients who had primary PCI versus 2.0% among patients who had intravenous thrombolysis.[27] The risk of re-infarction was significantly lower among patients undergoing PCI than patients with intravenous fibrinolysis[28]. The superiority of primary PCI is thought to be attributed to the fact that the rate of achievement of TMI 3 flow primary PCI is 90% whereas it ranges from 50-60% only in patients undergoing fibrinolytic therapy.[27,29] Some researchers, on the other hand, noted that there was no statistically significant difference between the efficacies of fibrinolysis versus PCI if performed during the first 3 hours without delay. In contrast, a study conducted in 2008 found that the primary PCI was superior to fibrinolysis even if delayed.[30] Additionally, primary PCI was reported to have lower rates of heart failure, cardiac arrest, and mechanical complications when compared to fibrinolysis ($p <0.05$).[17]

Conclusions

Despite the superiority and overgrowing popularity of primary PCI in management of acute MI, fibrinolysis is still widely utilized. Many factors play a role in choice of the reperfusion strategy to be adopted particularly at the time from the symptom onset, the time required for preparing for PCI, and patient co-morbidities e.g. risk for bleeding. Primary PCI is generally more efficacious in achieving reperfusion. It is safer with lower mortality rates, and it is associated with lower risk to develop restenosis, re-infarction, heart failure, shock cerebrovascular stroke, or intracerebral haemorrhage. However, the less availability and the variable outcomes with operator experience are the main disadvantages that make PCI not feasible in many situations.

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Pathophysiology of pulmonary hypertension in sickle cell diseases

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ABSTRACT

Background: **Pulmonary hypertension (PHT) is common in sickle cell diseases (SCDs).**

Methods: **All patients with SCDs were included.**

Results: **The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males (p<0.001 for both). Disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), transfused units of red blood cell (RBC) (48.1 versus 28.5, p=0.000), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were also higher in males. There were 31 mortality cases (17 males) with similar mean ages in males and females (30.2 versus 33.3 years, respectively, p>0.05). Mean ages of COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), deep venous thrombosis and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and benign prostatic hyperplasia (41.5 years) were higher.**

Conclusion: **SCDs are severe inflammatory processes on vascular endothelium particularly at capillary level, since the capillary system is the main distributor of hardened RBCs into tissues. Although various arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of PHT in SCDs.**

Key words: **Sickle cell diseases, chronic endothelial damage, atherosclerosis, pulmonary hypertension**

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Introduction

Chronic endothelial damage may be the leading cause of aging and associated morbidity and mortalities by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature and thus reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, and cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCDs are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failure in early years of life. We tried to understand the pathophysiology of PHT in the SCDs.

Materials and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, epilepsy, deep venous thrombosis (DVT), transfused units of red blood cell (RBC) in their lives, surgical operations, leg ulcers, stroke, priapism, and benign prostatic hyperplasia (BPH) symptoms including urgency, weak stream, incomplete emptying, and nocturia were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist. Patients with disseminated teeth loss (<20 teeth present) were detected. Cases with acute painful crises or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus (HIV), a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (5). Associated thalassemia minor was detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (6). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest X-ray film, fever, cough, sputum production, dyspnea, or hypoxia (8). An X-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is also diagnosed with the echocardiographic findings. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, thalassemia minor, smoking, alcohol, painful crises per year, and accelerated atherosclerotic endpoints of the SCDs were detected in both genders, and compared in between. Beside that, mean ages of these atherosclerotic endpoints were detected in them. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCDs (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, $p>0.05$). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, respectively, $p>0.05$). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males ($p<0.001$ for both) (Table 1). Disseminated teeth loss (<20 teeth present) (5.4% versus 1.4%, $p<0.001$), transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), COPD (25.2% versus 7.0%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%, $p<0.001$), leg ulcers (19.8% versus 7.0%, $p<0.001$), digital clubbing (14.8% versus 6.6%, $p<0.001$), CHD (18.0% versus 13.2%,

Table 1: Characteristic features of the study cases

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases

†Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases according to the gender distribution

Variables	Male patients with SCDs*	*p*-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Disseminated teeth loss (<20 teeth present)	***5.4% (12)***	***<0.001***	***1.4% (3)***
Transfused RBC‡ units	***48.1 ± 61.8 (0-434)***	***0.000***	***28.5 ± 35.8 (0-206)***
COPD§	***25.2% (56)***	***<0.001***	***7.0% (15)***
Ileus	***7.2% (16)***	***<0.001***	***1.4% (3)***
Cirrhosis	***8.1% (18)***	***<0.001***	***1.8% (4)***
Leg ulcers	***19.8% (44)***	***<0.001***	***7.0% (15)***
Digital clubbing	***14.8% (33)***	***<0.001***	***6.6% (14)***
CHD¶	***18.0% (40)***	***<0.05***	***13.2% (28)***
CRD*	***9.9% (22)***	***<0.05***	***6.1% (13)***
Stroke	***12.1% (27)***	***<0.05***	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
Acute chest syndrome	2.7% (6)	Ns	3.7% (8)
Respiratory sinus arrhythmia	4.9% (11)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)

*Sickle cell diseases

†Nonsignificant (p>0.05)

‡Red blood cell

§Chronic obstructive pulmonary disease

¶Coronary heart disease

**Chronic renal disease

***Pulmonary hypertension

****Deep venous thrombosis

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean ages of the patients
Respiratory sinus arrhythmia	27.2 ± 8.3 (18-50)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
Acute chest syndrome	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth loss (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD*	33.6 ± 9.2 (13-58)
PHT†	34.0 ± 10.0 (18-56)
Leg ulcers	*35.3 ± 8.8 (17-58)*
Digital clubbing	*35.4 ± 10.7 (18-56)*
CHD‡	*35.7 ± 10.8 (17-59)*
DVT§ and/or varices and/or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
CRD¶	*39.4 ± 9.7 (19-59)*
*BPH***	*41.5 ± 10.6 (27-58)*

*Chronic obstructive pulmonary disease

†Pulmonary hypertension

‡Coronary heart disease §Deep venous thrombosis

¶Chronic renal disease

**Benign prostatic hyperplasia

p<0.05), CRD (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in males, significantly. There were 11 males (4.9%) with BPH symptoms with a mean age of 41.5 ± 10.6 (27-58) years. All of the BPH patients could be treated with once daily 4 milligrams of doxazosin, orally. Additionally, there were 23 males (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 ± 8.4 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (p>0.05) (Table 2). When we evaluated the mean ages of the consequences of the SCDs, COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may be the alarming consequences indicating an advanced disease in such patients due to the significantly shortened survival of the SCDs in both genders (Table 3).

Discussion

SCDs are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (11, 12). Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBCs. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCDs patients with associated thalassemia minor, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammation, infection, or various stresses of the body. The abnormally hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (13, 14). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the abnormally hardened RBCs into the tissues. The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients.

As a result, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (16), whereas they were 30.2 and 33.3 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in the Antakya region of Turkey (17). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (8). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling-induced endothelial damage, inflammation, and edema all over the body.

COPD is the third leading cause of death with various causes and pathophysiologic mechanisms in the world (18). It is an inflammatory disease that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes. As also observed in the present study, regular alcohol consumption may also be important in the inflammatory process. For example, COPD was one of the most common diagnoses in patients with alcohol dependence (19). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (20). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (21, 22). For example, there may be close relationships between COPD, CHD, PAD, and stroke (23). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (24). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (24). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (25). As a result, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCDs patients associated with COPD (26).

PHT may also be found among one of the atherosclerotic terminal endpoints of the SCDs. PHT is defined as the increased BP in pulmonary artery, vein, or capillaries. It is seen in 60% of systemic sclerosis, 40% of SCDs, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal HT, and 0.5% of HIV patients (27). Whereas we detected PHT just in 12.2% (53 cases) of the SCDs patients in the present study. Younger mean ages of our study cases (30.8 years of males versus 30.3 years of females) may be the cause of the lower prevalence. PHT and COPD may actually have similar atherosclerotic underlying mechanisms during the development but PHT may be a more advanced disease since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2 versus 16.3%), and it is nearly equally seen in both genders (52.8 versus 78.8% in males) than the COPD in the present study. On the other hand, venous PHT is the most common cause of PHT in the society (28). In venous PHT, left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions. In chronic thromboembolic PHT, blood vessels are blocked or narrowed with clots, which leads to a similar pathophysiology with arterial PHT (29). In hypoxic PHT, hypoxia is thought to cause vasoconstriction or tightening of pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCDs due to the inflammated and edematous capillary endothelium, secondary to the damage of abnormally hardened RBCs in the lungs (30). Whatever the initial cause, PHT involves vasoconstriction or tightening of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of heart causes thickening and enlargement of right ventricle, right heart failure, and cor pulmonale. As blood flowing through lungs decreases, left heart receives less blood. This blood may also carry less oxygen than normal as in the SCDs due to the capillary endothelial inflammation and edema. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activity. Although various arterial and venous involvement mechanisms, capillary endothelial involvement may be the major underlying cause of PHT in the SCDs since the capillary system is the main distributor of the abnormally hardened RBCs into the lungs.

Digital clubbing is characterized by increase of the normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (31). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (32). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (10). But according to our experiences, digital clubbing is frequently associated with smoking alone and with pulmonary, cardiac, renal, or hepatic disorders which are characterized with chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs and those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCDs and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males ($p<0.001$) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (33), and the ratio was 13.5% in the present study. Its incidence increases with age, male sex, and HbSS genotype (34). Similarly, its ratio was higher in males (19.8% versus 7.0%, $p<0.001$), and mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, $p<0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (33). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (33). The abnormally hardened RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary

level may be the major underlying cause in the SCDs (34). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hardened RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood probably delays wound and fracture healings in the lower extremities. Beside the hardened bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are much more common in males. Hydroxyurea is the only drug that was approved by the Food and Drug Administration for the treatment of SCDs (15). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (17). Its main action may be the suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs (35). Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (36). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea therapy may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCDs.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are much more common in females and metabolic syndrome. Normally, leg muscles pump veins to return blood against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination must be performed in the upright position. Although the relatively younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively) and significantly lower body mass index of the SCDs cases in the literature (14), DVT and/or varices and/or telangiectasias of the lower limbs were higher among the study patients (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement of the SCDs.

Both frequency and complications of cirrhosis are increasing in the world, and it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, non-alcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in childhood at the moment (37). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (37). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (38). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (39). NAFLD may be considered as the hepatic consequences of the metabolic syndrome and SCDs (11, 40). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (41). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effect of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (42). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (42, 43). As a result, beside COPD, PHT, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among one of the atherosclerotic terminal endpoints of the metabolic syndrome and SCDs.

Both frequency and complications of CRD are increasing all over the world, too (44). The increased frequency and complications of CRD may be explained by aging of the societies and increased prevalence of excess weight all over the world, since CRD may also be found among one of the terminal atherosclerotic endpoints of the metabolic syndrome (45). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes may be the major underlying causes of the endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arterioles. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, tissue hypoxia, and tissue infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses during acceleration of tissue inflammation and immune cell activation (46). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with CIMT (45). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (47). Excess weight also causes renal vasodilation and glomerular hyperfiltration that initially serve as compensatory mechanisms to maintain

sodium balance due to the increased tubular reabsorption (47). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (48). With prolonged weight excess, there are increased urinary protein excretion, lost nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (47). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (49). The inflammatory and eventual atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (49), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (42). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (50). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure (51). In another definition, CRD may also be found among one of the atherosclerotic terminal endpoints of the metabolic syndrome and SCDs (52).

As a conclusion, SCDs are severe inflammatory processes on vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of hardened RBCs into tissues. Although various arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of PHT in the SCDs.

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Ano-Rectal Surgery: Clinical Assessment and Risk Management

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ABSTRACT

Background:
The perianal, anal and rectal region lend themselves to early clinical diagnosis without the need to resort to complex investigative processes. With adverse events increasing in hospitals worldwide Risk Management has become a major part of Quality Assurance.

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Procedures

The history followed by inspection, palpation, rectal examination, proctoscopy and then sigmoidoscopy are sufficient to clinically diagnose most conditions.

If a full local examination is not performed a delay in diagnosis of conditions such as carcinoma of the anal canal and rectum may occur.

Inappropriate treatment of other conditions such as pruritus ani, warts, haemorrhoids, polyps, abscesses and fistulas may result.

Functional Unit of Continence

The anus, anal canal and rectum are a functional unit responsible for the maintenance of continence of faeces and flatus as well as the co-ordinated process of defecation. Theories such as the valvular mechanism of the anorectal angle have been postulated to explain the process. Basic factors responsible for the maintenance of continence are:

1. The anorectal angle - formed by the puborectalis muscle,
2. The internal sphincter,
3. The external sphincter.

This is all controlled by a reflex interaction and integration between:

a) The sensory receptors in the pelvis,

b) The smooth muscle internal sphincter supplied by the autonomic nervous system and,

c) The striated muscle of the external sphincter - supplied by the somatic fibres of the pudendal nerve. It is postulated at rest with the faeces in the rectum that the anorectal angle acts like a valve. As pressure increases the valve is accentuated, maintaining continence. However as the bulk increases further receptive relaxation of the internal sphincter occurs. There is a sampling of the faecal material by the sensitive epithelium of the anal canal resulting in the desire to defecate and the sensation of the need to pass flatus.

This is further controlled by the voluntary external sphincter muscle.

Defecation

With straining the anorectal angle is reduced and straightened, the internal and external sphincter muscles relax and defecation occurs.

Pathological

Continence may be interfered with as a result of localised or generalised disease or following trauma or surgery.

Histological Features

The perianal skin is stratified squamous epithelium with keratinisation. Just above the anal verge the skin, hair, sebaceous glands and sweat glands there is a transitional type of epithelium for a distance of approximately 1 cm - to the pectinate line.

Above the pectinate line the glands of Lieberkuhn's and goblet cell appear a muscularis mucosa and lamina propria are found.

The pectinate line (dentate line):

a) The pectinate line is formed at the site of the fusion of the embryonic proctodermal plate and post-allantoic gut embryologically.

b) The pectinate line is a land mark not only histologically but is also the site at which there are major practical significant changes as it is a junctional zone between:

1) The somatic sensory supply to the skin, modified skin and the autonomic supply to the mucosa above the pectinate line.

2) The junction between the haemorrhoidal arterial supply derived from the mesenteric artery and the lower pudendal artery supply from the iliac.

3) Systemic circulation below the dentaline and portal venous system above.

4) The lymphatic drainage below the dentaline is to the inguinal node above the dentaline to the pelvic lymph nodes - there is some overlap with this particularly in pathological states.

c) Anal glands open at the pectinate.

History and Examination

Symptoms indicate disease but a more detailed analysis then indicates the diagnosis:

1. Bleeding,
2. Pain,
3. Protruding or prolapsing lump,
4. Discharge - starting on the underwear or associated bowel action with pus and mucous,
5. An irritation,
6. Faecal incontinence,
7. Unsatisfied defecation,
8. Changes in bowel habit and urgency with either diarrhoea or constipation,
9. "Haemorrhoids" - often patients complain of "haemorrhoids".

The diagnosis of haemorrhoids cannot be taken at face value as patients often use this term for any anorectal problem.

All the above symptoms may be associated with disease:

a) In the anorectal region,

b) From a higher level in the bowel,

c) As a result of some generalised problem.

The history and examination are directed at differentiating these possible signs:

1. The type of bleeding is critical and needs further description; the blood may be dark or bright, mixed with the stool, on the paper or dripping in the bowl. The bleeding may be associated with pain or painless.

2. Blood mixed with the stool can suggest a cause of bleeding higher up in the bowel.

3. Bright red blood on the toilet paper suggests haemorrhoids.

4. Black stools may indicate bleeding from higher in the stomach.

5. A few drops of blood associated with severe pain on and after defecation could suggest a fissure.

6. The presence of pus or mucous might suggest an inflammatory condition.

7. A sexual history may be necessary to diagnose HIV or AIDS or gonococcal disease. Infected proctitis can occur in either. This needs to be differentiated from non-specific proctitis.

These inflammatory conditions can present with an abscess or fistula, an atypical fissure, which is of an opportunistic infection such as amoebiasis or cryptos porous.

The Examination

1. A general inspection. The general appearance of the patient may suggest a cause of bleeding and its severity. It may be signs of pallor with excessive bleeding due to anaemia or jaundice for example where there are liver problems. There may even be signs of cachexia.

2. The examination of the abdomen is carried out first to detect masses or other features such as an enlarged liver e.g. cirrhosis of the liver may be associated with portal hypertension and bleeding haemorrhoids.

3. The left lateral position may be used for the examination.

4. The rectal examination may be difficult in the apprehensive, sensitive, overweight patient with severe pain. An examination under anaesthesia is required in some circumstances:

a) The anal verge is inspected.

b) The anal skin has ridges which irradiate peripherally. The anal orifice is usually closed but a gaping sphincter may be present.

c) The surrounding area is examined.

d) There may be signs of ulceration, irritation, excoriation, swelling or the external opening of a sinus or fistula with a discharge. Skin tags are often present and may point to underlying haemorrhoids or fissures.
e) Scars from obstetric injuries or trauma or previous surgery can be important in the assessment - particularly of incontinence.
f) A protruding lump may be present. The commonest cause of this would be haemorrhoids.
g) Several different types of polyps may be present - particularly if the patient is asked to strain or they may be prolapsed down from the rectum by the examining finger on rectal examination.

1) A pedunculated fibro epithelial polyp,
2) A pedunculated tubular adenoma,
3) A sessile villous tumour,
4) A myeloma or other connected tissue tumour such as a lipoma,
5) Even a malignancy can be protruding.

There may be skin lesions such as, rarely, melanoma, but occasionally conditions such as squamous cell carcinoma in situ.

Haemorrhoids, polyps or a rectal prolapse may appear with straining.

Abnormal laxity or descent of the perineum may occur in disorders of the pelvic floor, which can be associated with incontinence.

The anal verge can then be gently parted to demonstrate any protruding lesion or the presence of an anal fissure. Parting the anal verge may be painful with an anal fissure and the sphincter can be seen to contract with the pain.

Rectal Examination
Rectal examination is part of the routine examination for any abdominal or rectal problem. The glove must be well lubricated first. An explanation is given regarding the examination and the patient reassured. Gentle pressure is applied over the anus and this tends to overcome spasm and resistance and allows the gloved finger into the anal canal without pain. The finger is introduced posteriorly along the anal canal and the tone of the sphincter is assessed. The walls of the anal canal are palpated. Four to five centimetres into the anal canal is the upper level of the surgical anal canal. The ridge of the anorectal ring can be palpated. The finger then enters the rectum.

The finger palpates the mucosa thoroughly and then two specific structures are sought:

a) Anterior - the prostate in males. The cervix and uterus in females,
b) Posteriorly - the hollow of the sacrum and,
c) Laterally - the lateral ligaments and pelvic lymph nodes,
d) The tip of the finger palpates the Pouch of Douglas looking for a mass - for example, secondary deposits or pelvic abscess.

Palpation of the mucosa may detect lesions such as:

1) Benign polyps - pedunculated tubular adenomas or sessile villous adenomas,
2) Malignant lesions such as carcinoma of the anus or rectum - ulcerated or nodular,
3) Anal papillae,
4) The internal opening of a fistula.

Haemorrhoids may be palpated as a soft cushion but are not readily palpable unless very large or thrombosed. If a painful condition such as an abscess or fissure is present, resistance to examination by the patient will be obvious and should not be pursued.

On withdrawal of the glove this is inspected for the presence of blood or mucous and the colour of the faecal material.

The rectal examination should be performed before any instrumentation

Proctoscopy and Sigmoidoscopy

Proctoscopy
The mucosa is visualised and this is particularly useful in the diagnosis of haemorrhoids. The haemorrhoids will bulge into the lumen of the proctoscope as it is withdrawn and the patient is straining.

Procedures such as injection of haemorrhoids or rubber band ligation can be performed through a proctoscope.

Sigmoidoscopy
Sigmoidoscopy can be performed in the left lateral position. It is usually a little uncomfortable particularly when the area is inflated but is usually readily tolerated. The area is inflated to allow visualisation of the mucosa or lumen or when attempting to negotiate the rectosigmoid junction which is at the level of 15 - 18 cms.

It may not be possible in about 50% of patients to pass the rectosigmoid junction which is at about 15 cms due to discomfort because of the angulation to the site.

Sigmoidoscopy shows mucosal changes - signs of inflammation, melanosis coli (patchy dark pigmentation) attributable to excessive use of laxatives, and lesions arising from the mucosa such as polyps or malignancies. These may be biopsied as necessary.

A high percentage of bowel tumours occur within reach of the sigmoidoscope. Sigmoidoscopy is one of the most cost effective ways of detecting the presence of any carcinoma. It should be used more frequently especially as bowel cancer is the second most common cancer in males and females.

Up to 50% of polyps and carcinomas of the colon are within reach of the sigmoidoscope.

Further investigation of the region may include flexible sigmoidoscopy, sigmoidoscopy and barium anaemia.

Management of Ano-rectal conditions

Some of the conditions may be treated with conservative or appropriate ointments or creams.

Many of the conditions can be treated in the office - such as haemorrhoids. Injection sclerotherapy and rubber band ligation are effective ways of treating haemorrhoids. Perianal haematomas may be incised or excised under Local Anaesthetic. A small perianal abscess can be drained. Skin tags can be removed.

Experienced Surgeons may treat the more complex conditions in the office. Anal fissures can be treated with sphincterotomy under Local Anaesthetic. A variety of degrees of haemorrhoids may be excised under Local Anaesthetic in the office as appropriate.

Even polyps may be pulled down and ligated.

The same techniques can be used in hospital with the addition of light sedation. Many cases can be treated as a day case.

Thus after a comprehensive examination of the history and examination which includes the abdomen, inspection of the perianal region, palpation of the perianal region, rectal examination, proctoscopy and sigmoidoscopy, a plan of action can be carried out.

This may involve further investigative procedures or surgery in hospital. However in many cases a definitive diagnosis can be made and a treatment carried out at that time or arranged for the near future.

Other serious problems must not be overlooked and must be taken into account before instituting a plan of action.

It must be remembered when treating the anorectal region that patients are apprehensive, may fear the presence of a possible cancer and may find the examination embarrassing and uncomfortable. This needs to be assessed thoroughly before attempting any procedures. There must be some explanation of the possibility of pain in the post-operative period.

Of course it is part of a risk management plan. The advantages and disadvantages of having a procedure are discussed and the alternative methods of treatment available also discussed.

The option may be to do nothing or to wait and see. A further review may be judicious.

It is however helpful to have literature available for the patient to read which will explain their condition in detail.

Rectal Prolapse

Normally, the rectum is securely attached to the pelvis with the help of ligaments and muscles. This attachment firmly holds the rectum in place.

Various factors, such as age, long-term constipation, and the stress of childbirth, may cause these ligaments and muscles to weaken, which means that the rectum's attachment to the body also weakens. This causes the rectum to prolapse, meaning it slips or falls out of place.

In the early stages of rectal prolapse, the rectum becomes poorly attached but stays within the body most of the time. This stage of rectal prolapse is called mucosal prolapse, or partial prolapse, meaning that only the inner lining of the rectum (rectal mucosa) protrudes from the anus.

As the rectum becomes more prolapsed, the ligaments and muscles may weaken to the point that a large portion of the rectum protrudes from the body through the anus. This stage is called complete prolapse, or full-thickness rectal prolapse, and is the most commonly recognized stage of the condition.

Rectal prolapse is an uncommon disease and primarily affects elderly people. In people older than 65 years, the prevalence is 1%.

Surgical Treatment

Various operations have been used to treat this disease. The choice of operation is tailored to suit the patient and their comorbidities.

Younger patients who have rectal prolapse without major medical problems, may be offered an abdominal rectopexy. This involves an abdominal incision and rectal dissection with suture fixation of the rectum to the vertebra. The bowel is not resected.

A resection rectopexy removes the sigmoid colon and joins the bowel together (anastomosis).

For more frail elderly patients a Delorme's operation is offered. This is a mucosal sleeve resection that is performed trans anally. The lining of the bowel is resected and the muscle wall is bunched up with sutures and placed above the muscle sphincters.

The risk of recurrent rectal prolapse is higher in Delorme's operation compared to resection rectopexy, but the Delormes operation has lower risks for patients with medical comorbidities.

n the clinical assessment of the ano-rectal region the following general principles of history, examination and patient management need to be applied.

History

For every clinical case a thorough history is taken. There are particular questions that should be asked.

First presentation

"*Why has the patient attended the Doctor*?"

- How did the lesion occur?
- When did it happen or when was it first noticed?

- What were the associated circumstances?

- What changes have occurred, for example: in size, shape, colour, discharge and when did the changes occur?

- Has there been any pain or discomfort?

- What are the features of the discomfort or pain?

- Has there been any change in the quality or the intensity of the pain or discomfort? When did this happen?

- Has there been any associated features such as fever, loss of weight, swelling, lymph gland enlargement or jaundice?

Present situation

"What is happening now?"

- When, where, how and why did the condition develop?

- What are the associated features of other symptoms, which can aid in diagnosis of the lesion?

- Are there any family or other contacts who have a similar problem?

The General History of the Patient

General Assessment

Are there any factors which may affect (positively or negatively) The presenting complaint, its treatment or the patient's recovery?

"What are present effects of past activities?"

"What are present effects of his/her present lifestyle?"

Are there any factors in the past or present social, economic, educational, religious, occupational, family history, or involvement with sporting clubs or to her social networks or people in the patient's life, which may affect (positively or negatively) the cause, treatment or outcome of the presenting problem?

"What predictions are present which will influence future management and health of the patient?"

Are there any factors in the past medical (including surgical and anaesthetic) history, socio-economic or belief systems of the patient which may influence the intended therapy? Is the intended treatment the most appropriate in the circumstances?

The Ethical Issues

What does the patient want, understand and expect?

Is the intended treatment necessary and affordable by the patient or patient's family; is it best performed by the attending doctor at this or a later time?

What is the best, and the most appropriate surgical procedure and method or anaesthesia for this patient at this time by his surgeon, in these circumstances?

What can be done? What should be done? And who should do it? Where should it be done? And who else should be present, if anyone? Can or should the treatment be delayed or deferred?

Will the optimal result be achieved (immediately or later) by not doing anything, or by undertaking a definitive procedure?

Written or verbal, consent must be given by the patient to the doctor, before any procedure is performed.

Aspects of Every Problem

A definitive or provisional diagnosis decision should be made in every case. Systematic methods of analysis are then applied to each aspect of every case presenting

Anatomical

Including histological, surgical and imaging techniques where indicated.

Functional

Including genetic or chromosomal abnormalities. Including normal and pathological physiology, biochemical, function and predicted response to the surgical intervention itself, as well as to the anaesthetic drugs and processes used.

Psychological

Including normal responses to illness and recovery, psychological reactions to health and disease, in those with emotional or psychiatric disorders.

Social

Including family history of abnormal healing or unusual drug responses. Also including the socio-cultural expression of illness in the patient's particular tribal or racial group, in the patient's socio-economic status, past and present, expected or real, occupational, sport, recreational and artistic activities, ethnicity, nationality and background of the family etc., educational level aspired to, reached or expected, refugee status if any, diet and food requirements, and what can be afforded, obtained and understood.

Spiritual

Spiritual or belief structures of the society, the patient and the doctor, will influence the presentation, the illness, the treatment and the recovery, probably more than any other single factor.

All these factors constantly influence each of the others.

Each of these factors varies in importance and effect from patient to patient, from day to day, and sometimes from minute to minute.

The following are related to specific areas of ano-rectal conditions:

Colorectal Cancer

All adult patients should be screened regularly for colorectal cancer.

The GP needs to be able to recognise the wide variation in clinical presentations.

Any patient over age 40 with even minimal rectal bleeding, should be considered for colonoscopy. High risk symptoms are:

Bleeding which is not bright in colour

Change in bowel habits

Unexplained weight loss

Abdominal pain

Mucous discharge

The technique of history taking, combined with the art and skill involved in the physical examination, still remains the basis of diagnosis, despite continuing advances in medical technology.

The diagnostic process requires correlation and interpretation of the patient's history, symptoms and signs. The skill arises in placing all these factors in a proper perspective.

After arriving at a provisional clinical diagnosis, a decision is then made regarding the need for further investigation or for surgical intervention.

Many factors must be taken into account before deciding to operate. The most important of these is to have arrived at a precise clinical diagnosis.

This is becoming increasingly important in terms of medical economics, hospital priorities, patient convenience and safety.

Topics which form the basis of all surgery:

1. Clinical diagnosis

2. Method of anaesthesia, analgesia and pain control; and

3. Surgical technique and postoperative care.

Surgery should only be undertaken by those who have had appropriate training and whose skills have been developed under the supervision of acknowledged teachers and experts in each field, as well as by practice under supervision.

Any surgical condition requires a thorough preoperative and postoperative assessment in addition to evaluation of progress during the operation.

The reasons for the decision to operate, the result expected by the patient, the family and by the treating doctors, depend on thorough assessment and detailed explanation.

A method is presented which in most cases allows for such evaluation.

It involves:

1. The history of the presenting problem;

2. A general history of the patient

3. An analysis of factors which may affect the problem; and

4. The clinical examination

Risk Assessment

Risk Area - Adverse event management

Risk - Reoccurring adverse events may be undetected resulting in unexpected adverse patient outcomes

Quality Assurance Self Assessment

- Adverse events (including sentinel events and 'near misses') occurring within the practice are documented in a designated register or database.

- Remedial action/changes to practices can be demonstrated where appropriate as a result of reviewing adverse events.

- Changes made with the intention to prevent adverse event occurence are communicated with colleagues in order to ensure a similar event does not occur elsewhere (e.g. publication in College newsletter with de-identification of practice/patient particulars).

- Risk Area - Clinical audit

- Risk - Variations in clinical practice resulting in adverse patient outcomes

- Quality Assurance Self Assessment

There is regular participation in clinical audit/peer review.

The audit covers:

- Patient diagnosis/condition
- Legibility
- Practitioner sign off

The audit:

- reviews specific cases, e.g. unexpected patient death, unexpected development of infection, etc.

- includes a multidisciplinary patient record review. i.e case is discussed in a multidisciplinary setting.

- involves review of clinical incidents reported within the practice.

Risk Area - Continuing education and training

Risk - Insufficient skills or knowledge to ensure best practice medicine is practised

Haemorrhoids

The risk management here is to:

a) Establish a diagnosis,

b) Recommend treatment.

Not all haemorrhoids require surgical intervention and alternative treatments for each problem should be offered.

It should be remembered for any anal procedure that the postoperative recovery can be very painful particularly if a complication occurs. Thus the patient needs to be adequately warned about the possibility of pain and the possibility of fainting with pain or due to psychological responses.

The patient often comes for reassurance that they have not got a cancer. If cancer cannot be completely ruled out as a local cause of the problem then further examination with sigmoidoscopy and colonoscopy will be required.

For haemorrhoids, the treatment may consist of diet alone and review may be required. Other alternative treatments are local applications, which may sting, injection sclerotherapy, rubber band ligation and surgical intervention.

Haemorrhoids may be treated with injection or rubber band ligation but it should be remembered that either technique can be painful and complications such as infection or bleeding may occur - in particular secondary haemorrhage eight to ten days later or even reactionary haemorrhage within 24 - 48 hours of the procedure.

There needs to be adequate explanation for the procedure. If an office procedure is to be carried out the patient needs to be fully informed about the extent of the procedure and the aftercare. In particular risks of fainting and causing damage to oneself. The appropriate supervision afterwards is required.

Rectal prolapse

It should be explained to patients and relatives particularly with elderly frail patients that surgery is not always successful because:

a) it may fail to correct the problem permanently

b) it may not alleviate some of the symptoms such as excessive constipation or diarrhoea

The pros and cons need to be evaluated with the patient and relatives prior to surgery. How disabling is the problem to the patient and carers. The precise risks of each specific operation should be explained including the risks of any surgery or anaesthesia.

Anal fissure

Anal fissure can be a persistent problem or an acute problem, which resolves. This needs to be considered in the treatment.

There are a variety of local treatments available, which do not involve cutting the sphincters - sphincterotomy. These include use of local application and injections. There is a debate as to how effective these are but patients may prefer to try these such as Botulinum toxin injections. Anal stretch has been widely discredited.

The surgical treatment is usually a subcutaneous lateral sphincterotomy with or without excision of tag and the fissure itself. The patient should be warned that the operation does not actually remove the fissure but allows it to heal up or removes the pain. The fissure in itself may not always heal but the pain should be relieved.

The risk of incontinence should be discussed but it is rarely a factor in experienced hands.

The procedure can be done in the office in the appropriate setting but it can also be carried out under Local Anaesthetic with light sedation as a day case.

Possible risks of the procedure are excessive bleeding, infection or development of a fistula, but the incidence of complications is low.

One of the other risks would be not cutting sufficient sphincter to relieve the spasm. The sphincter can be difficult to find if not experienced so care is taken in carrying out the procedure to ensure the correct muscle is divided.

Anal polyps

There are a variety of different types of polyps in the anorectal region. Some are benign and never become malignant, such as anal tags and hyperplastic polyps. There are others however, which have a high potential to become malignant. These may be a single or multiple polyps. There are the tubular adenoma type or the villous adenoma type. The tubular adenoma type often has a stalk whereas the villous adenoma type is flat and velvety.

The Risk Management here is that an incomplete rectal examination or failure to do a rectal examination can miss these potentially malignant conditions. Other aspects of the Risk Management are in the treatment of which there are a variety of techniques, which can be used.

The important thing with all of these of course is to remove a benign lesion completely and also to remove a malignant lesion completely. However it is important to recognise that there are risks in operating in this area even though it is below the puborectalis level such as perforation of the full thickness and developing infection. Bleeding is also one of the severe complications in this area.

Abscesses and Fistula

At the age of 80, particularly in females there is a high risk of developing faecal incontinence — to flatus and solid, when performing these procedures. A subcutaneous sphincterotomy can lead to incontinence if excessively plied. In a similar way fistulotomy has a high risk of developing anal incontinence in the aged. An increasingly popular method of treating these fistulas is to use a Seaton whereby the sphincter is only gradually divided over time and replaced by scar tissue. Many feel that this is less likely to cause incontinence. Thus one must be judicious when recommending sphincterotomy or fistulotomy in the aged. Other factors may play a part in the elderly such as patients who have neuromuscular discoordination.

Warts

Anal Warts, Perianal Warts, Low Anal Warts:

Often the area is infected multifocally. Thus obliteration of one set of warts may still not eradicate the rest.

There are a variety of treatments, which include use of Podophyllin paint as an application, liquid Nitrogen and freezing. Other techniques are diathermy and surgical excision.

Some procedures can be carried out in the office whilst others require Anaesthesia and inpatient or Day Surgery treatment.

Sometimes further investigation is required for example HIV status etc. Anal warts may be associated with other perianal conditions such as haemorrhoids because of their frequency.

Pilonidal sinus

Pilonidal disease may present in two main ways. There is the acute abscess or the discharging sinus.

With the abscess in the early stage there is swelling and discomfort and this is followed by increasing pain, swelling and erythema until eventually an abscess presents and may even spontaneously discharge. Following this a sinus may persist particularly when there are underlying hair follicles deep in the natal cleft. Multiple sinuses may occur.

Thus the abscess is dealt with by drainage. Once the abscess has formed it does not respond to antibiotics. Local applications are not effective.

With the discharging sinus it may be blood and pus and acute exacerbations. The treatment is complete excision. The wound is treated either with primary closure in the less infected cases, or by healing under second intention where the wound is allowed to heal.

It is important in treating these patients to explain the process, which is going to occur — the risk of further infection with primary closure, and severe pain, which might occur as a result or the long time that the healing process takes when attempting to close by second intention.

The other risk with pilonidal sinus is the type of Anaesthesia. Many Surgeons have the patient placed in the prone position, which increases the Anaesthetic risk. Positioning can be important.

Anal tags SCC

Anal tags may signify internal disease such as a fissure.

Patients often have difficulty cleaning their anal area and may present with discomfort, itch, a bad odour and a mucous discharge.

They will consequently be embarrassed to present and discuss their condition

Pruritis ani may be an associated condition.

Treatment

Treatment can be symptomatic e.g. with use of creams.

Treatment can be carried out under local anaesthesia, in the office. It may require suturing.

There may be some swelling after surgery as the perianal region expands and contracts.

Colorectal Cancer Guidelines

2015 Colorectal Cancer Guidelines have been made available from the MEJIM November 2018 menu.

www.me-jim.com/November2018/colorectal_cancer_guidelines_short_form.pdf

Summary of Contents:

EVIDENCE-BASED RECOMMENDATION GRADES

- Primary prevention
- Dietary and lifestyle strategies
- The use of aspirin for prevention of colorectal cancer
- Population screening for colorectal cancer (with Evidence Based Recommendations)
- Signs & symptoms predictive of colorectal cancer
- Optimal maximum time from referral to diagnosis and treatment (diagnostic interval)
- Strength of association between family history and colorectal cancer risk
- High-risk familial syndromes
- Familial adenomatous polyposis (FAP)
- MUTYH-associated Polyposis
- Lynch syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome

- Imaging a patient with a diagnosis of colon/rectal adenocarcinoma
- Pathology and staging
- Preparation for surgery and peri-operative optimisation
- Elective and emergency surgery for colon and rectal cancer
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- Recommendations – Management of resectable locally recurrent disease and metastatic disease
- Management of resectable locally recurrent disease and metastatic disease
- Recommendations – Management of non-resectable locally recurrent disease and metastatic disease
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- The role of systemic therapies in non-resectable metastatic disease

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