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This work was left to humankind as a parting gift of artist, cartoonist and philosopher Michael Leunig who died in December 2024. Michael spent his life focusing on the human condition and was a fearless advocate of peace and of respect for all life on our planet as well as the planet itself. He was a truly great man.
Thank you Michael.

Editorial

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In the first issue of 2025, the Middle East Journal of Family Medicine (MEJFM) continues to illuminate the dynamic field of family medicine with ground breaking research and comprehensive reviews that address critical health issues prevalent in the Middle East and beyond. This edition includes pivotal studies by Kharel et al. and Helvaci et al., exploring the impacts of lifestyle choices on pulmonary and renal health respectively, and insightful reviews by Olol & Zbaidi and Zbaidi & Olol on emerging strategies for managing chronic diseases through intermittent fasting and mobile health technologies. Each piece contributes to our understanding of complex health dynamics in a rapidly changing world, emphasizing the journal's commitment to fostering a healthier future through robust scientific inquiry and innovative medical practices.

Kharel et al., looked at the pulmonary function test (PFT) in smokers and non-smokers between 25-45 years. Healthy male subjects, 120 smokers and 120 non-smokers, between 25-45 years without any symptoms were included as subjects. Patients with uncontrolled debilitating diseases were excluded. Collected data was analysed using Statistical Package for the Social Service (SPSS) software version 21. Total of 240 males, 120 smokers and 120 non-smokers matched for age, height, weight were enrolled in this study. From the result, the FEV1, FVC, FEF, FEV1/ FVC ratio were obtained and analysed. The mean difference in values for pulmonary function was highly significant ($P < 0.05$) between smokers and non-smokers. The mean FVC in smokers was 1.88 ± 0.61 L and in non-smokers was 2.83 ± 0.55 L. The decrease in FEV1 in smokers (1.34 ± 0.47 L) as compared to non-smokers (2.52 ± 0.62 L) clearly indicates the obstructive pulmonary disease. The authors concluded that smoking is common in males between 25-45 years age group. Smoking is highly associated with an abnormal PFT. Avoiding of smoking in any form should be encouraged and PFTs from time to time in adults both smokers and non-smokers will be useful for early detection of the respiratory ailments.

Helvaci*, et al., looked at the use of Metformin in the treatment of chronic renal disease. All patients with sickle cell diseases (SCD) were included. We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, $p>0.05$, respectively). Smoking (23.8% vs 6.1%, $p<0.001$), alcohol (4.9% vs 0.4%, $p<0.001$), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, $p=0.000$), disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), chronic renal disease (CRD) (9.9% vs 6.1%, $p<0.05$), coronary heart disease (18.0% vs 13.2%, $p<0.05$), cirrhosis (8.1% vs 1.8%, $p<0.001$), chronic obstructive pulmonary disease (25.2% vs 7.0%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher in males, significantly. The authors concluded that as a prototype of systemic atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis and end-organ insufficiencies in human being. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight,

it should be prescribed for the treatment of CRD even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight in adults.

Olol & Zbaidi, reviewed Intermittent Fasting and glycaemic control in Type II Diabetes : A review. Type II diabetes is a chronic metabolic condition characterised by hyperglycaemia secondary to the inadequate utilisation of insulin .The incidence of Type II Diabetes continues to increase globally and remains a significant healthcare concern(3). Prevention and early intervention are key to reducing
the health burden on individuals and healthcare systems(10). Health professionals have always
encouraged general lifestyle and dietary changes in patients; however, in recent years, intermittent fasting has become a specific pattern of eating that could aid patients with Type 2 diabetes. This paper explores the impact of intermittent fasting on Type 2 Diabetes and its role as an adjunct to pharmacological interventions.

Zbaidi- &Olol , reviewed mobile health through a review of current and emerging evidenceDigital health is a diverse field encompassing various technologies targeting or specialising in healthcare(1). Mobile health specialises in wireless or mobile technology, including digital applications, wearables and remote monitoring. Digital health in general, and mobile technology in particular, aim to improve health outcomes by using technology to advance the prevention, diagnosis and treatment of diseases and health-related conditions. Mobile technology distinguishes its services from other digital health by providing remote, continuous or on-demand access and potentially higher consumer control and ownership of their health.

Evaluation of Pulmonary Function Tests among Smokers and Non-Smokers in an urban area of Nepal

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Abstract

Background: Tobacco smoking is common in the world and the trend is more in developing countries. Smoking has a hazardous effect on respiratory functions. Smoking is the single most potent risk factor for the development of chronic obstructive airway diseases (COPD). PFT by a trained professional gives an indication of lung health by measuring airway ailments. Objectives were to study pulmonary function test (PFT) in smokers and non-smokers between 25-45 years.

Materials and Methods: Healthy male subjects, 120 smokers and 120 non-smokers, between 25-45 years without any symptoms were included as subjects. Patients with uncontrolled debilitating diseases were excluded. Collected data was analysed using Statistical Package for the Social Sciences (SPSS) software version 21.

Results: A total of 240 males, 120 smokers and 120 non-smokers matched for age, height, and weight were enrolled in this study. From the results, the FEV1, FVC, FEF, FEV1/ FVC ratio were obtained and analysed. The mean difference in values for pulmonary function was highly significant ($P < 0.05$) between smokers and non-smokers. The mean FVC in smokers was 1.88 ± 0.61 L and in non-smokers was 2.83 ± 0.55 L. The decrease in FEV1 in smokers (1.34 ± 0.47 L) as compared to non-smokers (2.52 ± 0.62 L) clearly indicates obstructive pulmonary disease.

Conclusions: Smoking is common in males between 25-45 years of age. Smoking is highly associated with an abnormal PFT. Avoiding of smoking in any form should be encouraged and PFTs from time to time in adults both smokers and non-smokers will be useful for early detection of the respiratory ailments.

Keywords: COPD, PFT, Smoking

Introduction

The World Health Organization proclaimed that tobacco smoking killed 100 million people worldwide in the 20th century and warned that it could kill more than one billion people across the world in the 21st century as well (1). Cigarette smoking is the principal preventable cause of mortality. Smokers who quit smoking are relatively safe from dying from smoking-related diseases (2). Tobacco smoke contains more than 4,000 chemicals and around 40 carcinogens (3). Smokers have decreased lung functions compared to non-smokers. Smoking is the most dangerous risk factor for the development of COPD. On an average, cigarette smokers have a high tendency of decrease in FEV1 of about 50 ml, which is nearly double the average value of 30 ml annually present in non-smokers (4). The classification criteria as suggested by WHO (5) (1998) is:

• **Smoker:** Someone who, at the time of the study, smoke tobacco products either daily or occasionally.
• **Non-smoker:** Someone who, at the time of the study, did not smoke at all.
• **Ex-smoker:** Someone who was formerly a daily or occasional smoker, but currently does not smoke at all

Tobacco smoke contains 60 known carcinogens which have the capability to develop lung carcinoma. The major known compositions of tobacco smoke include Acetone, Butane, Arsenic, Naphthalene, Cadmium, Carbon monoxide, Hydrogen Cyanide and Vinyl chloride. Cigarette smokers therefore, have a high rate of mortality due to lung carcinoma (6). Pulmonary function testing is a routine procedure for the assessment and monitoring of respiratory diseases. Tests are also useful because they cause minimum discomfort for the subjects. Pulmonary function tests vary according to age, height, sex, and body size (7, 8). Pulmonary function tests are economic, non-invasive and reproducible (9). PFT may play a role in convincing the patient to give up smoking of any form. The smoking trend is huge and proper effort is needed to launch effective campaigns to generate awareness regarding the consequences of smoking and pulmonary diseases. PFTs by a qualified health professional give an indication of lung health by measuring airway abnormality. An attempt has been made to study the pulmonary function tests among the healthy population including smokers who are asymptomatic.

Materials and Methods

A cross sectional study was conducted in the Department of Physiology, Kathmandu Medical College, Kathmandu, Nepal after obtaining clearance and approval from the Institutional Review Committee (IRC) of Kathmandu Medical College. The study was conducted from 15th January 2023 to 15th February 2024. The study population included 240 healthy male subjects aged between 25 to 45 years. They comprised 120 smokers and 120 non-smokers. Females were not included in this study, because of the low incidence of tobacco smoking among females in Nepal and also non-reporting tendency of the females in our society.

Healthy smokers were selected from among patients coming to OPD of KMCTH, Nepal.

Inclusion criteria
• Healthy subjects, 120 smokers and 120 non-smokers between 25-45 years without any symptoms were included as subjects
• Smoker: Someone who, at the time of the study, smoked any tobacco products either daily or occasionally for the last five years.
• Non-smoker: someone who, at the time of the study, did not smoke at all.

Exclusion criteria
• Patients with uncontrolled debilitating diseases were excluded
• Ex-smokers were excluded from study

The pulmonary functions were done on a computerized spirometer in 240 male subjects comprising 120 smokers and 120 non-smokers. PFTs were recorded by a spirometer (RMS Medispiror, Recorders and Medicare system (P) Ltd. Model: RMS Helios) and FVC, FEF, PEFR, FEV, FEV/FVC ratio were recorded. For evaluating the pulmonary physiology, the subjects were asked to sit comfortably. The complete procedure was explained and informed written consent was taken. The subjects were told to breathe fully by deep inspiration and after that, with their nostrils closed, sealing their lips, were asked to forcefully expire air. The best three readings were recorded and analysed. FVC, FEF, PEFR, FEV1, FEV1/FVC ratio were recorded and noted. Collected data were analysed using Statistical Package for the Social Sciences (SPSS) software version 21.

Results

The physical variables of the smokers and the non-smokers are shown in Table 1. Age range of the subjects was 25 – 45 years with mean age of smokers 33 ± 6.86 and of non-smokers 36.45± 5.58. Mean height of the smoker group was 1.68 ± 0.07 meters and of the non-smoker group was 1.65 ± 0.12 meters. Whereas, mean weight of smokers was 68±9.27 Kg and non-smokers was 66±7.85 Kg. A total of 240 males, 120 smokers and 120 non-smokers matched for age, height, and weight were enrolled in this study. From the result, the FEV1, FVC, FEF, FEV1/FVC ratio were obtained and analysed. The mean difference in values for pulmonary function was highly significant ($P < 0.05$) between smokers and non-smokers. The mean FVC in smokers was 1.88 ± 0.61 L and in non-smokers was 2.83 ± 0.55 L (Table 2). The decrease in FEV1 in smokers (1.34 ± 0.47 L) as compared to non-smokers (2.52 ± 0.62 L) clearly indicates the obstructive pulmonary disease (Figure 2 &3).

Table 1: Anthropological details of study participants (n=240)

No	Variables	Frequency	Percentage
1	*Age in Years*		
	25-35	110	45.83
	36-45	130	54.17
2	*Height (centimetres)*		
	≤ 160	89	37.08
	161-175	102	42.50
	≥ 176	49	30.48
3	*Weight (KG)*		
	≤ 60	45	18.75
	61-75	124	51.67
	≥ 76	71	29.58

Table 2: Comparison of various pulmonary function tests between smokers and non-smokers

S. No	Pulmonary Function Test (PFT)	Non-smokers (120) (Mean ± SD)	Smokers (120) (Mean ± SD)	P Value
1	FVC (L)	2.83 ± 0.55	1.88 ± 0.61	P < 0.05
2	PEF_{25-75} (L/S)	2.72 ± 0.95	1.70 ± 0.49	P < 0.05
3	PEFR (L/S)	5.84 ± 1.82	3.78 ± 1.78	P < 0.05
4	FEV_1 (L)	2.52 ± 0.62	1.34 ± 0.47	P < 0.05
5	FEV_1/FVC (%)	82.88 ± 8.85	72.56 ± 9.66	P < 0.05

Table 2: Comparison of various pulmonary function tests between smokers and non-smokers

PFT outcomes	Smokers	Non-smokers	Total
Obstructive	36 (15%)	5 (2.08%)	41(17.08%)
Restrictive	8(3.33%)	1(0.41%)	9(3.75%)
Mixed	4 (1.67%)	1(0.41%)	5(2.08%)
Normal	72 (30%)	113 (47.08%)	185 (77.08%)
Total	120 (50%)	120 (50%)	240 (100%)

Figure 1: Physical characteristics of smokers and non-smokers

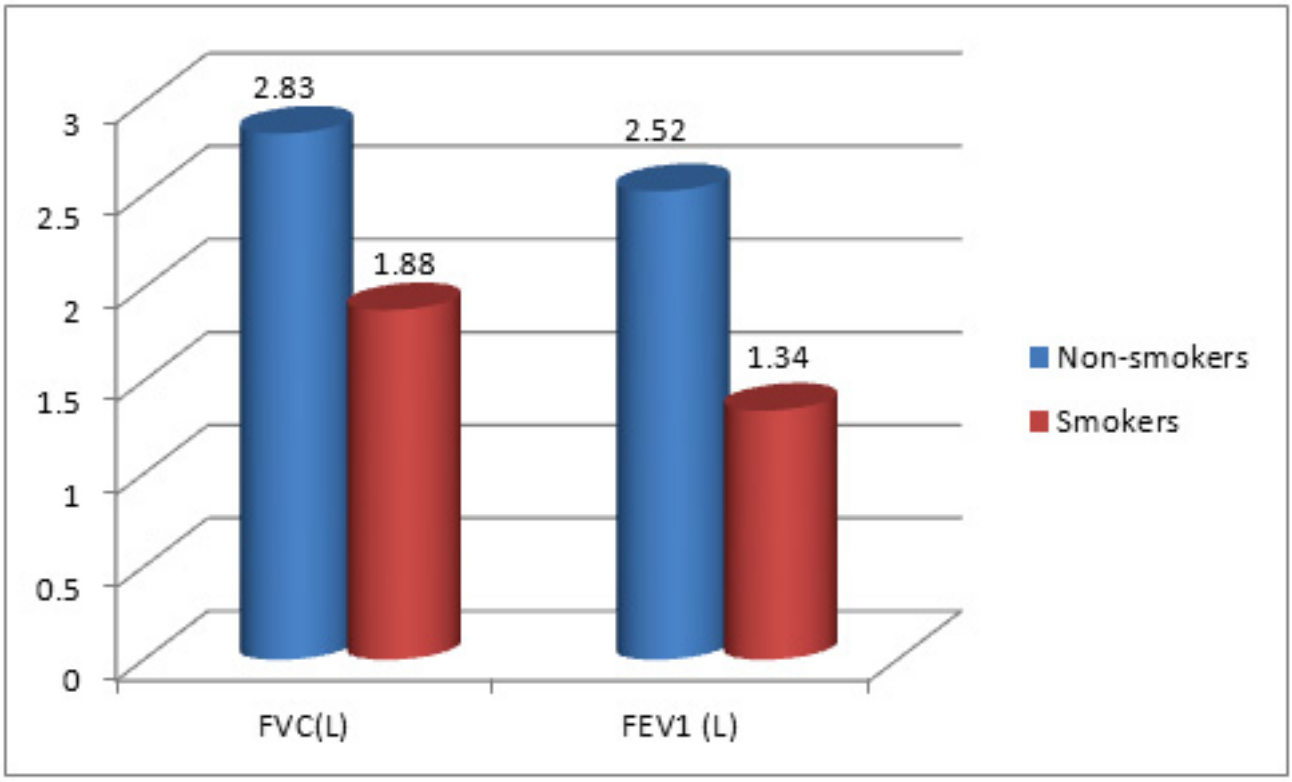


Figure 2: Comparison of variations in pulmonary function test (PFT) among smokers and non-smokers

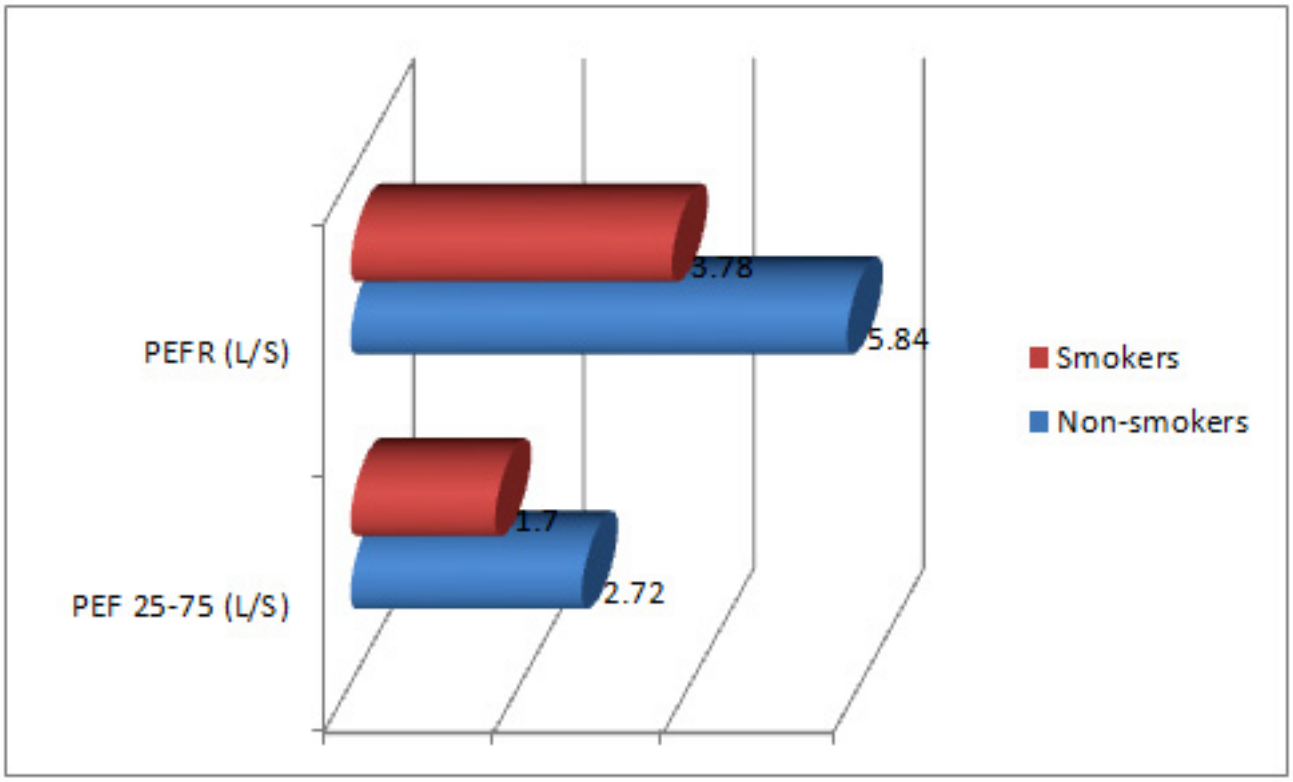
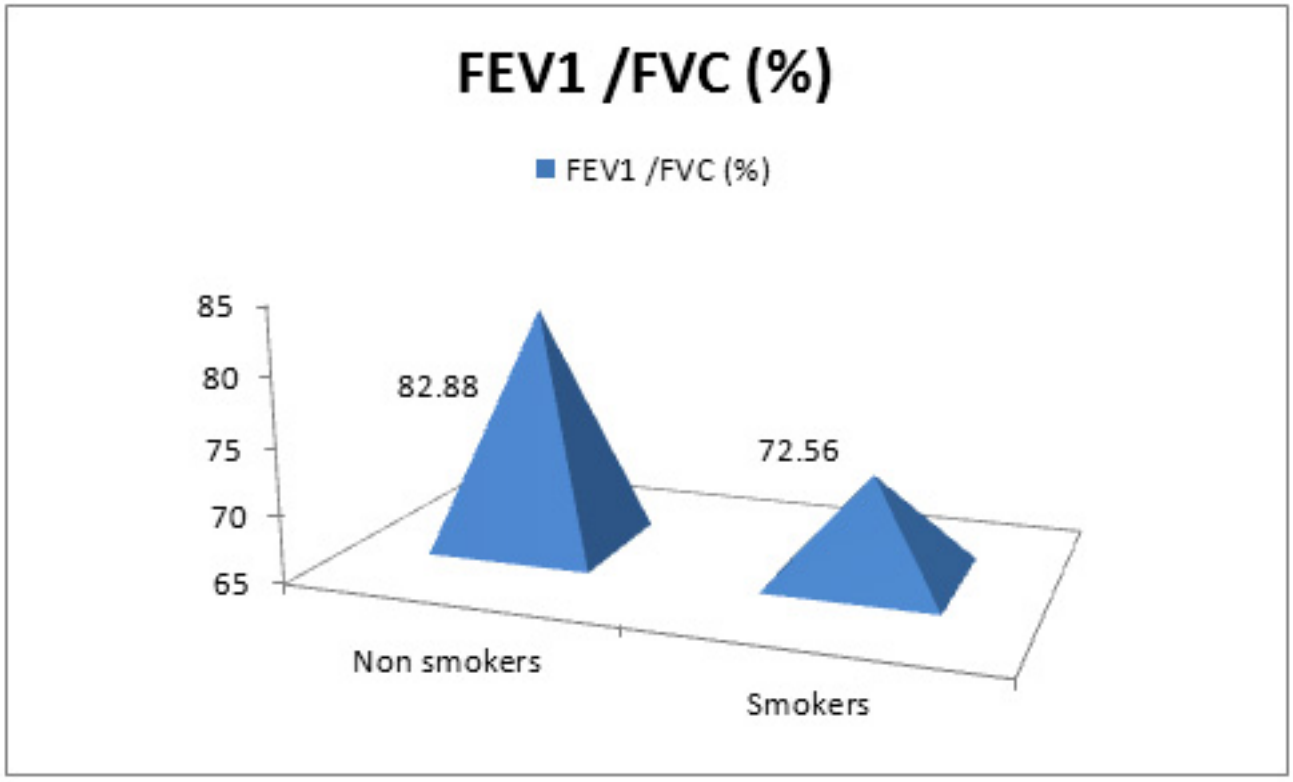


Figure 3: Comparison of FEV1/FVC (%) among smokers and non-smokers



Discussion

In recent days pulmonary function tests have become useful tools for respiratory physiology and evaluation of respiratory condition of the patient. They are also a part of routine health examination in respiratory medicine, exercise physiology and public health monitoring. FVC, PEFR, FEV1, FEV1/FVC ratio were the pulmonary function tests selected for the present study. In ourstudy, all the Pulmonary Function Tests like FVC, FEV1,FEV/FVC, PEFR, FEF2575% showed a highly significant association between the smokers and the nonsmokers ($P < 0.05$). The number of cigarettes smoked per day among 120 smokers is 7 cigarettes per day. Duration of smoking among smokers was more than 5 years. In a similar study done by Gold and Rees it has been well stated that the acute effect of smoking on the airways was the decrease of air-way conductance (10, 11). In our study the tendency was the reduction in the values of PFT in smokers which showed similar trends to the study done by Wihelmensen and Tibblin (12). Smoking may directly induce an arterial endothelial injury and an increased platelet consumption may reflect the adherence or the deposition of these cells,to damage site, was suggested by Hind C.R. (13). Hani A et al conclude in their study of pulmonary function test among smokers and non-smokers that mean FVC, FEV1 and PEFR were higher in non-smokers in each age group and BMI was not significantly associated with most of the PFT values (14).

Conclusions

The results of the present study demonstrated the significant effect of smoking on PFTs especially those indicating large airways. There were also elevated respiratory ailments among smokers.

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Metformin in the treatment of chronic renal disease

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Abstract

Background: Atherosclerosis may be the major underlying cause of aging and death.

Methods: All patients with sickle cell diseases (SCD) were included.

Results: We studied 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), coronary heart disease (18.0% vs 13.2%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly.

Conclusion: As a prototype of systemic atherosclerosis, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis and end-organ insufficiencies in human being. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight, it should be prescribed for the treatment of CRD even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight in adults.

Key words: Sickle cell diseases, chronic renal disease, excess fat tissue, vascular endothelial inflammation, atherosclerosis, smoking, aging

Introduction

Chronic endothelial damage may be the major cause of aging and death by causing end-organ insufficiencies in human being (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, emotional stress, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, and dementia-like end-organ insufficiencies and aging, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the vascular process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). On the other hand, sickle cell diseases (SCD) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the cases with associated thalassemia minors (TM), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hardened RBC into the tissues. The hardened RBC-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the final consequences, so the mean life expectancy is decreased by 25 to 30 years for both genders in the SCD (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. 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, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis 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, and C, 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 by means of MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, since the SCD with associated TM show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). 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. Systolic BP of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). 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. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0, and with the presence of Schamroth's sign (17, 18). 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 movement disorders in the cardiac walls. Rheumatic heart disease is

diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively), and there was no patient above the age of 59 years in both genders. Prevalences of associated TM were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CRD (9.9% vs 6.1%, p<0.05), COPD (25.2% vs 7.0%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes (Table 2). On the other hand, mean ages of the other atherosclerotic consequences in the SCD were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	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) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	*48.1 ± 61.8 (0-434)*	*0.000*	*28.5 ± 35.8 (0-206)*
Disseminated teeth losses (<20 teeth present)	*5.4% (12)*	*<0.001*	*1.4% (3)*
CRD§	*9.9% (22)*	*<0.05*	*6.1% (13)*
CHD¶	*18.0% (40)*	*<0.05*	*13.2% (28)*
Cirrhosis	*8.1% (18)*	*<0.001*	*1.8% (4)*
*COPD***	*25.2% (56)*	*<0.001*	*7.0% (15)*
Ileus	*7.2% (16)*	*<0.001*	*1.4% (3)*
Leg ulcers	*19.8% (44)*	*<0.001*	*7.0% (15)*
Digital clubbing	*14.8% (33)*	*<0.001*	*6.6% (14)*
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)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic renal disease ¶Coronary heart disease
**Chronic obstructive pulmonary disease ***Pulmonary hypertension ****Deep venous thrombosis
*****Acute chest syndrome

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

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	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 losses (<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)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Excess fat tissue may be the most common cause of disseminated vasculitis all over the world at the moment, and it may be one of the terminal endpoints of the metabolic syndrome, since after development of excess weight, nonpharmaceutical approaches provide limited benefit either to improve excess weight or to prevent its complications. Excess fat tissue may lead to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess fat tissue in all age groups (19). The low-grade chronic inflammation may also cause genetic changes on the epithelial cells, and the systemic atherosclerotic process may decrease clearance of malignant cells by the immune system, effectively (20). Excess fat tissue is associated with many coagulation and fibrinolytic abnormalities suggesting that it causes a prothrombotic and proinflammatory state (21). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (22). For example, elevated C-reactive protein (CRP) levels in serum carry predictive power for the development of major cardiovascular events (23). Overweight and obesity are considered as strong factors for controlling of CRP concentration in serum, since excess fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (24). On the other hand, individuals with excess fat tissue will have an increased circulating blood volume as well as an increased cardiac output, thought to be the result of increased oxygen demand of the excess fat tissue. In addition to the common comorbidity of atherosclerosis and HT, the prolonged increase in circulating blood volume may lead to myocardial hypertrophy and decreased compliance. Beside the systemic atherosclerosis and HT, fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased with increased body mass index (BMI) (25). Similarly, the prevalences of CHD and stroke increased parallel with the increased BMI values (26). Eventually, the risk of death from all causes including cardiovascular diseases and cancers increased throughout the range of moderate and severe excess fat tissue for both genders in all age groups (27). The excess fat tissue may be the most common cause of accelerated atherosclerotic process all over the body at the moment, the individuals with underweight may even have lower biological ages (27). Similarly, calorie restriction extends lifespan and retards age-related chronic diseases in human being (28).

Smoking may be the second most common cause of disseminated vasculitis all over the world. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in whole body (29). Its atherosclerotic effect is the most obvious in the COPD and Buerger's disease (30). Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been documented in the absence of smoking. Its characteristic findings are acute inflammation and stenoses and occlusions of arteries and veins of the hands and feet. It is usually seen in young males between the ages of 20 and 40 years. Claudication may be the most common initial symptom. It is an intense pain caused by insufficient blood flow during exercise in feet and hands but it may even develop at rest in severe cases. It typically begins in extremities but it may also radiate to more central areas in advanced cases. Numbness and tingling of the limbs are also common. Raynaud's phenomenon may also be common in which fingers or toes turn a white color upon exposure to cold. Skin ulcerations and gangrene of fingers and toes are the final consequences. Gangrene of fingertips may even need amputation. Unlike many other forms of vasculitis, Buerger's disease does not keep other organs with unknown reasons, yet. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be important in the development of Buerger's disease, particularly in the lower extremities. Angiograms of upper and lower extremities are diagnostic for Buerger's disease. In angiogram, stenoses and occlusions in multiple areas of arms and legs are seen. In order to rule out some other forms of vasculitis by excluding involvement of vascular regions atypical for Buerger's disease, it is sometimes necessary to perform angiograms of other body regions. Skin biopsies are rarely required, since a biopsy site near a poorly perfused area will not heal, completely. Association of Buerger's disease with tobacco use is clear. Most of the patients are heavy smokers, and the disease can also be seen in users of smokeless tobacco. The limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed stenoses and occlusions are irreversible. Due to the clear evidence of inflammation of the disorder, anti-inflammatory dose of aspirin plus low-dose warfarin may probably be effective to prevent microvascular infarctions in fingers and toes at the moment. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and C-reactive protein may be positive acute phase reactants indicating such inflammatory effects of smoking on vascular endothelium (31). Similarly, it is not an unexpected result that smoking was associated with the lower values of BMI due to the systemic inflammatory effects on vascular endothelium (32). In another definition, smoking causes a chronic inflammation in human body (33). Additionally, some evidences revealed an increased heart rate just after smoking even at rest (34). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Smoking may be associated with a postcessation weight gain, but the

risk is the highest during the first year, and decreases with the following years (37). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher prevalences of white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (38). Beside that the prevalence of myocardial infarction is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day (39). In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature (40). There may be several underlying mechanisms to explain these associations (41). First of all, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis, loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) (40).

CRD is increasing all over the world which can be explained by aging of the human being, and increased prevalence of excess weight all over the world (43). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the chronic renal endothelial inflammation. The chronic inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (44). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (45). 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 the CIMT (43). 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 fat tissue (46). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (46). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (47). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess fat tissue, CRD progresses much more easily (46). On the other hand, the efficacy of metformin in weight loss is well known for several years, and it is a safe, cheap, and orally used drug for hepatosteatosis and DM. According to the literature, metformin inhibits the mitochondrial respiratory chain, imparing the main site of energy generation through aerobic metabolism. This results in a shift toward anaerobic metabolism, of which lactate is a by-product, and less energy for gluconeogenesis. Reduced hepatic glucose production may be a major mechanism of the antihyperglycemic effect of metformin, although it has been recently proposed that some glucose lowering may be mediated through the enteroendocrine axis (48). According to our experiences, the main effect of metformin may be a mild to moderate loss of appetite. Similarly, metformin is eliminated as unchanged in the urine. Although mild to moderate CRD reduces metformin clearance, the drug levels typically remain within a safe range (49). Additionally, circulating lactate levels among metformin-treated patients are typically normal, even among patients with CRD (50). Beside that the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (51). Although some authors reported that alcohol was not related with the CRD (51), 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 processes may also terminate with the accelerated atherosclerosis in the renal vasculature (47). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (52, 53). For example, the most common cause of death was the cardiovascular diseases in the CRD again (54). The hardened RBC-induced capillary endothelial damage in the renal vasculature may be the main cause of CRD in the SCD. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (55).

Stroke is one of the two terminal causes of death with any underlying etiology, and develops as an acute thromboembolic event on the chronic atherosclerotic background. Although the aging, male gender, smoking, and alcohol may be found among the major underlying causes, excess fat tissue may actually be the most common cause all over the world at the moment. There are around 20 kg of excess fat tissue between the lower and upper borders of normal weight, 35 kg between the lower borders of normal weight and obesity, 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2), and 81 kg between the lower borders of normal weight and super obesity (BMI ≥ 45 kg/m2) in adults. In fact, there is a significant percentage of adults with a heavier fat mass than their organ plus muscle masses in their bodies. This excess fat tissue brings a heavy stress on liver, lungs, kidneys, heart, and of course on brain. Beside the above underlying etiologies, stroke is also a common complication of the SCD (56). Similar to the leg ulcers, stroke is particularly higher in the SCA and cases with higher WBC counts (57). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial inflammation, edema, and fibrosis (58). Probably, stroke may not have a macrovascular origin in the SCD, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced exaggerated capillary inflammation, edema, and fibrosis (59).

CHD is the other terminal cause of death with any underlying etiology. The most common triggering event is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaque is a gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial wall in decades. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue forms in its place. This scar tissue may also cause potentially life threatening arrhythmias since the injured heart tissue conducts electrical impulses more slowly than the normal heart tissue. The difference in conduction velocity between the injured and uninjured tissue can trigger re-entry or a feedback loop that is believed to be cause of many lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Another life threatening arrhythmia is ventricular tachycardia that may also cause sudden cardiac death. Ventricular tachycardia usually results in rapid heart rates which prevent effective pumping. Cardiac output and blood pressure may fall to dangerous levels which can lead to further coronary ischemia and extension of infarct. This scar tissue may even cause ventricular aneurysm, rupture, and sudden death. Physical inactivity, sedentary lifestyle, emotional stress, animal-rich diet, excess fat tissue, smoking, alcohol, chronic infection and inflammations, and cancers are important in atherosclerotic plaque formation in time. Physical inactivity is important since moderate physical exercise is associated with a 50% reduced incidence of CHD (60). Probably, excess fat tissue may be the most frequent cause of CHD, too.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). 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 fat tissue all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (61). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (61). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (62). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (63). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCD (64). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (36).

Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (65). For instance, 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 (65, 66). As a result, cirrhosis may also be another atherosclerotic consequence of the SCD.

Acute painful crises are the most disabling symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (67). The increased basal metabolic rate during such stresses aggravates the sickling, capillary endothelial damage, inflammation, edema, tissue hypoxia, and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with

the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (68, 69). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (68, 69). According to our experiences, simple and repeated transfusions are superior to RBC exchange in the SCD (70, 71). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during the crises (72). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBC on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCD. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (73), and it was associated with the risk of stroke in a cohort of Jamaican patients (74). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (75), but according to our practice, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the chronic inflammatory background of the SCD.

Hydroxyurea may be the only life-saving drug for the treatment of the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (76, 77). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial damage-induced edema, ischemia, and infarctions in whole body (78). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (79). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (80).

The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (80). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (80). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (80). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) in the previous study (68). Parallel to our results, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (81). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (81). The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (82). Hydroxyurea therapy in early years of life may protect splenic function, improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for prostaglandins (PG) and thromboxanes (TX) synthesis. PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation in the body. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (83). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (84). According to the literature, aspirin may also be effective in prevention of colorectal cancers (85). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 12 years (86). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (87). Reye syndrome is a rapidly worsening brain disease (87). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (88). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (88). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (87). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (87). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (87). The cause of Reye syndrome is unknown (88). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (88, 89). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (87). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (88). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (88). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (90).

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (91). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (92). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (93). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days.

The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable

with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (94). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (93). The risk is particularly increased once the INR exceeds 4.5 (94). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (95). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (96). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) (96). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (97). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin (p= 0.009) (97). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002) (97). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between (p>0.05) (97). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTE), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTE in patients with CVT (98). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (99). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (100). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (100). The mortality was markedly lower in the warfarin group, too (p= 0.005) (100). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (100). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (101). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (101). The average daily dose was 2.6 mg, and the mean INR was 1.5 (101). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (102). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (103). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (104). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCD (105). So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCD (106).

COPD is the third leading cause of death with various underlying etiologies in whole world (107). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess fat tissue, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the most significant cause of COPD all over the world due to the excess fat tissue-induced systemic atherosclerotic process in whole body. After smoking and excess fat tissue, regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (108). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (109). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are 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 fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (110).

For example, there may be close relationships between COPD, CHD, PAD, and stroke (111). Furthermore, two-third 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 (112). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (112). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (113). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBC in the SCD (107).

Leg ulcers are seen in 10% to 20% of the SCD (114), and the ratio was 13.5% in the present study. Its prevalence increases with aging, male gender, and SCA (115). Similarly, its ratio was higher in males (19.8% vs 7.0%, p<0.001), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (114). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (114). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (115). 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 SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities, again. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (116). 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 (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (117). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems in the SCD. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (79). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial inflammation and edema instead of the terminal fibrosis alone.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (118). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (119). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, 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 SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, p<0.001) may also show some additional role of male gender in the systemic atherosclerotic process.

As a conclusion, hardened RBC-induced capillary endothelial damage initiating at birth terminates with end-organ failures in much earlier ages in the SCD. Excess fat tissue may be much more important than smoking and alcohol for the development of atherosclerosis and end-organ insufficiencies in human being. The efficacy of metformin in loss of appetite is well known for several years. Since metformin is a safe, cheap, orally used, and effective drug for excess weight, it should be prescribed for the treatment of CRD even in normal weight individuals, since there are nearly 20 kg of excess fat tissue between the upper and lower borders of normal weight in adults.

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Mobile Health : A review of current and emerging evidence

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Abstract

Background: Mobile health (mHealth), a subset of digital health, uses mobile applications, wearables, and monitoring technologies to enhance remote and continuous healthcare services. It aims to revolutionise healthcare through individualised, precise and on-demand care.

Objectives: This review explores current and future applications and potential of mHealth technologies. It examines the rapidly expanding and revolutionary role of mHealth in healthcare delivery and highlights potential barriers and dilemmas.

Methods: A synthesis of recent literature was conducted to provide an overview of mHealth developments, applications, and growing challenges, including data quality, governance, and regulatory gaps.

Results: mHealth applications rapidly expand into multiple health fields, from fitness to mental health and chronic disease. The rapidly evolving mHealth technology promises improved health outcomes through real-time monitoring and tailored interventions. Despite significant advancements, real challenges involving data privacy, accessibility and equity, technology validation, and concerns about commercial influence on governance and regulations further complicate the landscape.

Conclusions: mHealth offers transformative potential for medicine and achieving precise and individualised healthcare. However, addressing data quality, ethical, and governance challenges is critical for sustainable growth and fully realising mHealth's benefits in addressing global healthcare needs.

Key words : Mobile health ,Digital health, Wearables, Remote health monitoring, Digital health applications

An overview of mobile health (digital apps, wearables and remote monitoring)

• **Definition:** Digital health is a diverse field encompassing various technologies targeting or specialising in healthcare (1). Mobile health specialises in wireless or mobile technology, including digital applications, wearables and remote monitoring (2, 3).

• **Aims:** Digital health in general, and mobile technology in particular, aim to improve health outcomes by using technology to advance the prevention, diagnosis and treatment of diseases and health-related conditions (2, 4, 5). Mobile technology distinguishes its services from other digital health by providing remote, continuous or on-demand access and potentially higher consumer control and ownership of their health (3, 6).

The future of mobile health: Scope and potential applications in healthcare delivery

Mobile health is gaining momentum and is in a rapid acceleration mode. The industry is progressively evolving its core products and experimenting with new technology to expand and diversify its market reach (7, 8). Future health care is challenged by an explosion of the world population and pressure on resources, climate change and a global trend for urbanisation, disproportionate increase in the ageing populations in the developed countries, and rising chronic diseases, including mental health and the emergence of novel infectious diseases (9). The future of healthcare relies on the reinvention of traditional delivery models to match the increasing health demands and changing consumer' expectations (9). Mobile health, including digital applications, wearables and remote monitoring, is a promising development in the health information and technology sector (4, 5, 10). Since its introduction, manufacturers' efforts to enhance quality and diversify the product range have been reciprocated by unrelenting consumer interest and technology uptake (11). Mobile health technology has a role in preventing, detecting, diagnosing, and treating health conditions. Mobile technology allows health care to be personalised, adjusted to the consumer's treatment goals, delivered on-demand and delivered outside of the constraints of the traditional health facility (6, 7, 12). Mobile health is expected to continue to improve the accessibility to healthcare, especially for those who already face access problems; for example, vulnerable groups such as people living with mental illness, those who have a terminal illness, or those living remotely would benefit from remote and frequent access (8, 12, 13). Mobile technology allows access to uninterrupted real-time data. The increased amount and diversity of information can improve data quality and clinical decision-making(14). Inception medicine is an emerging field predicting improvements in the early prediction and prevention of diseases based on the algorithmic analysis of mobile health data (6, 14). Implantable devices with chemical and physiological monitoring capabilities could predict and prevent acute events such as cardiac attacks, one of the top mortality causes in modern society (14). Sensor technology also has a role in lifestyle and mental health and well-being monitoring, incorporating data about daily activities, physical movement, food intake, sleep, subjective well-

being and relating the data to vital signs and blood chemistry (10). Health care can be extended beyond the brick-and-mortar health facilities and delivered in a virtual environment, bypassing the constraints of existing delivery models and recouping savings on the traditional costs of buildings, infrastructure and the time and cost of commute and transport (3, 7, 13).

Current applications of mobile health

Mobile health use is incrementally but steadily extending into numerous healthcare fields and disciplines (7). Tens of thousands of health applications are available in mobile App Stores, and more are regularly added to the market (15). The production and use of wearables are also growing, with manufacturing companies competing for consumer traction. Consumers have built an expectation for a broader product range and advanced features with every version update.

• **Mental health and well-being:** Mental health was an early adopter of mobile and digital applications. E-mental health programs offer self-guided web- and application-based prevention and treatment programs for common mental health issues (2). Some of these programs offer remote clinician support and supervision of treatment progress (16). The literature supports the efficacy of mobile mental health programs in treating several mental health conditions, such as anxiety and depression (17). Australian-based programs such as This Way Up clinician-supported programs(16), Beyond Blue Smiling mind app for mental health prevention (17) and Black Dog youth mental health well-being digital programs (18) are accessed by thousands yearly. Other uses of mobile technology in mental health are SMS or text messaging for treatment follow-up or well-being checks. The wide use, simplicity and low cost of text messaging make it a practical and low-cost intervention (8).

• **Physical exercise and fitness:** the fitness industry is a pivotal innovator of digital health applications and wearables. As wearables become more popular amongst all age groups, the industry is claiming to offer more advanced models with improved capabilities and health- tracking features (19). Current wearable tracking capabilities include monitoring and recording the type, frequency and amount of movement and physical exercise. It also detects and compares some of the body's physiological parameters, e.g. heart rate and rhythm, during exercise and at rest (19). Wearables are competing to be our preferred and highly-recommended personal trainer and health coach. They can track progress over days, weeks, and months and provide summaries and analyses of cumulative physical movement. They also send regular

reminders and motivating messages to encourage us to move regularly and exercise. Sleep trackers are also featured on some wearables and claim to analyse sleep quality.

• **Cardiovascular health:** globally, cardiovascular disease is one of the top causes of mortality. The disease burden of chronic cardiovascular conditions such as hypertension and heart failure significantly affects the individual's quality of life and exerts pressure on health services (20). The diagnosis and treatment of these conditions benefit from advancements in mobile technology (14, 21). For example, mobile blood pressure monitors improve the accuracy of the diagnosis of hypertension (14). Mobile blood pressure monitors allow continuous 24-hour or more extended measurement periods rather than episodic stents. It also solves the issue of "white-coat hypertension" for patients with increased blood pressure only during medical encounters (14). For heart failure patients, more digital apps are available to simplify some aspects of managing this complex disease. Medication administration apps can help guide patients in managing polypharmacy, especially those with a new diagnosis (21).

The challenges and pitfalls of mobile health

• **Data quality and validity:** A significant share of the marketed mobile technology, digital apps or wearables are manufactured by private commercial enterprises (15). The current laws and regulations are not prescriptive of guidelines or processes to measure data quality and validity (7). There are growing concerns that some commercially available wearables have faulty monitoring features, such as the heart rate and rhythm tracking functions, leading to false results, unnecessary alarm to the consumer and increased use of traditional health resources (15). Health advice and guidance offered by digital apps are often not based on the best available evidence and can divert from acceptable medical practice (15).

• **Data governance:** Data governance is a framework or structure that defines the organisational data guidelines, rules and principles, the authorities issuing the rules and how the rules are communicated and monitored (22). Data governance is a quality assurance tool and an adequate safety and security measure throughout the data life cycle. Good data governance allows organisations to develop an informed approach and deep understanding of the benefits and risks of data (22). Mobile digital health, developed by private companies, is presumed to be subject to the governance structure of the manufacturer. These structures are often unclear and lack representation from key stakeholders representing consumers and the health sector (2, 7, 15, 23).

• **Equality and access:** Access to digital technology requires a minimum of physical resources and individual skills to connect with the information and utilise it for the betterment of health (24). The prerequisites for valid and effective digital access favours the affluent and educated over the socioeconomically disadvantaged (25). Internet and connectivity infrastructure in rural and remote areas complicates access to all digital health services, including mobile health (26). The cost of mobile devices and wearables is another barrier to equal access for all. The digital capability to fully engage and utilise mobile technology is limited for several population groups, such as the elderly and people living with a disability (24, 25).

• **Data privacy and security:** The modern view of data is that it is an organisational asset and should be invested in to maximise the benefit for the organisation (7, 23). Personal data collected by mobile health devices and apps include detailed and extensive personal information from name, date of birth and contact details to health information and habits (7, 15, 23). This "gold mine "of data is increasingly attractive for commercial enterprises for traditional purposes such as marketing and to use to feed and develop AI technology capable of understanding and predicting consumer behaviour (23). The fine print privacy policies imposed by companies on consumers are geared towards commercial benefit, allowing companies to use and share consumers' data for financial gain. The vulnerability of consumer and their data remain a significant challenge for mobile technology (23).

• **Professional and consumer attributes and skills needed to use the technology:** Generic digital health apps and wearables are designed with the assumption of a certain level of digital literacy and capability(24). All consumers are expected to have the digital skills, access and capability to use the information and benefit from it to the same level. The assumption that most young people are technology savvy is probably true (11, 25). However, several barriers restrict access for many individuals and population groups. Physical disability, loss of dexterity, hearing or vision obstructs full and equal access to mobile health. Education level, literacy and age, and health determinants also impact digital access (6, 11, 24, 26).

• **The potential impact of the involvement of the corporate sector in healthcare:** The commercialisation of mobile health and the unopposed influence and power of the private sector can potentially compromise the quality and equity of digital healthcare (15, 23). Policy and legislation are lagging in this area, leaving a significant gap in market regulations and risking the loss of consumer power and voice in the absence of protection from governments and health authorities (5, 7). Private enterprises have a long and strong history of innovation, producing and constantly evolving quality products that are highly attuned to consumer demands. However, we cannot ignore that these are commercial enterprises driven mainly by financial gain and health safety, accessibility, and equity are merely secondary agendas (26).

The prospects of mobile digital technology and healthcare delivery in the next decade

Mobile digital health is expected to influence and substantially impact healthcare delivery in the next ten years and the longer term (5, 6, 11). The current use patterns of digital apps and wearables indicate an upward trend of steady expansion and evolution of the mobile health market (6, 7, 11). Advocates and digital optimists are predicting mobile technology to revolutionise

are predicting mobile technology to revolutionise individualised and accurate healthcare, personalise health prevention, diagnosis and management and lay the basis for innovative healthcare models (19). Digital apps, wearables and implantables are predicted to be the catalyst for individualised and accurate healthcare and novel models such as “inception medicine“ (14). In the era of genetic mapping and testing, consumers’ expectations of their healthcare are rapidly changing, and there is a general sense of dissatisfaction with the “one size fits all “healthcare models (3, 7). Mobile health offers technological features capable of continuously monitoring and collecting vital physiological data with the promise of using the data to individualise prevention, diagnosis and treatment plans and, therefore, an overall improvement to individual health outcomes (10). Inception medicine claims to improve the prevention, early intervention and treatment processes through the triangulation of multi-source data from mobile physiological monitoring, genetic testing and AI- enhanced technology (10). However, for mobile health to deliver on its positive forecast for the next decade and maintain the momentum for leading innovative and agile healthcare delivery, it needs to address the defaults in the accuracy, quality and validity of current technological models and operations (7, 15). The “validity “of mobile products is increasingly questionable as more products fail to deliver the results they claim or promise. Digital apps are observed to measure “proxies “in a tick-box fashion rather than pursuing actual and fit-for-purpose indicators (23). Weight loss and fitness apps collect vital signs and physical movement measures, but the evidence for “validity by improving fitness or achieving the desired weight” is lacking (27). Blood glucose and blood pressure monitors display similar deficiencies and a mismatch between the health issue they claim to address and the final health outcome (23, 28). Attention and investment in the scientific rigour of future mobile technology are critical to embedding validity (3). Current regulations and data governance structures must be revised to improve app design and development governance and processes. The industry would benefit from adopting a co-design approach and complementing IT expertise with the perspective and knowledge of health experts and consumer representatives (5, 15, 23). In addition, the next decade will increasingly challenge mobile health to rectify its inherent preference for a generic techno aware and savvy customer typology. Mobile technology is increasingly scrutinised for excluding the socioeconomically and technologically challenged by design, and technology developers are under mounting pressure to produce inclusive technology that contributes rather than halts health equity and advantage. Health equity is mobile technology’s next frontier (26).

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Intermittent Fasting and glycaemic control in Type II Diabetes: A review

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Abstract

This paper reviews the impact of intermittent fasting on glycaemic control and subsequently Type 2 diabetes.Type 2 Diabetes has been labelled a disease of modern lifestyle causing significant health burden on individuals and overall health care systems. Research highlights that poor glycaemic control can lead to insulin resistance, metabolic syndrome and potentially Type 2 Diabetes. Periodic calorific restriction is hypothesized to reduce insulin resistance and increased lipolysis. Intermittent fasting can cause a risk of hypoglycaemia and dietary measures alone may not be sufficient for weightloss and Type 2 Diabetes management.

Key words: Type 2 Diabetes, Intermittent Fasting, Glycaemic Control,Weight Loss

Introduction

Type II diabetes is a chronic metabolic condition characterised by hyperglycaemia secondary to the inadequate utilisation of insulin. The incidence of Type II Diabetes continues to increase globally and remains a significant healthcare concern (3). Prevention and early intervention are key to reducing the health burden on individuals and healthcare systems (10). Health professionals have alwaysencouraged general lifestyle and dietary changes in patients; however, in recent years, intermittent fasting has become a specific pattern of eating that could aid patients with Type 2 diabetes. This paper explores the impact of intermittent fasting on Type 2 Diabetes and its role as an adjunct to pharmacological interventions.

Discussion

Type II diabetes mellitus

Type II diabetes, also known as non-insulin-dependent diabetes or adult-onset diabetes, is a common metabolic disorder(1-3). People with type II diabetes develop a hyperglycaemic state due to insulin resistance or insufficiency. Insulin is secreted by the pancreatic cells (B-islet cells) and is the primary hormone responsible for glucose metabolism(1). Type II diabetes is characterised by high insulin resistance leading to inefficient metabolism of glucose, lipids and proteins(1). Insulin resistance, leading to type II diabetes, is a multi-factorial pathological process including lifestyle factors, biomedical characteristics and genetic predisposition (1).

Type II diabetes has often been labeled an epidemic of modern life and lifestyle disease(2, 3). The fast-paced modern society increased the global popularity of highly-processed calorie-dense diets and sedentary lifestyles and, consequently, the prevalence of obesity and overweight(3). According to the WHO, in 2022, 14% of adults aged 18 years and older were living with diabetes, an increase from 7% in 1990 (3).

Diabetes-related mortality and morbidity are also exponentially increasing (10). People with diabetes experience significant acute and chronic complications(1). Uncontrolled hyperglycaemia can be life-threatening in the short term but also leads to chronic complications and end-organ damage, including vasculopathy, neuropathy, retinopathy and nephropathy(1). Type II diabetes and its related complications are significant contributors to the global disease burden, increased mortality and morbidity, reduced quality of life and shortened life expectancy (1-3).

Type II diabetes is a disease of social and economic disadvantage. People living in lower socioeconomic areas have a higher incidence and prevalence of type II diabetes and associated comorbidities (1, 2). The prevalence of diabetes is rapidly increasing in low to medium income countries compared to affluent countries (10).

Intermittent fasting

Fasting is an eating or dietary pattern characterised by periodic or timed abstinence from eating (4). Fasting has been practised for thousands of years as a form of religious or spiritual belief associated with self-discipline and morality (5). Followers of different religious faiths, including Islam, Buddhism and Christianity, continue to follow this practice for its religious significance and the many claimed mental and physical health benefits (5).

Intermittent fasting is a modernised, health-orientated form of fasting that has become increasingly popular in recent years(4). It involves the restriction of caloric intake for specified periods. There are different models of intermittent fasting, including fasting up to 16 hours per day or eating one meal a day for two days of the week (5, 6). The intermittent fasting eating patterns do not nominate the type of foods consumed nor are prescribed to a specific diet (4).

In addition to weight loss and many other health benefits, periodic caloric restriction through intermittent fasting is proposed to improve glycaemic control and reduce insulin resistance (4-6). Metabolism and glycaemic control are complex biological processes regulated by multiple physiological pathways; gastrointestinal and pancreatic hormones are responsible for achieving a balanced physiological response in the starvation (fasting) and the eating (active digestion) phases (6). Prolonged fasting states are hypothesised to reduce insulin resistance and increased lipolysis or the use of body fat stores as a source of energy (5). Type II diabetes is characterised by high insulin resistance leading to inefficient metabolism of glucose, lipids and proteins (5). The literature suggests potential benefits of intermittent fasting on the glycaemic control of type II diabetes (4-6). The risk of hypoglycaemia, particularly in patients using hypoglycemic agents and those with multi-morbidity, remain of concern (5).

Weight and Type 2 Diabetes

The mainstay of type II diabetes treatment is weight loss through a balanced healthy diet and physical exercise (1, 4, 5, 7). Obesity, especially truncal obesity and increased waist circumference, is a risk factor for metabolic syndrome, insulin resistance and poor glycaemic control.

Modest weight loss, as low as 5% of the total body weight, is associated with significant improvements in blood glucose levels and diabetes control (1, 8). The Australian Exercise guidelines recommend 2.5 to 5 hours of moderate intensity physical activity – such as a brisk walk and 1.25 to 2.5 hours of vigorous intensity physical activity – such as jogging (9) for adults per week. A low glycaemic index, Mediterranean style diet is recommended; Diets rich in vegetables, fruits, legumes and fish and low in polyunsaturated fats, highly processed products and red meat are shown to assist in weight loss and improve glycaemic control but should be eaten in moderation (11).

Adherence to long-term caloric-restriction dietary plans is often suboptimal (4, 6).

Pharmacological interventions

When lifestyle changes alone are insufficient to achieve diabetic control and treatment targets, a range of pharmacological agents is available to augment treatment (1, 7).

Glucose-lowering agents include oral preparations and injectables (1, 7). Oral agents target different steps of the glycaemic control pathway, from decreasing glucose production to increasing insulin secretion (1, 7). Insulin has been traditionally used as the only injectable form of glucose-lowering agent and a last-resort treatment for advanced or treatment-resistant diabetes (1, 7). Insulin is cheap and very effective in reducing blood glucose levels. However, insulin has serious side effects, including acute life-threatening hypoglycaemia. Insulin precipitates hunger and causes weight gain, which worsens glycaemic control (1, 7).

Recently, the market has witnessed the revolutionary introduction of new diabetes injectables; Glucagon-like peptide-1 receptor agonists (GLP1 agonists) work on stimulating insulin and inhibiting glucagon (1, 7). Unlike insulin, these agents cause significant weight loss and are increasingly used as weight loss agents in non-diabetics (1, 7).

Despite the expansive range of hypoglycaemic agents available, oral Metformin remains the first line pharmacological treatment for type II diabetes and is considered both safe and effective (7).

Conclusion

The research highlights that poor glycaemic control can lead to insulin resistance, metabolic syndrome and potentially Type 2 Diabetes. Intermittent fasting appears to positively impact glycaemic control in Type II Diabetic patients. It has also been utilised by patients in addition to pharmacological therapy, and this can potentially cause hypoglycaemia. Therefore, dietary patterns, such as a Mediterranean diet with less calorie restriction, may be more beneficial in patients at risk of hypoglycaemia. The introduction of GLP1 agonists is a significant addition to tackling weight and metabolic syndrome; although we are yet to see the data for long-term side effects and impact on sustained weight, intermittent fasting may be an appropriate tool for some patients, with alternative options, including dietary and pharmacological for others.

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Red and Processed Meats and Health Risks: How Strong Is the Evidence? Frank Qian 1,2, Matthew C Riddle 3, Judith Wylie-Rosett 4, Frank B Hu 1,5,6
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Special Editorial: Peace, Reconstruction and Justice for Palestinians - in Gaza, the West Bank and beyond

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In Gaza today (29/1/2025) as we celebrate our global status as close to self-annihilation (the Doomsday Clock) I wonder if sane and decent humans will now be allowed to take our world out of the hands of the commercial and political tyrants who have brought us collectively to this stage. They put personal wealth and their psychopathic needs to control, above the existence of all life. We didn't need a meteorite this time - all the destruction was done by greedy and evil humans - sadly they will also take the life of so many other innocent creatures.

Genocide in Gaza and the West Bank

We have all seen the great injustice and horror of the genocide in Gaza and now when there is nothing left to destroy, we have the 'peace process' where Palrstinian 'prisoners' are being returned to a wasteland – and a situation where it is impossible for Palestinians to live in their own country, so the attacks are now happening in the West Bank. Can we trust that once the Israelis get their hostages released Netanyahu will not start killing all remaining Palestinians?

The genocide of ordinary innocent Palestinians we are told, was based on the activities of Hamas but Hamas was born of decades of Israeli attacks on Palestinians and their land in multiple areas because Israel was wrongly and unfairly given Palestinian land by colonisers of the ME region after World War 2. There were 2 million Palestinian refugees who fled their own land at that time. It seems Israel's position is that after taking Palestinian land and murdering or throwing Palestinians out of their own country, they now want all of it. Israel's lies and protestations have no basis. Fortunately the sane world condemns Israel's violence and murder but that does not help the people of Gaza as Israel has overcome this issue by reducing their civilization to rubble. The Gaza situation is also aligned with, and aided by the machinations of the commercial and political tyrants destroying our wider world around us for personal gain. Palestinians, the nicest people in the world, are yet another Middle Eastern victim of ignorant aggression. How we got to this stage and what we can do about it is a critical concern for all of us as we share the same fate. None of us are safe from the criminally insane despots, who are proliferating everywhere.

It would seem the ferocity in which Israel is killing Palestinians and destroying their county is total madness as they leave the country despoiled and unproductive so that no-one can live in it but that seems to be Netanyahu's main aim. Israel would prefer it remain a desolate barren land than a place Palestinians or Israelis can live.

Since the start of the war against Gaza/the Palestinians the ongoing Israeli attacks on the region also include Lebanon, Iran, Syria and the West Bank and have involved ongoing murder. The Israeli PM has used the death of innocents for his own agenda (why did he not protect his own population with his military might and spy network in Gaza and beyond, and prevent death and hostage taking). He began his war to stop the Israeli people marching in the streets every day against his government. It is an age old despot policy of tyrannical governments and arms merchants. Rather the names of 365 dead plus the death of an unknown but a relatively small number of hostages, have been sullied with the blood of so many innocent Palestinian people and will forever remain so. They will be associated with Netanyahu's genocide, propaganda and lies - it is yet another dark spot on the lives of humanity. We are better than that but our so-called leaders are not.

It is the same evil and ignorance of arms manufacturers of other nations who have conducted their wars in the Middle East to boost sales or get rid of stock sitting unsold on their shelves; the same sort of commercial tyrants who have contributed to the destruction of this once beautiful planet. The only country supporting Israel's genocide is the country selling them arms.

The situation is not dissimilar to Nazi Germany when 17,000,000 Jews were murdered and caused the great exodus. That is the bit that is so hard to comprehend or do Palestinians have to pay the price for Nazi Germany's evils. Humans who have suffered greatly mostly work to never have such evils happen to anyone else.

It is difficult to ascertain the full loss of life in Palestine as Israel has acted in secrecy by killing Aid Workers and foreign journalists. Most of the country is rubble. Scorched earth policy is far more effective these days with over-supply of modern armaments. Indeed the manufacturing countries need ongoing wars to maintain their profits. There has been an estimated 64,000 deaths due to violence between October 2023 and June 2024. A UN report estimates it will take 350 years to rebuild Gaza. The outcome in Gaza will be mass movement of Palestinians - literally to survive - and have their children survive. This is what the aggressor wants and always wanted. It will be easier to claim their land when it is devoid of people. They don't care that it won't be fit for Israelis to live in - they just don't want Palestinians to be able to live there. They have even dug up sewerage and water pipelines to make the destruction complete. Not all Israelis are condemned, just those who support Netanyahu's genocide.

The new President of the US, an ally of Israel, suggests shifting the Palestinian people out of Gaza 'temporarily or longterm' along with his son in law who says it is '*time to try something new'* – shifting Palestinians to the Negev desert!!!! We are talking about people's lives! Such is the moral bankruptcy and deception of despots.

This attack on Gaza is coupled with the deliberate dehumanising of Muslims generally and the endless wars against the region over centuries.

The first time I visited the ME region I found Muslims to be the nicest people in the world. They are. I wondered who is behind the propaganda and to what purpose? It would seem to be the world's political and commercial tyrants as usual. Yes some fight back, such as Hamas. How stupid would you be to think you can inflict many decades of torture on people without them fighting back? This time, like Russia in Ukraine, Netanyahu has also destroyed Palestinians' lives, their schools, places of worship their hospitals and their towns, their mothers and fathers and children and babies, their culture and way of life…

It is part of the bigger world picture now playing out globally; how the criminally insane get to run the majority of countries is something we urgently need to look into before they commit genocide globally. We also need to review the system where the unconscionable greedy make all the decisions that destroy our ecosystems and planet viability. Okay some people are easily duped but that is a factor we also need to consider. It is a catastrophe. The dinosaurs lasted 177 million years before they were wiped out by a meteor. Humans have only been around about 300,000 years and will destroy themselves and nearly all other life forms with their appalling brutality and negligence. We are good at tool making but are not an overly intelligent or decent species it seems– the facts speak for themselves and we are not addressing the real problem as today's self-annihilation status is mostly at the hands of greedy commercial tyrants. They own the companies that poison our land and sea and the commercial monsters who skin animals alive to make fake potions or cut off their tusks to make ornaments. There are even humans who kill frightened animals with big guns to show how 'brave' they are. As a whole we deserve extinction through our negligence and lack of care and attention to the real issues of life, but not as individuals as it is the greedy who make most decisions on this planet.

The commercial tyrants are aided and abetted by governments in return for 'political donations'. We all know that –but people are jailed for speaking the truth. They are called 'whistle blowers' – truth is a dangerous pastime in this world. I know.

Peace and working together to repair and save our planet and our species is the only way humanity will survive. We can do it but we must change and find a way to rid ourselves of these monsters in our midst - it requires a whole new system that criminals cannot infiltrate.

The people of the world are dismayed and shocked that Israel can commit such crimes given their history and the US sadly can no longer be trusted to be a good world citizen. Just when we need decent leaders we have none – well apart from the President of Colombia!

Rather we have egotists, robbers, fools and psychopaths - the criminally insane - and they are deliberately killing sane and decent people everywhere. Look at Navalny in Russia - it is rare a brave and steadfast man like that arises on this planet. Sadly he was murdered by the man he tried to save his people from.

How did we get into this state of endless lies and propaganda and with the majority of the global population under ruthless insane dictatorships and the planet dying before our eyes?

The right wing media, and commercial and political tyrants of the world are totally unconcerned about ordinary humans globally. Never before has the world and prospects of ordinary people, including basic human rights and a viable planet to dwell upon been at risk at the hands of the self-serving, tyrannical few. Never before have we faced planetary ecosystem death. The basic wants and needs of ordinary humans, including peace and the right to dwell on a tiny piece of planet are becoming impossible.

The political tyrants are of course supported practically by the commercial tyrants including Social Media giants and the right wing press, weapons of war manufacturers, and those mining **vital resources that belong to all the people of earth for all time**. The politicians in turn allow the

commercial tyrants to destroy the planet and take what that want– as long as they give them back a bit of the cash. It is called capitalism. Interestingly Islam doesn't approve of capitalism or people charging interest on loans.

January 28 2025

The entire world has just recognised Holocaust day commemorating a time when Germany murdered 17 million Jews after forcing them to move from their homes and killed them en masse. The world has always shown its sympathy.

Now Israelis are complaining about anti-Semitism increasing in the world but the Netanyahu government is acting just like Adolf Hitler did - evil, cruel genocide but Netanyahu is going further to include destruction of an entire country. Simply the world is shocked and appalled by Israel's evil and barbarity.

The Palestinian fight for justice and their homeland is that same fight we are all now potentially facing. Every tyrant in the world is using the same tactics of destroying civilisation. How has the world fallen into the evil manacles of self-serving tyrannical men who would rather destroy an entire civilisation than have anyone question their own arrogance and sanity.

This is no longer conjecture.

Humans are not a greatly gifted species and it would seem in many cases quite a nasty and ignorant species as death and destruction has been our (written) history to date.

We live in an era where extreme violence and misogyny is one of the biggest forms of entertainment for men. This brutalises men and gives women mental health issues with many women disfiguring themselves to look like the grotesque women displayed in such entertainment. Why do some of the media companies provide this entertainment for men? It is because appealing to base instincts makes money for big media companies *and* there are other hidden agendas. They openly spread lies to support despotic 'governments' again for money and favours.

The big media companies also attack the self-esteem and mental health of children - again deliberately. Some countries are just waking up.

We need to turn off the dystopian fare of the tech and media giants and use our own intelligence, our emotional intelligence - we may even learn something.

I believe the vast majority of people would prefer to be good and decent and would be if they were educated properly and treated properly at all levels of society. Positive education is our only protection against the anarchy and evil that has brought us to the precipice overlooking the end of our time on this planet.

The tyrants may be slaves to their biology and mental fitness, but humans are also meant to be intelligent and apply reasoning, and conscience, compassion, empathy and wisdom and many do. But the commercial and political tyrants seem to have no heart or soul at all. They are vessels full of greed, hate and revenge.

Is this the race to the moral bottom - and is joining the ranks of the evil dictatorships now a badge of honour? This is the greatest test of humans – at this very late stage - to learn from the adverse events of their lives and work to make sure no such evil ever happens again.

Our enemies are political tyrants, the commercial tyrants, the right wing press including Social Media giants (the money worshippers), weapons of war manufacturers, and those mining vital resources that belong to all the creatures of earth for all time.

The future for the Palestinians

The horror to which Palestinians have been subject will result in extreme psychological distress and mental health issues far beyond the talents of the best mental health counselling. Seeing your parents, your children, your home, your community, your schools and hospitals, your places of worship and gathering places cannot be replaced or healed in a lifetime. Those mental scars will be passed down through the ages as will the fact that few tried/were able to help and those who did were also brutally killed for their efforts

Attacks on the Middle East go back in history to the Crusades, the 'Holy Roman Empire' and the European colonisers - but we all have a history of being wronged and dispossessed in the historical machinations of mad men. The key is to become civilised and stop it, not perpetuate it - we need another focus for humans to survive in this filthy, poisoned, bombed world of the tyrants.

We could try to perform a miracle for Palestine though - God knows they deserve it. Foreign aid (with a huge contribution frorn Israel) will help regional relationships and rebuild a country. Sadly we can never give those murdered babies and children their lives back.

We need a system where tyrants can never ever exist. I suggest so called 'governments' are the problem - they facilitate these egotistical monsters and abusers. From my own observations we should allow those benign experts in their fields make any necessary national or global decisions - like a plan to clean up this garbage dump planet and take measures to stop global warming. We may not always get the best people but currently we tend to always have the worst people in positions of power.

The people of the world need to join together and save our planet and humanity from the rubbish humans that have prevented us all from living full and proper lives; peace and harmony where the riches of the world belong to all people and not just commercial and political tyrants

who want it all for themselves. Currently ‘they’ ‘own’ over 90% of the planet - we barely subsist. We have to take our planet back and work together to repair it and prevent these despots from destroying us all with their greed and violence.

I have come across some wonderful people and most people on the planet are the same. The Middle East is the birth place of 2 great religions, Islam and Christianity, both trying to teach humans a bit of basic decency and how to get on with each other.

The only ‘winner’ in any war will be the one who says enough people have died in this insanity and I will not fight back and continue this evil. Indeed a great middle easterner said just that 2025 years ago and we are still as primitive as we were then. But we have brains and hearts and may just surprise ourselves if we try.

Accuracy of Ultrasound vs. Magnetic Resonance Imaging in Diagnosing Placenta Accreta Spectrum: A Systematic Review

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Abstract

Aim of Study: To assess the clinical value of MRI for the diagnosis of placenta accreta by systematic review of published related diagnostic studies.

Methods: An exhaustive electronic search was conducted based on the relevant terms and MeSH (Medical Subject Headings of the National Library of Medicine) descriptors in PubMed, Embase, and Ovid databases. The literature screening process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: A total of 108 records were identified through database searching. After applying the inclusion and exclusion criteria, only seven records could be included. Two studies followed a prospective research design, while the other five studies followed a retrospective research design. The sensitivity and specificity of ultrasonography and MRI, both separately and combined for the diagnosis of placenta previa complicated with placenta accreta, were shown in each included study.

Conclusions: Ultrasonography is more sensitive and also more specific than MRI for the diagnosis of placenta previa complicated with placenta accreta. Ultrasound combined with MRI produces higher accuracy and sensitivity than ultrasound alone or MRI alone in the diagnosis of placenta previa with placenta accreta.

Key Words: Placenta Accreta Spectrum, Ultrasonography, Magnetic Resonance Imaging, Sensitivity, Specificity, Systematic Review.

Introduction

Placenta accreta (PA) is one of the serious complications of pregnancy, where the placenta does not spontaneously separate after delivery and cannot be forcibly separated without causing catastrophic obstetric hemorrhage (1). It is caused by abnormal placental implantation over a myometrial scar, and results in the extrusion of placental tissue beyond the usual confines of the intrauterine cavity with fibrinoid deposition, and massive neovascularity (2).

The spectrum of PA describes the abnormal attachment of placental trophoblasts to the myometrium. According to the depth of the invasion into the myometrium, it is further graded according to the extent of placenta involvement into: placenta accreta (PA), with abnormal adherence to the myometrium, placenta increta (PI), with deep myometrial implantation, or placenta perforata (PP), when it breaches the serosal surface or involves other surrounding structures. The main risk factors for PA include advanced maternal age, scarred uterus, and uterine lesions (3).

With the worldwide increase in abortion and Cesarean section (CS) rates, the incidence of PA has shown an increasing trend. However, about 50-60% of PA is not diagnosed antenatally (4). The primary pathophysiological mechanism of PA may be related to several factors, e.g., basal decidua loss, abnormal local oxygen tension, excessive trophoblast invasion, and abnormal vascular remodeling (5).

In PA, the placenta can be detached if there is sufficient myometrium underlying the placenta that enables adequate uterine contractions to prevent severe hemorrhage. However, in PI and PP, any attempt to manually remove the placenta may cause uterine rupture and heavy bleeding (6).

Placenta accreta is associated with a very high risk of maternal mortality, especially if the surgeon is caught unaware. In resource-limited settings, it is likely that women with PA have a much greater risk of death due to technical, diagnostic, logistic, and resourcing inadequacies (7). Studies have shown that the perinatal mortality of PA is about 7% (8).

The early diagnosis of PA is essential for decreasing maternal mortality or morbidity. Doppler ultrasound is the primary imaging technique for diagnosing PA, thanks to its non-invasiveness, economic advantage, and wide availability. However, its diagnostic yield for PA is adversely influenced by amniotic fluid, intestinal gas, and placental position (9). In recent years, magnetic resonance imaging (MRI) has been increasingly adopted in the diagnosis of prenatal placental implantation in the realization of its advantages of high-resolution, multiangle imaging, and limited influence by amniotic fluid and intestinal gas (10).

Previous literature has reported different diagnostic accuracies of MRI for PA with inconsistent sensitivity and specificity. Therefore, this study aimed to assess the clinical value of MRI for the diagnosis of PA by systematic review of published related diagnostic studies.

Materials and methods

Several inclusion and exclusion criteria were considered to retrieve a study in this systematic review. The accepted research designs were prospective, randomized controlled trials (RCTs) or a comparative cohort study.

An exhaustive electronic search was conducted based on the following combined relevant terms and MeSH (Medical Subject Headings of the National Library of Medicine) descriptors in the PubMed, Embase, and Ovid databases. The search was based on the following: (“placenta accreta” OR “Accreta, placenta” OR “placenta increta” OR “placenta percreta”) AND (“MRI”, “magnetic resonance imaging”) AND (“diagnosis” OR “diagnostic accuracy” OR “sensitivity” OR “specificity”). The literature screening process is shown in Figure (1) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Inclusion and exclusion criteria

The references of the identified articles were also searched. The search was limited to articles published in English during the period from January 2020 to January 2023). Only studies that included both ultrasound and MRI diagnostic measures for PA were included. On the other hand, studies published in the form of a letter to the editor or comments, meta-analyses, or review articles, were excluded.

This systematic review was conducted in line with the protocol agreed upon by all authors. Two reviewers (MA and AA) independently assessed the quality of studies using the Newcastle–Ottawa Scale quality assessment tool for observational studies (12). To reach a consensus, all different opinions about quality assessment were discussed with a third reviewer (HA).

Results and Discussion

A total of 108 records were identified through database searching. However, after applying the inclusion and exclusion criteria, only seven records could be included.

Two of the included studies followed a prospective research design (13-14), while the other five studies followed a retrospective research design (15-19).

The sensitivity and specificity of ultrasonography and MRI, both separately and combined for the diagnosis of placenta previa complicated with placenta accreta, were sought in each included study. The results are shown in Table (1).

The sensitivity of ultrasonography ranged from 78% (14) to 96% (13). On the other hand, the specificity of ultrasonography ranged from 60% (13) to 91.78% (15). Moreover, the area under the curve (AUC) was reported by only one study, An et al., (16) to be 0.858.

The sensitivity of MRI ranged from 62% (18) to 94.4% (18). On the other hand, the specificity of MRI ranged from 40% (13) to 87.67% during the second trimester (15). Moreover, the area under the curve (AUC) was reported by only one study, An et al. (16) to be 0.709.

Regarding the combined yield of ultrasound with MRI, their combined sensitivity for the diagnosis of placenta previa complicated with placenta accreta ranged from 94.67% (19) to 97.78% (14). On the other hand, their combined specificity ranged from 72% (14) to 87.88% (19). Moreover, the area under the curve (AUC) was reported by only one study, An et al. (16) to be 0.931.

Conclusions

Ultrasonography is more sensitive and also more specific than MRI for the diagnosis of placenta previa complicated with placenta accreta. Ultrasound combined with MRI produces higher accuracy and sensitivity than ultrasound alone or MRI alone in the diagnosis of placenta previa with placenta accreta.

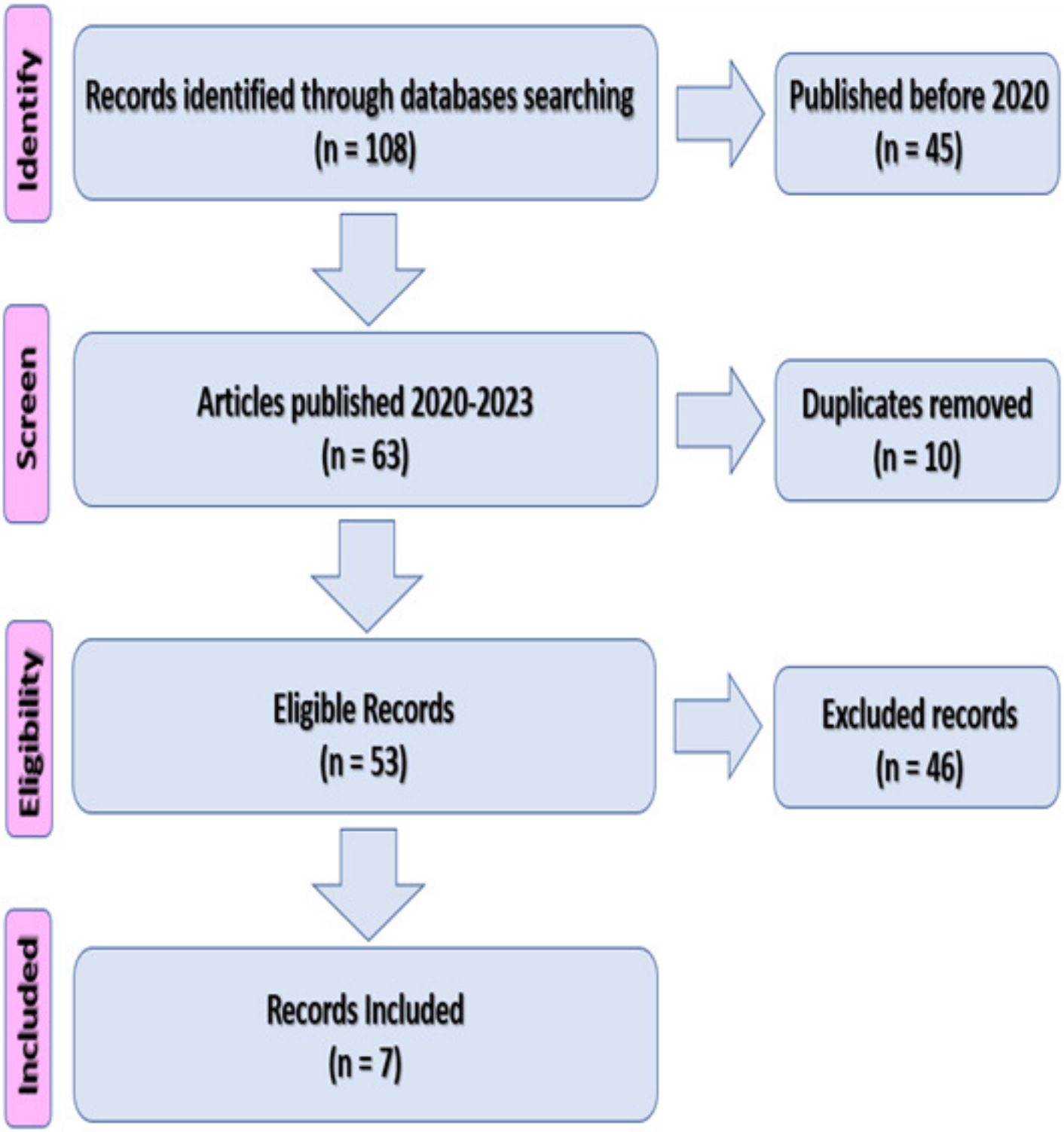

Figure 1: PRISMA flow chart for the search process

Table 1: Summary of the main results

Authors	Study design	No. of Participants	US	MRI	Combined	Conclusion
Barzilay et al. [13]	Prospective	28	Sen: 96% Sp: 60%	Sen: 83% Sp:40%	---	US is more sensitive and specific than MRI
Xia et al. [15]	Retrospective	86 cases, 46 in the 2nd trimester and 40 in the 3rd trimester	Sen: 95.65% (2nd trimester), and 97.50% in the 3rd trimester) Sp: 91.78% (2nd trimester), and 90.70% (in the 3rd trimester)	Sen: 89.13% (2nd trimester), and 92.50% in the 3rd trimester) Sp: 87.67% (2nd trimester), and 87.21% (in the 3rd trimester)	---	Abdominal US and MRI for PA in the 2nd and 3rd trimesters provide meaningful imaging evidence
An et al. [16]	Retrospective	132 women with PA	AUC: 0.858	AUC: 0.709	AUC: 0.931	US/MRI-based signature is a powerful predictor for the degree of PA spectrum
Guo et al. [14]	Prospective	70	Sen: 77.78% Sp: 68%	---	Sen: 97.78% Sp: 72%	Compared with ultrasound or MRI alone, ultrasound combined with MRI has higher accuracy and sensitivity in the diagnosis of placenta previa with placenta accreta, along with lower false positive diagnosis rates
Thiravit et al. [17]	Retrospective	62 cases	Sen: 91.7% Sp: 76.9%	Sen: 94.4% Sp: 84.6%	---	Placental bulge
Pain et al. [18]	Retrospective	82 women with PA	Sen: 55% Sp: 68%	Sen: 62% Sp: 72%		Loss of the normal retro-placental clear space had the highest sensitivity
Zhang and Dong [19]	Retrospective	108	Sen: 88% Sp: 66.67%	Sen: 92% Sp: 72.73%	Sen: 94.67% Sp: 87.88%	Combining prenatal US score of the placenta with MRI plays an important role in the diagnosis of placenta accreta during the 2nd and 3rd trimesters.

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